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THE AORTIC WRAP PROCEDURE: A SURGICAL METHOD OF TREATING AGE-RELATED AORTIC DILATATION AND STIFFNESS

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Introduction: There is progressive stiffening and dilatation of the aorta and large elastic arteries with aging as a result of the repetitive cyclic stress they are exposed to throughout life. Aortic stiffening has a number of detrimental effects including an increase in aortic pulse wave velocity and early wave reflection, isolated systolic hypertension, ventricular-vascular mismatch, impaired coronary blood flow reserve, and is the fundamental cause of heart failure in the elderly. The aim of this thesis is to provide proof of concept for the aortic wrap procedure; a surgical treatment of stiffening and dilatation of the ascending aorta with aging. The surgical procedure involves wrapping an elastic material around the ascending aorta of elderly patients, to reduce the stiffness and diameter of the ascending aorta towards that seen in youth.
Methods: Proof of concept is investigated in the following studies. 1. The effect of the elastic wrap on the in-vivo stiffness of the normal aorta. 2. The effect of the elastic wrap on the in-vivo stiffness of the dilated and stiffened aorta. 3. The effect of the elastic wrap on the in-vitro stiffness of the aged human ascending aorta and on aortic pressure. 4. The effect of wrapping the aged human ascending aorta on pulse pressure (mathematical model). 5. The effect of chronic implantation on the structure of the normal aorta. 6. The mechanical properties of the ovine thoracic aorta and the elastic wrap material.
Results: 1. Elastic wrap application increased the in-vivo stiffness of the normal aorta. 2. Elastic wrap application decreased the stiffness of the stiffened and dilated aorta. 3. Elastic wrap application decreased the in-vitro stiffness of the elderly human ascending aorta and pulse pressure. 4. A reduction in ascending aortic stiffness was sufficient to reduce ascending aortic pulse pressure.
Conclusion: Application of the elastic wrap to the aged human ascending aorta is expected to reduce aortic stiffness, as well as systolic and pulse pressure, and to increase diastolic pressure with a reduction in cardiac load. The aortic wrap procedure may be an effective surgical procedure for the treatment of heart failure and isolated systolic hypertension.

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“Ω ξειν’, αγγέλλειν Λακεδαιμονίοις ότι τηιδε κείμεθα, τοίς κείνων ρήμασι πειθόμενοι.”

“Go tell the Spartans,

Passerby,

That here, obedient to their laws,

We lie.”

Simonides, Epitaph for the Spartans who fell at Thermopylae

Greek poet (556 BC - 468 BC)

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CHAPTER 1: INTRODUCTION

Heart failure is a disease that has reached epidemic proportions in Western industrialised nations (Braunwald 1997; NHF/CSANZ 2002; AHA 2005). Heart failure is the only cardiovascular disorder increasing in incidence and prevalence (NHF/CSANZ 2002; AHA 2005). As a result of increased survival in patients with cardiovascular disease as well as aging of the population, the incidence and prevalence of heart failure is expected to rise significantly in the future (Kelly 1997; Chobanian, Bakris et al. 2003).

Heart failure is primarily a disease of the elderly, with the prevalence of the disease rising with aging (Kannel, Castelli et al. 1972; Ho, Pinsky et al. 1993; Lloyd-Jones, Larson et al. 2002). In the United States, heart failure occurs in 1-2% of people aged 45-50 years; 2-6% of people aged 55-64; 4-6% of people aged 65-74; and 10% of people aged 75 years or more (AHA 2005). In the United States, heart failure is responsible for 6.5 million hospital days each year, and is the leading cause of admission and readmission in patients aged 65 years or older (Gooding and Jette 1985; Massie and Shah 1997; Rich and Nease 1999; Jessup and Brozena 2003). The economic burden of treating heart failure in Western industrialised countries is considerable. In the United States, the total estimated cost of treating heart failure in 2005 amounted to approximately 27.9 billion U.S. dollars (AHA 2005).

The fundamental basis of cardiac failure in the elderly is aortic stiffening and dilatation (Nichols, O'Rourke et al. 1985; O'Rourke, Avolio et al. 1986; Westerhof and O'Rourke 1995; Nichols and O'Rourke 2005). With aging, the aorta and large elastic arteries stiffen and dilate as a result of the repetitive cyclic stresses they are subjected to throughout life (Nichols and O'Rourke 2005). Repetitive cyclic stresses in these vessels

produce fracture and fragmentation of inert elastic fibres with an increase in collagen content in the tunica media (Schlatmann and Becker 1977; Virmani, Avolio et al. 1991; Nichols and O'Rourke 2005). As a result there is a progressive increase in the stiffness and pulse wave velocity of the large elastic arteries with aging (Nakashima and Tanikawa 1971; Gozna, Marble et al. 1974; Merillon, Motte et al. 1978; Langewouters 1982; Avolio, Chen et al. 1983; Avolio, Deng et al. 1985; Lanne, Sonesson et al. 1992; Sonesson, Hansen et al. 1993; van der Heijden-Spek, Staessen et al. 2000; Hundley, Kitzman et al. 2001). This process is accompanied by progressive dilatation of the aorta and large elastic arteries (Gould 1960; Learoyd and Taylor 1966; Nakashima and Tanikawa 1971; Gerstenblith, Frederiksen et al. 1977; Nichols, O'Rourke et al. 1985; Towfiq, Weir et al. 1986; Kawasaki, Sasayama et al. 1987; Virmani, Avolio et al. 1991; Lanne, Sonesson et al. 1992; Pedersen, Aslaksen et al. 1993; Sonesson, Hansen et al. 1993; Lanne, Hansen et al. 1994; Pearson, Guo et al. 1994; Sonesson, Lanne et al. 1994; Vasan, Larson et al. 1995a; Lakatta and Boluyt 2000; Lakatta and Levy 2003a).

Stiffening of the aorta and large elastic arteries with age is largely responsible for the changes in blood pressure that are seen with aging (Avolio, Chen et al. 1983; Avolio, Deng et al. 1985; Nichols, Nicolini et al. 1992; Franklin, Gustin et al. 1997; Lakatta and Levy 2003a; O'Rourke and Nichols 2005). There is a progressive increase in brachial artery systolic arterial pressure from age 30 (Kannel, Gordon et al. 1971; Kannel, Dawber et al. 1980; Kannel, Wolf et al. 1981; Burt, Whelton et al. 1995; Franklin, Gustin et al. 1997). In contrast, brachial artery diastolic pressure rises until 50 years of age then progressively declines. With the increase in systolic pressure and decrease in diastolic pressure, there is a progressive increase in brachial artery pulse pressure with aging. This form of hypertension

is termed isolated systolic hypertension and is the commonest form of hypertension in the elderly (Franklin, Jacobs et al. 2001a; Chobanian, Bakris et al. 2003).

The increase in systolic pressure with age has generally been regarded as benign until recent times. The Systolic Hypertension in the Elderly Program (SHEP) study and subsequent trials demonstrated that isolated systolic hypertension is associated with a greater risk of heart failure, stroke, and myocardial infarction, and that treatment of isolated systolic hypertension reduces the risk of developing these conditions (SHEP 1991; Staessen, Fagard et al. 1997; Staessen, Wang et al. 1999; Wang, Staessen et al. 2000).

A number of studies have shown that pulse pressure is a more accurate predictor of cardiovascular risk (especially coronary risk) and cerebrovascular risk than systolic pressure or diastolic pressure (Benetos, Safar et al. 1997; Mitchell, Moye et al. 1997; Benetos, Rudnichi et al. 1998; Chae, Pfeffer et al. 1999; Domanski, Davis et al. 1999; Franklin, Khan et al. 1999; Vaccarino, Holford et al. 2000; Safar 2000a; Safar, Blacher et al. 2000b; Franklin, Larson et al. 2001b; Safar, Blacher et al. 2002). Furthermore, a reduction in diastolic pressure is associated with an increased risk of coronary heart disease; possibly due to a reduction in coronary blood flow (Madhavan, Ooi et al. 1994; Benetos, Safar et al. 1997; Franklin, Khan et al. 1999; Franklin, Larson et al. 2001b). Large artery stiffening and the increase in pulse pressure with age produce microvascular disease in the brain and kidney that results in cerebrovascular accident, dementia, and renal failure (O'Rourke and Safar 2005).

Stiffening of the aorta and large elastic arteries produce a progressive increase in aortic and left ventricular systolic pressure, and therefore, left ventricular load with aging (Merillon, Motte et al. 1982b; Nichols, O'Rourke et al. 1986; O'Rourke, Avolio et al. 1986;

Kelly, Tunin et al. 1992; Westerhof and O'Rourke 1995). Stiffening of the aorta and large elastic arteries results in a greater peak pressure at the time of peak flow as well as early return of wave reflections from peripheral sites to augment pressure in the ascending aorta during late systole (Nichols, Nicolini et al. 1992; Nichols and O'Rourke 2005).

In adolescent humans, wave reflection is beneficial in that the reflected wave returns to the ascending aorta in diastole, thereby augmenting diastolic pressure and increasing coronary blood flow to the left ventricle without increasing left ventricular afterload (Nichols, Nicolini et al. 1992; Nichols and O'Rourke 2005). As a result of the increase in arterial stiffness and pulse wave velocity with aging, there is early return of the reflected wave to the ascending aorta during ventricular ejection that augments systolic pressure and increases ventricular afterload (Nichols, Nicolini et al. 1992; Nichols and O'Rourke 2005).

Early return of the reflected wave to the ascending aorta during ventricular ejection is detrimental since the augmentation caused by the reflected wave increases systolic pressure and ventricular afterload, and also reduces diastolic pressure and myocardial perfusion (Kelly, Tunin et al. 1992; Nichols, Nicolini et al. 1992; Watanabe, Ohtsuka et al. 1993; Ohtsuka, Kakihana et al. 1994; Nichols and O'Rourke 2005). These changes predispose elderly subjects to left ventricular hypertrophy and myocardial ischaemia.

Left ventricular failure may result from systolic dysfunction or diastolic dysfunction (Levy, Larson et al. 1996; Hunt, Abraham et al. 2005). Left ventricular systolic dysfunction or failure occurs when there is a reduction in left ventricular ejection secondary to impaired myocardial contractility (Little 2001; NHF/CSANZ 2002; Bristow and Lowes 2005; Hunt, Abraham et al. 2005; Zile, Baicu et al. 2005). Left ventricular diastolic dysfunction or failure occurs when there is a reduction in left ventricular diastolic filling at normal

diastolic pressures, despite normal ventricular contraction (Zile and Brutsaert 2002). Left ventricular diastolic dysfunction may result from increased myocardial stiffness and/or impaired ventricular relaxation (Zile and Brutsaert 2002).

Stiffening of the aorta and large elastic arteries and isolated systolic hypertension is central to the pathogenesis of both diastolic and systolic dysfunction in the elderly. Hypertension is the most common condition antedating heart failure in the elderly (Levy, Larson et al. 1996). In the Framingham and Olmsted County studies, about half of the patients with heart failure had predominantly diastolic dysfunction (Senni, Tribouilloy et al. 1998; Vasan, Larson et al. 1999). Aortic stiffening and isolated systolic hypertension, increase left ventricular load to produce left ventricular hypertrophy and diastolic dysfunction (Girerd, Laurent et al. 1991; Levy, Larson et al. 1996; Vasan and Levy 1996; Hundley, Kitzman et al. 2001; Morita, Asou et al. 2002; Kawaguchi, Hay et al. 2003). Aortic stiffening and isolated systolic hypertension also accelerate coronary artery disease and precipitate myocardial ischaemia and infarction (therefore systolic dysfunction) by increasing cardiac load and myocardial oxygen demand, while decreasing coronary blood flow (Marcus, Harrison et al. 1987; Houghton, Carr et al. 1992; Kelly, Tunin et al. 1992; Watanabe, Ohtsuka et al. 1993; Ohtsuka, Kakihana et al. 1994; Kass, Saeki et al. 1996; Benetos, Safar et al. 1997; Franklin, Khan et al. 1999; Safar and Smulyan 2004).

The most effective treatment of heart failure is the reduction of mechanical load, either pharmacologically or mechanically (Westerhof and O'Rourke 1995; Katz 1998; Nichols and O'Rourke 2005). Angiotensin converting enzyme inhibitors, angiotensin receptor blockers, and beta-blockers are pharmacologic agents that reduce cardiac load (Chen, Ting et al. 1995; Bristow 2000; London, Asmar et al. 2004; Hirata, Vlachopoulos et al. 2005). These agents have been shown to improve survival, functional class, and left

ventricular geometry in heart failure patients (CONSENSUS 1987; Cohn, Johnson et al. 1991; SOLVD 1991; Konstam, Rousseau et al. 1992; SOLVD 1992; Konstam, Kronenberg et al. 1993; Packer, Bristow et al. 1996; Lang, Elkayam et al. 1997; CIBIS-II 1999; MERIT-HF 1999; Pitt, Poole-Wilson et al. 2000; Cohn, Tognoni et al. 2001; Packer, Coats et al. 2001; Wong, Staszewsky et al. 2002). Use of angiotensin converting enzyme inhibitors has also been shown to prevent the development of heart failure in patients at high risk of cardiovascular disease (Yusuf, Sleight et al. 2000; Arnold, Yusuf et al. 2003).

Mechanical reduction of cardiac load using intra-aortic balloon counter pulsation and ventricular assist devices has proven very effective as a treatment of heart failure (Creswell, Rosenbloom et al. 1992; Baskett, Ghali et al. 2002; Anastasiadis 2003; Cohn and Edmunds 2003; Dec 2004). However, intra-aortic balloon counter pulsation can only be used as a temporary treatment and long-term use is limited by potential thromboembolism and infection (Kantrowitz, Wasfie et al. 1986; Baskett, Ghali et al. 2002; Cohn and Edmunds 2003; Bojar 2005). Ventricular assist devices have been used effectively for the treatment of severe heart failure but are also limited by their high complication rate, as well as by their expense and limited availability to specialist heart failure and transplant centres (El-Banayosy, Korfer et al. 1999; El-Banayosy, Arusoglu et al. 2000; Farrar 2000; Deng, Loebe et al. 2001; Robbins, Kown et al. 2001; Rose, Gelijns et al. 2001; Dembitsky, Tector et al. 2004; Morgan, John et al. 2004).

Conventional cardiothoracic surgical procedures such as coronary artery bypass surgery and mitral valve reconstruction are also useful for the treatment of heart failure and have been shown to improve survival, functional class and left ventricular geometry (Coles, Del Campo et al. 1981; ECSS 1982; CASS 1983; Elefteriades, Tolis et al. 1993; Elefteriades, Morales et al. 1997; Bolling, Pagani et al. 1998; Chen, Adams et al. 1998;

Bishay, McCarthy et al. 2000; Topkara, Cheema et al. 2005). Heart transplantation provides excellent results for the treatment of patients with severe heart failure; however its effectiveness is limited in that it can only be used for a minority of patients with heart failure (AHA 2005). The severe shortage of donor hearts means that heart transplantation is not available to patients over the age of 65 and is reserved for use in younger patients (Steinman, Becker et al. 2001). There is a great disparity between the number of heart transplants performed annually and the number of patients that would benefit from this procedure (AHA 2005).

Pharmacologic and surgical treatments of heart failure have been effective in reducing mortality in patients with heart failure (Levy, Kenchaiah et al. 2002; Roger, Weston et al. 2004). In the Framingham study, 1-year and 5-year mortality declined from 30% to 28%, and 70% to 59%, respectively in males (Levy, Kenchaiah et al. 2002). In the Olmsted County study, 1-year mortality and 5-year mortality declined from 30% to 21%, and 65% to 50%, respectively in males (Roger, Weston et al. 2004). Despite the improvement in survival produced by these treatments, the prognosis for patients with heart failure remains poor (Levy, Kenchaiah et al. 2002; Roger, Weston et al. 2004).

The increasing incidence and prevalence of heart failure, as well as increasing number of hospitalizations and deaths resulting from heart failure have made heart failure a major health issue in Western industrialised nations (Braunwald 1997; NHF/CSANZ 2002; AIHW 2004; AHA 2005). The economic burden of treating heart failure patients in the United States alone has been estimated at 30 billion dollars annually (AHA 2005). There is an impetus to develop new pharmacologic agents, and surgical procedures and devices for the treatment of heart failure. At present there is no effective treatment for the fundamental cause of heart failure in the elderly- aortic dilatation and stiffness.

This thesis describes the proof of concept for a surgical treatment of stiffening and dilation of the ascending aorta with age- the **Aortic Wrap Procedure**. An elastic material is wrapped around the ascending aorta of elderly patients, to reduce the stiffness of the ascending aorta towards that seen in youth. The procedure exploits the dilatation of the aorta seen in aging with the elastic material reducing the diameter of the aorta to take the load of pulsatile pressure and flow.

A reduction in the stiffness of the ascending aorta is expected to ameliorate the adverse effects of aortic stiffening on cardiovascular function in the elderly and treat heart failure as well as isolated systolic hypertension. Positive effects of a reduction in the stiffness of the ascending aorta are expected to include: a reduction in systolic pressure and pulse pressure; an increase in diastolic pressure (and coronary blood flow); and an improvement in ascending aortic impedance; ventricular load; and ventricular-vascular interaction (Nichols, O'Rourke et al. 1985; Nichols, O'Rourke et al. 1986; O'Rourke, Avolio et al. 1986; Kelly, Tunin et al. 1992; Watanabe, Ohtsuka et al. 1993; Ohtsuka, Kakihana et al. 1994; Westerhof and O'Rourke 1995; Franklin, Gustin et al. 1997; Hundley, Kitzman et al. 2001; Morita, Asou et al. 2002; O'Rourke and Nichols 2005). A reduction in ascending aortic stiffness and pulse pressure is also expected to arrest (or improve) microvascular disease of the kidney and brain (O'Rourke and Safar 2005).

This thesis encompasses the diverse fields of cardiovascular medicine and surgery, cardiovascular physiology, biomechanical engineering, and biomaterials science. The literature review broadly touches on all these subjects, but is by necessity limited, and an in-depth review of these subjects is beyond the scope of this thesis.

Proof of concept of the aortic wrap procedure is provided using an ovine model of the aorta and aortic stiffening, an in-vitro model of the aged human aorta, and a

mathematical model of the cardiovascular system. The study also involved investigation of the uniaxial tensile properties of the wrap materials and the ovine descending aorta, and the alterations in these properties with two month implantation of the elastic material in an ovine model.

Two elastic silicon polymers were used as the wrap material. The materials were developed by Medtronic (Medtronic, Inc., Minneapolis, MN) for use as a simulator of the aorta (4% stiffness material) and pulmonary artery (12% stiffness material) in the in-vitro testing of artificial aortic and pulmonary valves. The materials come in prefabricated cylindrical lengths and simulate the stiffness of the healthy young human aorta and pulmonary artery.

The 4% material shows a 4% increase in diameter with each pulsation when exposed to physiologic pressure and flow in an in-vitro circuit, and so simulates the stiffness of the young human aorta. Similarly, the 12% material simulates the stiffness of the human pulmonary artery. Silicon polymers are immunologically inert, durable, and securable (Park and Lakes 1992; Wynne and Lambert 2004). The cylindrical lengths were cut longitudinally for placement around the aorta, and secured using a clamp.

In chapter 3, the effect of application of the elastic wrap on the stiffness of the ovine descending thoracic aorta is described. Application of an elastic wrap to the ovine descending thoracic aorta increased the stiffness of the aorta but did not abolish pulsation. The increase in stiffness is not as great as the increase in stiffness that has been reported in the literature following application of a non-elastic wrap (e.g. Dacron) to the thoracic aorta in experimental animals (Tropea, Schwarzacher et al. 2000). In this study, the stiffness of the wrapped aorta was dependent on the stiffness of the elastic wrap, suggesting that the

stiffness of the elastic wrap plays a major role in determining the stiffness of the wrapped vessel.

In chapter 4, an ovine model of aortic dilatation and stiffness is described and the effect of application of an elastic wrap on vascular stiffness is investigated. An oversized inelastic Dacron graft was anastomosed as an interposition graft in the ovine descending thoracic aorta to provide an animal model of aortic dilatation and stiffness. Application of an elastic wrap onto the Dacron graft that reduced the diameter of the graft reduced the stiffness of the graft. These findings suggest that application of an elastic wrap onto a stiffened vessel or conduit will unload the vascular or conduit wall and take up the load of pulsatile pressure and flow.

In chapter 5 an in-vitro pressure model of the aged human ascending aorta is described and the effect of application of the elastic wrap on aortic stiffness and pressure is investigated. Human ascending aorta from elderly subjects was attached to a pressure circuit and subjected to pulsatile pressure to provide an in-vitro pressure model of the aged human ascending aorta. Application of an elastic wrap to the human ascending aorta in-vitro reduced its stiffness and decreased maximum and pulse pressure, and increased minimum pressure. The greatest reduction in stiffness and alteration in pressure was seen with the 4% material applied at 70% of the original aortic diameter. The human thoracic aorta dilates by 40% or more between ages 20 and 80 years, and the 4% wrap simulates the properties of the human ascending aorta in young subjects (Nichols, O'Rourke et al. 1985; Pearson, Guo et al. 1994; Hager, Kaemmerer et al. 2002). The most optimal result is therefore seen when a material that simulates the stiffness of the young ascending aorta is applied to reduce diameter towards that seen in youth i.e. when there is restoration of aortic elasticity and diameter.

In chapter 6, the effect of reducing ascending aortic stiffness on ascending aortic pulse pressure is investigated using a multi-branched model of the human arterial system. The computer model showed that a reduction in ascending aortic stiffness is expected to produce reduction in ascending aortic pulse pressure. Application of a 4% material to reduce aortic diameter to 70% of the original aortic diameter is predicted to reduce pulse pressure by 23%. Wrapping the ascending aorta alone is therefore sufficient to reduce ascending aortic pressure by levels that are expected to produce significant improvement in ventricular-vascular interaction and clinical outcome (London, Asmar et al. 2004; Hirata, Vlachopoulos et al. 2005).

In chapter 7, uniaxial tensile testing of the ovine descending thoracic aorta and the elastic wraps is described. In chapter 8, the alterations in the uniaxial tensile properties of the ovine descending aorta and the 4% elastic wrap material with chronic implantation in an ovine model are described. There were no alterations in the uniaxial tensile properties of the 4% elastic wrap material with chronic implantation.

In summary, the elastic wrap reduced the stiffness of the aged human aorta in the in-vitro model as well as the stiffness of a non-elastic vascular graft in the animal model. The reduction in ascending aortic stiffness reduced systolic pressure and pulse pressure, and increased diastolic pressure in the in-vitro and computer models.

Application of an elastic wrap to a stiffened and dilated vessel, that reduces the diameter of the vessel, is expected to reduce the stiffness of the vessel. The elastic wrap may act by unloading the native vessel wall and taking the load of pulsatile pressure and flow. Application of the elastic wrap to the aged human ascending aorta (that is stiffened and dilated), is expected to reduce systolic and pulse pressure, and increase diastolic pressure, with a reduction in cardiac load and improvement in coronary perfusion.

Application of an elastic wrap to the ascending aorta in elderly human subjects may be an effective surgical treatment of aortic dilatation and stiffness and its detrimental sequelae such as isolated systolic hypertension, left ventricular hypertrophy, and ultimately heart failure.

Possible clinical indications may include the treatment of heart failure (by reduction of mechanical load and improved coronary blood flow) and isolated systolic hypertension. The procedure may be a useful adjunct to the medical and surgical treatment of myocardial ischaemia (by reduction of ventricular load, regression of myocardial hypertrophy, and improved coronary blood flow). Elastic wrap application to the thinned and dilated ascending aorta may be useful for the prevention of aortic rupture (reduction aortoplasty), and for the treatment of microvascular disease of the brain and kidney.

CHAPTER 2: LITERATURE REVIEW AND AIM

2.1 OVERVIEW OF THE CARDIOVASCULAR SYSTEM

2.1.1 The Cardiovascular system

The cardiovascular system consists of a central pump (the heart) and a vast array of tubes (the blood vessels) that carry blood to and from the organs and tissues of the body. The cardiovascular system is divided into the systemic circulation and the pulmonary circulation; two separate loops that are connected in series and centred on the heart (Netter 1969; Gabella 1995). The heart consists of two muscular pumps; the right side propels blood into the pulmonary circulation, and the left side propels blood into the systemic circulation (Netter 1969; Gabella 1995).

2.1.2 Systemic circulation

Blood flow into the aorta, the trunk of the arterial tree, is pulsatile and under high pressure due to the rhythmic contraction of the left ventricle. The aorta and large elastic arteries transform the pulsatile output of the left ventricle to the smoother pattern seen in the peripheral circulation (Berne and Levy 1977; Milnor 1989; Boudoulas and Wooley 1996; Nichols and O'Rourke 1998). During ventricular contraction there is distension of the aorta and large elastic arteries. During ventricular relaxation the elastic recoil of the aorta and large arteries maintains blood flow to the organs and tissues of the body.

Major arteries branch from the aorta and divide further to form arteries that carry oxygenated blood to the organs and tissues of the body (Gray 1858; Milnor 1989; Schmid-Schoenbein and Ross 1991; Nichols and O'Rourke 1998). Arterioles are the smallest

branches of the arteries. They are small thick walled muscular vessels that regulate blood flow through the organs and tissues of the body. The blood vessels eventually divide to form tiny, thin-walled capillaries through which exchange of materials occurs by diffusion and ultrafiltration. Venules collect deoxygenated blood from the capillaries and combine to form progressively larger veins that transport blood to the right side of the heart.

2.1.3 Volumes of blood in different parts of the circulation

The total volume of blood contained in a normal human subject is about 7% of total body weight (5 litres in a 75kg man) (Schmid-Schoenbein and Ross 1991). The greatest proportion of blood in the circulation is contained in the systemic veins (Table 1) (Milnor 1989),which serve a secondary function as a blood volume reservoir for the body.

	Blood Volume ml	%
Heart (diastole)	282	5.0
Pulmonary Circulation		
Arteries	119	2.1
Capillaries	142	2.5
Veins	197	3.5
	458	8.1
Systemic circulation		
Arteries	640	11.4
Capillaries	300	5.4
Veins	3920	70.0
	4860	86.8
TOTAL	5600	100

Table 1 Estimated distribution of blood volume in a human adult male (Milnor 1989)

2.1.4 Distribution of Cardiac Output

The systemic circulation consists of numerous circuits arranged in parallel that supply the organs and tissues of the body (Milnor 1989; Gabella 1995; Nichols and O'Rourke 1998).

	Blood Flow ml/min	% total
Upper Body		
Brain and Heart	1000	
Muscle and skin	500	
	1500	26
Trunk		
Liver, intestines, spleen	1400	
Kidneys	1100	
Muscle and skin	300	
	2800	48
Terminal aorta		
Pelvic organs and legs	1500	26
TOTAL	5800	100

Table 2 Distribution of blood flow in humans at rest (Nichols and O'Rourke 1998)

2.1.5 Cross-sectional areas, velocities of blood flow, and intravascular pressures of the systemic circulation

At any point in the circulatory system, the mean linear velocity of blood flow equals the total volume flow divided by the cross sectional area (CSA) of the segment of the circulation (Schmid-Schoenbein and Ross 1991).

Equation 1 Velocity (cm/s) = Volume flow (cm^3/s) / CSA (cm^2)

The aorta has the smallest cross sectional area of the systemic circulation (about $6cm^2$) and therefore has the highest mean flow (approximately 18 cm/s) (Milnor 1989; Hager, Kaemmerer et al. 2002). As the arteries progressively divide into smaller vessels,

the cross sectional area increases, and flow velocity falls (Milnor 1989; Schmid-Schoenbein and Ross 1991; Nichols and O'Rourke 1998).

There is a progressive fall in intravascular pressure in the systemic circulation from high arterial levels to low venous values with the greatest pressure fall occurring at the level of the arterioles (Milnor 1989; Schmid-Schoenbein and Ross 1991; Nichols and O'Rourke 1998).

2.1.6 The normal haemodynamic state

Cardiac output may be defined as the volume of outflow from the ventricle per unit time and has been measured in a large group of human subjects 16-60 years of age at 6.5L/min per minute with a standard deviation of 1.44L/min (Milnor 1989). The right and left ventricular outputs are equal except for small beat-to-beat variations.

The stroke volume may be defined as the volume of blood ejected by the ventricle with each beat and is the difference between end-diastolic volume and end-systolic volume (Milnor 1989; Little 2001). The ejection fraction (EF) is the ratio between stroke volume (SV) and end-diastolic volume (EDV) (Milnor 1989; Little 2001).

The ventricle only ejects a part of the end-diastolic volume with each contraction, and the average ejection fraction in humans at rest is 0.67 +/- 0.8 (Little 2001).The normal range of stroke volumes in humans at rest is 68-100 ml (Milnor 1989). Resting heart rate averages 72 beats per minute, with a normal range of 60 to 86 beats per minute (Milnor 1989).

2.1.7 The cardiac cycle

The sequence of events in each cardiac cycle produces the characteristic pulsatile pressure and flow transmitted to the circulation. Wiggers' diagram describes the sequence of events in the cardiac cycle (Wiggers 1915; Lewis 1920).

Each cardiac cycle is initiated by spread of the wave of depolarisation through the heart muscle and is followed by the mechanical events of atrial and ventricular contraction (Opie 1998; Katz 2001; Opie 2001). The three basic events in the cardiac cycle are left ventricular contraction, left ventricular relaxation, and left ventricular filling.

During ventricular ejection, the rate of ejection is determined not only by the pressure gradient across the aortic valve but also by the elastic properties of the aorta and large arteries (Milnor 1989; Nichols and O'Rourke 1998; Opie 1998; Opie 2001). The aorta and large elastic arteries expand during ventricular ejection. During left ventricular relaxation, although the left ventricular pressure is decreasing, blood flow through the arterial tree is maintained by elastic recoil of the aorta and large elastic arteries (Milnor 1989; Nichols and O'Rourke 1998; Opie 1998; Opie 2001).

2.2 ANATOMY OF THE HEART AND ARTERIAL SYSTEM

2.2.1 Anatomy of the heart

The heart is a four-chambered organ composed of specialised muscle cells (myocardial cells) (Netter 1969). The heart consists of two separate pumps (the right and left side), with each side consisting of an atrium and a ventricle (Gray 1858; Netter 1969; Gabella 1995).The heart is enclosed in the pericardium with the great vessels and occupies the middle mediastinum between the lungs.

The ventricles are the main pumps of the heart. The right ventricle ejects blood into the pulmonary artery (pulmonary circulation), and the left ventricle ejects blood into the ascending aorta (systemic circulation) (Netter 1969; Gabella 1995). Each ventricle is supplied by an atrium. The right and left atria receive blood from the systemic veins and pulmonary veins, respectively, and act as booster pumps for final filling of the ventricles (Gabella 1995).

The walls of the chambers are composed of cardiac muscle (myocardium). The walls of the atria are thin (approximately 2mm in the normal human heart) reflecting the low pressure that they generate (Netter 1969; Ross 1991a). The ventricles generate higher pressures and have thicker walls (3-4mm thick in the right ventricle, and 8-9mm thick in the left ventricle in the normal human heart) (Netter 1969; Ross 1991a).

The atrioventricular valves (tricuspid valve and mitral valve) separate the atria and ventricles and prevent backward leakage of the blood from the ventricle to the atria (Netter 1969; Ross 1991a; Gabella 1995). The semilunar valves (pulmonary valve and aortic valve) separate the ventricles and the great vessels into which they eject blood (Netter 1969; Ross 1991a; Gabella 1995). The two sets of valves function out of sequence in the cardiac cycle to maintain the forward flow of blood (Netter 1969).

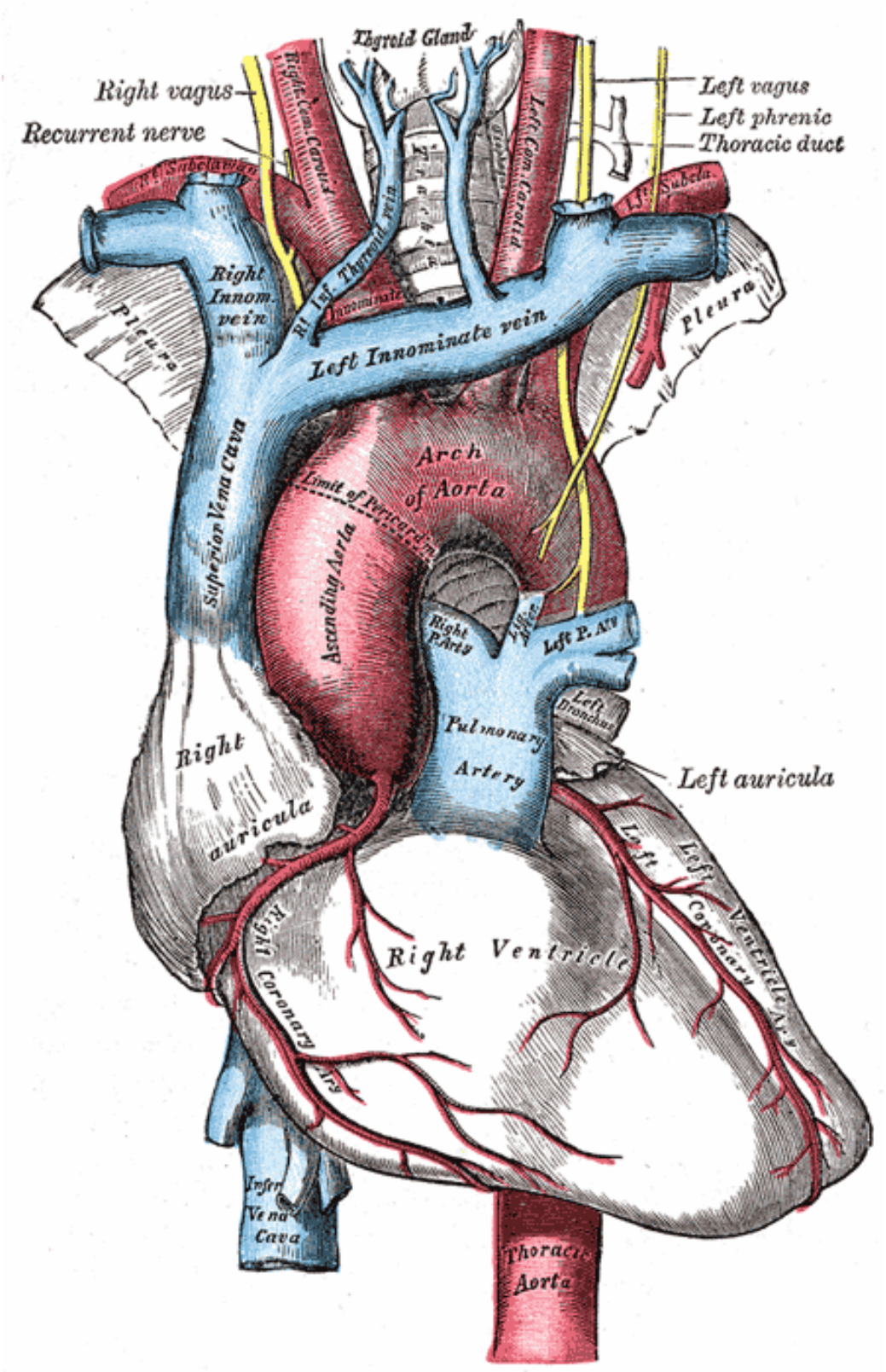


Figure 1 Anatomy of the heart and thoracic aorta (Gray 1918)

2.2.2 Coronary arteries

The blood supply to the ventricular myocardium is via the coronary arteries. The right and left coronary arteries are the first branches of the aorta and arise from the aortic sinuses of Valsalva, just above the aortic valve leaflets (Netter 1969; Gabella 1995; Baue, Geha et al. 1996). The branches of the coronary arteries penetrate the ventricular myocardium to supply the subendocardial myocardium. In the subendocardial regions of the left ventricle, the intramyocardial pressure during ventricular systole exceeds the coronary blood pressure, and coronary flow occurs predominantly in diastole (Berne and Levy 1977). The subendocardial regions of the left ventricle are particularly susceptible to impaired coronary blood flow (Buckberg, Fixler et al. 1972; Buckberg, Towers et al. 1972).

The major determinants of coronary blood flow are the calibre of the epicardial coronary arteries, the duration of diastole, and the coronary perfusion pressure (Ferro, Duilio et al. 1995; Nichols and O'Rourke 1998; Ganz and Ganz 2001). Myocardial ischaemia occurs when there is insufficient blood supply to the myocardium and is usually due to atherosclerotic narrowing of the epicardial coronary arteries (coronary artery disease) (Ganz and Ganz 2001). Disease states such as arterial stiffening , and the consequent isolated systolic hypertension and left ventricular hypertrophy, that alter the length of diastole and reduce the coronary perfusion pressure, are also important in the induction of myocardial ischaemia (Watanabe, Ohtsuka et al. 1993; Ohtsuka, Kakihana et al. 1994; Kass, Saeki et al. 1996).

2.2.3 Anatomy of the arterial tree

The arteries are tubular structures that carry blood to the organs and tissues of the body, and were named arteries (to carry blood) from the belief that they contained air (Gray

1858). The distribution of the systemic arteries is like a highly ramified tree arising from a common trunk, the ascending aorta. The ascending aorta has an outer diameter of about 27mm (cross sectional area of about $6cm^2$) in a normal young adult male. The aorta successively branches to form hundreds of arteries of progressively smaller calibre that branch further to form about 4×10^6 arterioles (Gabella 1995).

Milnor has described a model of the vascular dimensions of the canine circulation. In a 20kg dog, the aorta has a mean diameter of 4.5 - 19mm and a total cross-sectional area of 0.2 - $2.8cm^2$. Diameter decreases along the arterial tree to reach 0.050mm in arterioles (sectional area of approximately $50cm^2$). The capillaries have a mean diameter of 0.008mm and a total cross-sectional area of $1350cm^2$ (Milnor 1989).

2.2.4 Aortic and major arterial dimensions

The aorta tapers from its origin at the left ventricle to its bifurcation into the common iliac arteries at L4 (Langewouters 1982; Latham, Westerhof et al. 1985; Latham, Rubal et al. 1987). Despite tapering of the aorta, the total cross-sectional area of the aorta and its branches added together shows little change. Beyond the major arterial branches, the total cross sectional area increases progressively to the capillaries (Milnor 1989; Nichols and O'Rourke 1998).

The cross sectional area (A) change in the dog aorta can be expressed by the following equation (Caro, Pedley et al. 1978):

Equation 2 $A = A_0 e^{-(kx / r0)}$

Where, A_0 and r_0 = area and radius at the upstream site

x = distance from the upstream site

k = taper factor (0.02 - 0.05)

2.2.5 Branching patterns

There is a large variation in the mode of division of arteries. The most common method is bifurcation or dichotomy into two terminal branches of roughly equal size (Gray 1858; Milnor 1989; Gabella 1995). Less commonly an artery divides into several branches at one point (e.g. coeliac artery), or the artery may give several branches in succession and continue as the main trunk (e.g. limb arteries) (Gray 1858; Milnor 1989; Gabella 1995).

2.3 ARTERIAL HAEMODYNAMICS

2.3.1 Laminar and Turbulent Flow

Osbourne Reynolds (1883) first described the factors determining the transition from turbulent to laminar flow (Milnor 1989; Nichols and O'Rourke 1998). The Reynolds number (Re) is a dimensionless term that expresses the tendency to become turbulent (Milnor 1989). The equation for the Reynolds number, when applied to steady flow in a cylinder is:

Equation 3 $N_R = 2r\bar{v}/v$ (Milnor 1989)

Where, $\bar{v}$ = mean velocity of flow

r = tube radius

v = kinematic viscosity = η/ρ (η is the viscosity and ρ is the density of the liquid)

In steady flow, transition to turbulence occurs at Reynolds numbers above approximately 2300.

Flow in the major systemic arteries is highly pulsatile, and peak ascending aortic flow is up to 6 times as high as mean flow (Milnor 1989).

Flow in the arterial circulation is predominantly laminar although turbulence has been demonstrated in the ascending (and descending aorta) in a number of species and in some humans (Seed and Wood 1971; Nerem and Seed 1972; Nerem, Rumberger et al. 1974; Stein and Sabbah 1976). In pulsatile flow, the transition from laminar to turbulent flow in the aorta depends on the non dimensional Womersley parameter (α) as well as the Reynolds number (Nerem and Seed 1972).

Equation 4 $\alpha = r. (\omega/v)^{1/2}$ (Milnor 1989)

Where, ω = frequency

r = radius

v = kinematic viscosity

At a constant N_R, α is a function of frequency (or heart rate), and heart rate variations are an important factor in determining the stability of arterial laminar flow (Nerem and Seed 1972; Milnor 1989; Nichols and O'Rourke 1998).

2.3.2 Pressures in the Systemic Circulation

The contour of the ascending aortic pressure wave shows different patterns in humans with aging as well as in different experimental animals. In dogs, sheep, and human adolescents, the pressure wave has a rounded systolic peak with a secondary diastolic wave after the incisura, whereas in elderly humans, aortic pressure rises to a late systolic peak and falls rapidly after the incisura without a secondary diastolic wave (Nichols and O'Rourke 1998). An intermediate pattern is seen in normal adult humans (Latham, Westerhof et al. 1985; Nichols and O'Rourke 1998).

The contour of the systemic arterial pressure is influenced by the pulse wave velocity and wave reflections (Nichols and O'Rourke 1998). Pressure waves reflected from

the periphery augment the incident pressure so that the pulse pressure increases as it travels peripherally. The contour of the pressure wave is altered as it moves peripherally so that the early portion rises steeply and the secondary diastolic portion becomes more prominent (Milnor 1989; Nichols and O'Rourke 1998). The incisura in the ascending aortic pressure wave becomes less prominent and disappears by the descending aorta (Milnor 1989; Nichols and O'Rourke 1998).

The pressure wave increases in amplitude as it travels distally to the peripheral vessels primarily as a result of wave reflection. Pressure wave transmission characteristics may be described as a transmission ratio of the distal and proximal pulse pressures. The transmission ratio from the ascending aorta to the iliac arteries is about 2.0 in the dog (McDonald 1974). In humans, the transmission ratio from the ascending aorta to the femoral arteries is 1.5 in children. Amplification of the pressure wave is small in children because of small body length and is greatest with full growth (i.e. in adolescence) (Nichols and O'Rourke 1998). There is a progressive loss of amplification with aging in humans and the transmission ratio progressively decreases to just above 1.0 in the elderly (O'Rourke, Blazek et al. 1968; Nichols and O'Rourke 1998).

With aging in humans there is an increase in the velocity of the pressure wave (pulse wave velocity) (Avolio, Chen et al. 1983). The increase in pulse wave velocity with age is responsible for the change in arterial pressure wave contour and pressure wave transmission with aging in humans (O'Rourke and Yaginuma 1984a; Nichols, O'Rourke et al. 1985; Kelly, Hayward et al. 1989; Nichols, Nicolini et al. 1992).

2.3.3 Wave Propagation

The relationship between the velocity of propagation of a pulse wave and the elastic properties of a blood vessel has long been known (Young 1808) (cited in Milnor 1989), and is best expressed by the Moens-Korteweg equation derived independently by Moens (1878) and Korteweg (1878) (Milnor 1989).

Equation 5 $C_o = [(Eh/2\rho R_i)]^{1/2}$

Where, c_o = pulse wave velocity

E = Young's' modulus of elasticity

h = wall thickness

R_i = inner vessel radius

ρ = fluid density

The commonest method used to measure pulse wave velocity is to measure the transit time of the foot of the pressure wave over a known distance (McDonald 1968). The foot is defined as the beginning of the steep rise of the pressure wave at the end of diastole. Pulse wave velocity may also be obtained from travel of the flow wave.

Pressure has been measured invasively (O'Rourke, Blazek et al. 1968; Latham, Westerhof et al. 1985) or non-invasively (Levenson, Sang et al. 1987), and blood flow velocity has been measured non-invasively (Avolio, Chen et al. 1983; Avolio, Deng et al. 1985), in studies of pulse wave velocity.

The elastic modulus (stiffness) of arteries increases non-linearly with increasing stress (pressure) (Roy 1880; Bergel 1961a), and therefore, pulse wave velocity increases with increasing arterial pressure (Nichols and McDonald 1972). Elastic modulus increases in arteries as a function of distance from the ascending aorta (Learoyd and Taylor 1966).

There is a progressive increase in pulse wave velocity with increasing distance from the ascending aorta (Nichols and McDonald 1972; Latham, Westerhof et al. 1985; Latham, Rubal et al. 1987).

The pulse wave velocities in systemic arteries in dogs and young humans are given in Table 3.

Artery	Species	Wave velocity (cm/s)
Ascending aorta	Man	440-520
	Dog	350-472
Thoracic aorta	Man	400-650
	Dog	400-700
Abdominal aorta	Man	500-620
	Dog	550-960
Iliac	Man	700-880
	Dog	700-800
Femoral	Man	800-1800
	Dog	800-1300
Popliteal	Dog	1220-1310
Tibial	Dog	1040-1430
Carotid	Man	680-830
	Dog	610-1240

Table 3 Pressure wave velocities in systemic arteries. All data are from relatively young subjects with normal cardiovascular systems, at approximately normal distending pressures (Milnor 1989)

2.3.4 Wave Reflection

Reflections of a travelling wave (pressure or flow) are generated in the arterial system wherever there is a mismatch in impedance (see section 2.3.5). Wave reflection occurs at arterial branches (Taylor 1966; McDonald 1974), along major branches due to elastic tapering (McDonald 1974), and at the arteriolar bed (Westerhof, Sipkema et al. 1972; O'Rourke 1982).

Wave reflection is responsible for the amplification and modification of the pressure wave as it is propagated peripherally (Noordergraf 1978; Nichols and O'Rourke 1998; Li 2000).

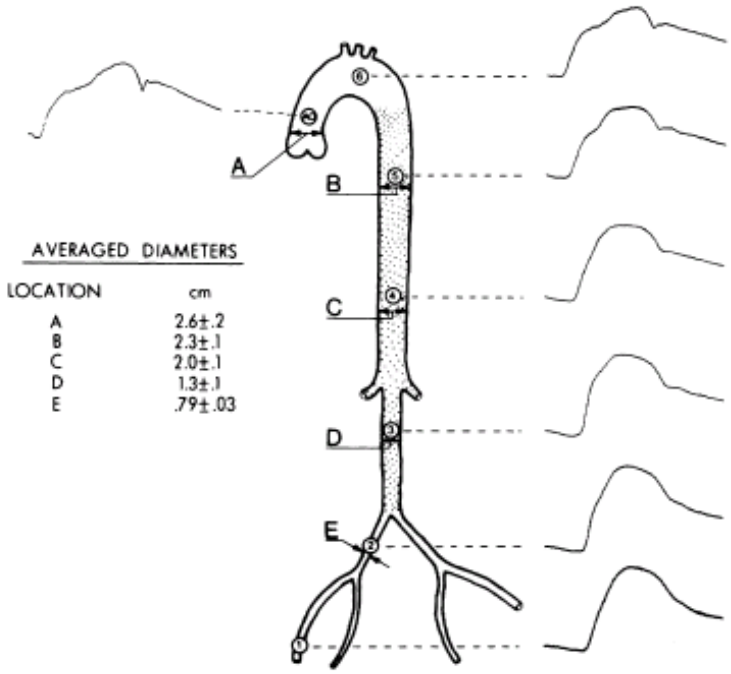


Figure 2 Amplification and modification of the pressure wave as it is propagated peripherally (Latham, Westerhof et al. 1985).

2.3.5 Impedance

The relationship between pulsatile pressure and flow is a function of the physical properties of the blood and the blood vessels, namely, the vessel diameter, the thickness and viscoelasticity of the wall, and the kinematic viscosity of the blood (Milnor 1989; Nichols and O'Rourke 1998).

Vascular impedance quantitatively expresses the relationship between pulsatile pressure and flow and is a measure of the opposition to pulsatile flow presented by a system. Vascular impedances are always ratios of pressure to flow although a number of

types have been described including longitudinal impedance, input impedance, and characteristic impedance (McDonald 1974; Milnor 1989; Nichols and O'Rourke 1998; Li 2000).

Impedance is a frequency dependant quantity and its measurement needs to be performed using frequency analysis techniques (i.e. Fourier analysis). Impedance values are expressed in terms of modulus (amplitude of pressure divided by amplitude of flow) and phase (phase delay between pressure and flow peaks) over a range of frequencies (spectra) obtained by Fourier analysis (McDonald 1974; Milnor 1989; Nichols and O'Rourke 1998; Li 2000).

2.3.6 Fourier analysis

The most common and effective way of converting arterial pressure and flow waves to numerical form involves Fourier analysis. Fourier analysis can be applied to any periodic form of a linear signal. The signal is decomposed into a series of sinusoidal waveforms whose frequencies represent a multiple of the fundamental signal frequency (McDonald 1974; Patel and Vaishnav 1980; Milnor 1989; Nichols and O'Rourke 1998).

Fourier's theorem expresses the general form of a periodic function, f (t), as:

Equation 6

$$f(t) = A_0/2 + \sum_{n=1}^{\infty} (A_n \cos n\omega t + B_n \sin n\omega t)$$

Where, $A_0/2$ = mean value of the function

A_n, B_n = modulus of the component cosine and sine waves at the harmonic

n = any integer

ω = angular frequency = $2\pi f$ (where f is the frequency in Hertz)

t = time

The mean value of the function is $A_0/2$, and for each value of n, the corresponding cosine-sine pair defines a sinusoidal wave of frequency nω, the nth harmonic. Each harmonic is a complex number equivalent to:

Equation 7 $M \cos (n\omega t - \Phi)$

Where, M = amplitude = $(A^2 + B^2)^{1/2}$

Φ = phase angle = arc tan (B/A)

Most information can be obtained from haemodynamic signals with analysis of the first ten harmonics, and reconstruction of pressure and flow waveforms can be reliably constructed from 10 harmonics (McDonald 1974; Patel and Vaishnav 1980; Nichols and O'Rourke 1998).

2.3.7 Longitudinal impedance (Z_L)

Longitudinal impedance is the ratio of the pressure gradient to flow. It is dependant on the physical properties of the vessel and the blood it contains, and is not influenced by the properties of the vascular bed downstream (Milnor 1989; Nichols and O'Rourke 1998; Li 2000).

Equation 8 $Z_L = (P_1 - P_2)/Q$

2.3.8 Input impedance (Z_i)

Input impedance is the ratio of pulsatile pressure and flow in an artery that feeds a vascular bed. The input impedance depends on the physical properties of the vascular tree downstream as well as the physical properties of the artery and the blood contained within it (Milnor 1989; Nichols and O'Rourke 1998; Li 2000).

Using complex number notation, the relations for the pressure (P) and flow (Q) waveforms expressed as modulus and phase are, for the nth harmonic:

Equation 9 $P_n = |P_n| e^{i(\omega t - \phi_n)}$

Where, i = the complex operator = $(-1)^{1/2}$

Equation 10 $Q_n = |Q_n| e^{i(\omega t - \beta_n)}$

The input impedance, for the nth harmonic is:

Equation 11 $Z_i = P/Q = (|P_n| e^{i(\omega t - \phi_n)}) / (|Q_n| e^{i(\omega t - \beta_n)})$

$= (|P_n| e^{i(\beta_n - \phi_n)}) / (|Q_n|)$

The real part of the equation is:

Equation 12 $Z_n = (|P_n| / |Q_n|) \cos(\beta_n - \phi_n)$

Where $|Z_n| = |P_n| / |Q_n|$ is the modulus and $\theta_n = (\beta_n - \phi_n)$ is the phase angle of the impedance.

Arterial input impedance characterises the properties of the arterial bed downstream and determines the amplitude and contour of the pressure wave generated by the flow wave into the bed. Both input impedance and longitudinal impedance can be determined from experimental data (Milnor 1989; Nichols and O'Rourke 1998; Li 2000).

2.3.9 Characteristic impedance

The characteristic impedance is the ratio of pulsatile pressure to flow in the absence of wave reflection i.e. assuming an infinitely long tube or perfect impedance matching. The presence of wave reflection in the arterial system makes the measurement of characteristic impedance difficult (Milnor 1989; Nichols and O'Rourke 1998). Characteristic impedance may be estimated by averaging the impedance moduli at high frequencies, where modulus

is uninfluenced by wave reflection (Bergel and Milnor 1965; O'Rourke and Taylor 1967a; O'Rourke 1970).

2.3.10 Ascending aortic impedance

The input impedance in the ascending aorta represents the input impedance of the arterial system and characterises the physical properties of the systemic arterial system (O'Rourke and Taylor 1967a; Noble 1979; Nichols, Pepine et al. 1980; Elzinga and Westerhof 1991). The input impedance in the ascending aorta also represents the hydraulic load presented to the left ventricle by the arterial system (afterload) (Milnor 1975; Nichols, Pepine et al. 1980; Milnor 1989; Nichols and O'Rourke 1998).

The modulus of ascending aortic impedance falls rapidly from a high value at zero frequency (the peripheral resistance) to a low value at higher frequencies (the characteristic impedance) (Patel, Defreitas et al. 1963; O'Rourke and Taylor 1967a). The high distensibility of the ascending aorta is responsible for its low characteristic impedance (Nichols and O'Rourke 1998).

The minimal values of impedance modulus occur early over a band of frequencies (2.0 to 8.0Hz in the dog) and fall below the characteristic impedance (O'Rourke and Taylor 1967a). The early minimal values of impedance modulus are the result of wave reflection from the periphery.

In young humans and experimental animals (such as dogs, sheep, and rabbits) there is efficient transfer of blood from the ventricle into the arterial system (O'Rourke, Kelly et al. 1992). In the ascending aorta, the highest values of the flow wave harmonics correspond to the lowest values of impedance modulus (Avolio, O'Rourke et al. 1976; Murgo, Westerhof et al. 1980; O'Rourke 1982; O'Rourke, Yaginuma et al. 1984b).

The input impedance in the ascending aorta is suggestive of two functionally discrete reflecting sites in the body; one relatively close in the upper body, and one further away in the lower body (O'Rourke and Taylor 1967a).

2.4 CARDIAC MECHANICS

2.4.1 Mechanical performance of isolated cardiac muscle

The mechanical performance of the left ventricle is affected by the loads imposed upon. Changes in loading conditions affect the left ventricle in they same way that they affected an isolated piece of cardiac muscle. The factors affecting the mechanical performance of isolated cardiac muscle include the preload and afterload, and the contractility (inotropic state) (Braunwald and Ross 1976; Fung 1981; Ross 1991b)

2.4.2 Preload

Studies of isolated cardiac muscle stimulated to contract isometrically show that as the resting muscle length is increased (increased preload) the peak tension developed during contraction is increased. The time to peak tension is unchanged, and the speed of tension development is increased (Braunwald and Ross 1976; Ross 1991b).

2.4.3 Afterload

Studies of isolated cardiac muscle stimulated to contract isotonically to obtain force-velocity relationships show that the velocity and extent of shortening declines as the afterload is increased (Braunwald and Ross 1976; Ross 1991b). The relationship between work (afterload times extent of shortening) and load, and between power (rate of work

performance) and load is bell-shaped. The work and power of isolated cardiac muscle is therefore highly dependent on afterload (Braunwald and Ross 1976; Ross 1991b).

2.4.4 Contractility

The contractility or inotropic state of the cardiac muscle relates to the strength of contraction and is dependant on the intracellular availability of calcium and the number of active bonds between contractile myofilaments at the level of the sarcomere. A change in contractility produces a change in the performance of isolated cardiac muscle independent of alterations in loading conditions (Braunwald and Ross 1976; Ross 1991b).

Positive inotropic stimuli (e.g. noradrenaline) produce an increased peak tension, increased velocity of tension development, and shortened duration of contraction in isolated cardiac muscle stimulated to contract isometrically (at any given preload). Negative inotropic stimuli have the opposite effects (Braunwald and Ross 1976; Ross 1991b).

Positive inotropic stimuli increase the extent of shortening in isolated cardiac muscle stimulated to contract isotonically (at any given afterload), with an upward and left shift of the force-velocity relation. Negative inotropic stimuli have the opposite effects (Braunwald and Ross 1976; Ross 1991b)

2.4.5 Mechanical performance of the left ventricle

The factors affecting the mechanical performance of isolated cardiac muscle are the same factors that affect the mechanical performance of the left ventricle (Ross, Covell et al. 1966; Braunwald and Ross 1976; Ross 1991b; Ross 1991c) Whereas the mechanical performance of isolated cardiac muscle is described in terms of tension and length, the

mechanical performance of the left ventricle may be described in terms of pressure and volume (Ross, Covell et al. 1966; Braunwald and Ross 1976; Ross 1991b; Ross 1991c).

2.4.6 Pressure volume loops of the left ventricle

The left ventricle undergoes a sequence of changes in pressure and volume during each cardiac cycle that can be illustrated as a pressure-volume loop (Suga, Sagawa et al. 1973; Sagawa, Maughan et al. 1988). The left ventricular pressure-volume loop passes through four distinct phases related to the cardiac cycle: isovolumic contraction, ejection, isovolumic relaxation, and ventricular filling. Each pressure volume loop is bounded by the end-systolic pressure volume relationship (ESPVR), and the end-diastolic pressure volume relationship (EDPVR) (Opie 1998; Katz 2001). The ESPVR marks the end of systole and is a reflection of the contractility or inotropic state of the left ventricle, whereas the EDPVR marks the end of diastole and reflects the filling or lusitropic properties of the left ventricle (Opie 1998; Katz 2001).

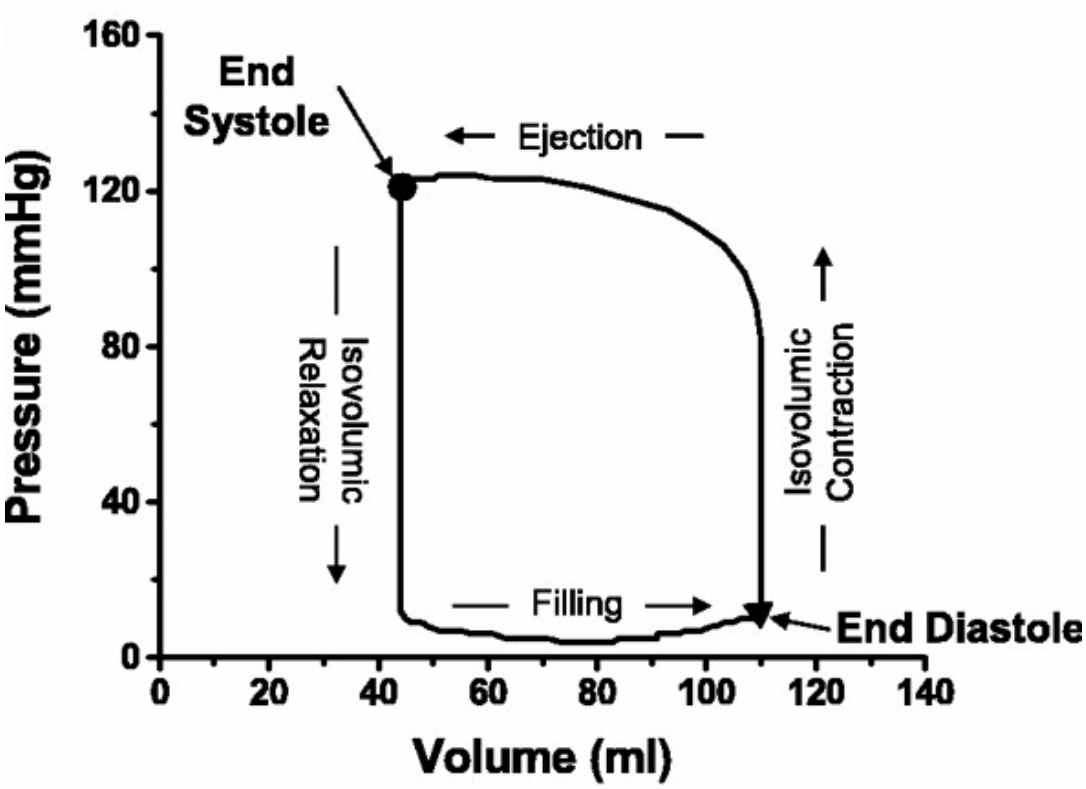


Figure 3 Pressure volume loop of the left ventricle illustrating the four phases of the cardiac cycle (Burkhoff, Mirsky et al. 2005).

2.4.7 End-systolic pressure-volume relationship

The ESPVR may be obtained in an isolated heart preparation, experimental animal, or intra-operatively by plotting the coordinates of the end-systolic pressure-volume point from variably loaded pressure-volume loops (Sagawa, Maughan et al. 1988; Opie 1998; Katz 2001; Little 2001). Although the ESPVR has been described as a linear relation, the relationship has been demonstrated to be curvilinear (Peterson, Tsuji et al. 1978; Hess, Ritter et al. 1984). The position and slope of the ESPVR can be used to assess acute changes in contractility (Sagawa, Maughan et al. 1988; Little 2001)

2.4.8 End-diastolic pressure volume relationship

Passive stretching of the left ventricle results from application of a distending pressure producing a curvilinear pressure-volume relationship (i.e. the ventricle becomes stiffer at higher ventricular volumes) (Braunwald and Ross 1976; Ross 1991c; LeWinter, Decena et al. 2000; Little 2001). The principle structural determinants of the passive pressure-volume relationship are the elastic properties of titin at low pressures, and the elastic properties of the connective tissue matrix (principally collagen) at higher pressures (LeWinter, Decena et al. 2000).

The passive pressure-volume relationship is also influenced by the geometry and thickness of the left ventricle, the amount of blood within the vessels of the myocardium, and by external constraints including the fibrous pericardium and right ventricle (LeWinter, Decena et al. 2000). The passive pressure-volume relationship determines the EDPVR of the pressure-volume loop (LeWinter, Decena et al. 2000; Little 2001).

2.4.9 Cardiac output

Cardiac output is maintained by the cyclic contraction and relaxation of the ventricles that generate pulsatile pressure and blood flow. Cardiac output is the product of the stroke volume (volume of blood ejected from the left ventricle or right ventricle during one beat) and the heart rate (Ross 1991a; Opie 1998; Katz 2001).

The stroke volume is the difference between the end-diastolic volume and the end-systolic volume, and the three major determinants of the stroke volume include preload, afterload, and myocardial contractility (Braunwald and Ross 1976; Ross 1991c).

All four factors affecting cardiac output operate simultaneously in vivo to regulate the mechanical performance of the left ventricle (Braunwald and Ross 1976; Ross 1991c).

2.4.10 Preload

The relationship between the end-diastolic volume (preload) and the pressure generated by the heart was first described for the amphibian heart by Otto Frank in 1895 and reproduced for the mammalian heart by Patterson, Piper and Starling in 1914 (Katz 2002).

The preload affects the mechanical performance of the left ventricle through the law of the heart: "The mechanical energy set free on passage from the resting to the contracted state is a function of the length of the muscle fibre i.e. the area of chemically active surfaces" (Starling 1918).

The "law of the heart" indicates that as ventricular filling (end-diastolic volume) is increased and the sarcomeres are stretched, force generation increases. According to the sliding filaments theory, increased force generation occurs with increased sarcomere stretch up to 2.2μm, at which there is maximal cross bridge interaction between thin actin and thick myosin filaments (Gordon, Huxley et al. 1966).

Operation of the "law of the heart" in the normal left ventricle increases the ability of the heart to empty as the preload increases. The response to increasing end-diastolic volume can be illustrated using pressure-volume loops. At increasing end-diastolic volumes the stroke volume is increased without a change in end-systolic pressure and volume (Braunwald and Ross 1976).

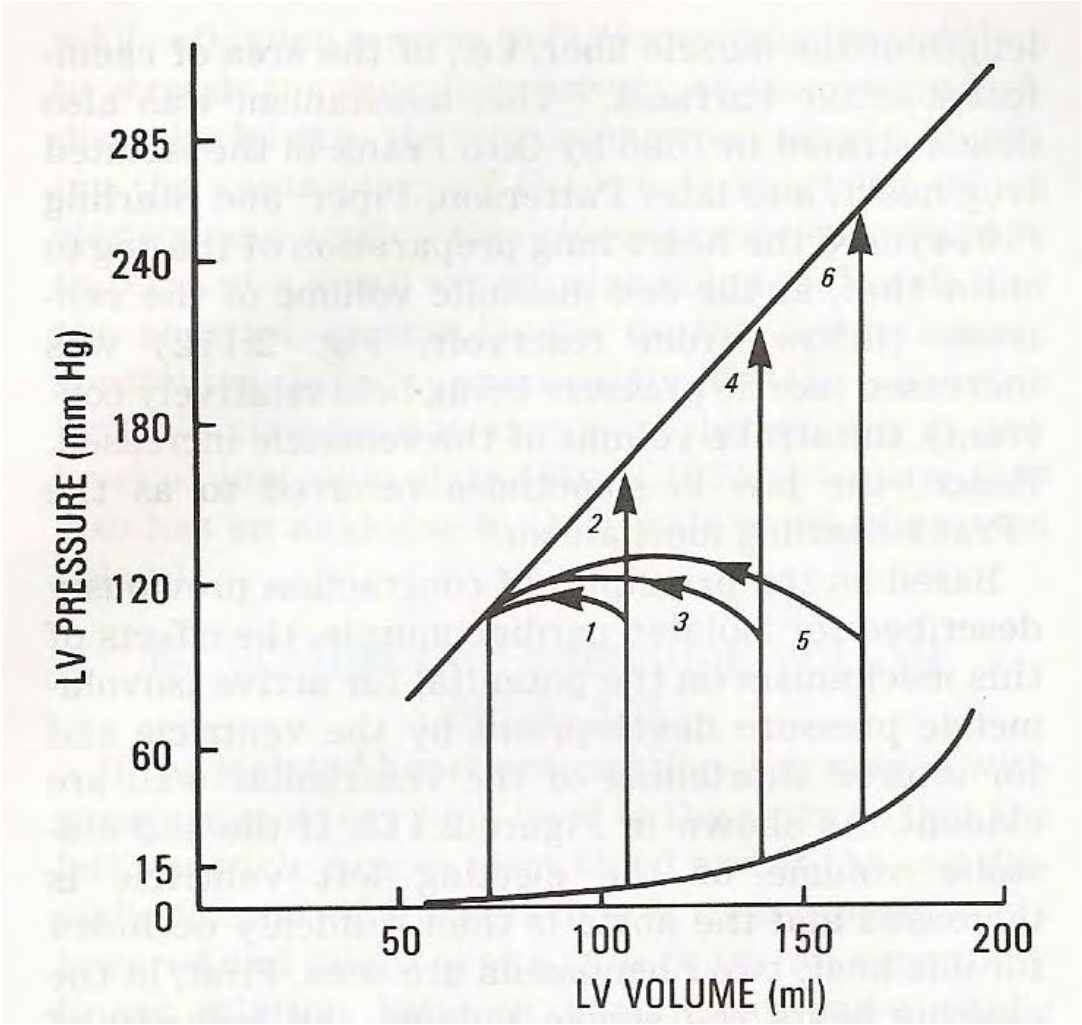


Figure 4 Pressure volume loops of the left ventricle illustrating the response to alterations in end-diastolic volume (Ross 1991c).

2.4.11 Afterload

The afterload is the force that the ventricular myocardium must overcome to eject blood. The term afterload describes the factors that oppose ventricular ejection and is best described by the ascending aortic input impedance (Nichols, Pepine et al. 1980; Nichols and O'Rourke 1998). The factors opposing left ventricular ejection include the inertial

properties of the blood and the physical properties of the systemic arterial tree (Nichols and O'Rourke 1998).

The ascending aortic impedance spectrum is a function of blood viscosity, arterial elasticity, and dimensions of the systemic arterial tree, and includes resistance, stiffness, and wave reflection (Nichols, Pepine et al. 1980; Nichols and O'Rourke 1998). The peripheral resistance is the modulus at zero frequency, and the characteristic impedance is the modulus at higher frequencies (i.e. above the first minimum) (Nichols and O'Rourke 1998). The modulus and phase between very high and very low frequencies is largely reflected by wave reflection (Nichols and O'Rourke 1998).

The effect of afterload on left ventricular function has been investigated using a number of techniques including pressure-volume loops, and pump function graphs (Westerhof and O'Rourke 1995).

The inverse relationship between stroke volume and pressure generated has been illustrated through the use of pressure volume loops (Suga, Sagawa et al. 1973; Kass, Maughan et al. 1987; Spratt, Tyson et al. 1987; Kass and Kelly 1992; Starling 1993; Burkhoff, Mirsky et al. 2005). Pump function curves relate mean ventricular pressure to cardiac output and also illustrate the inverse relation between ventricular pressure and cardiac output (Elzinga and Westerhof 1976; Elzinga and Westerhof 1978; Elzinga and Westerhof 1979).

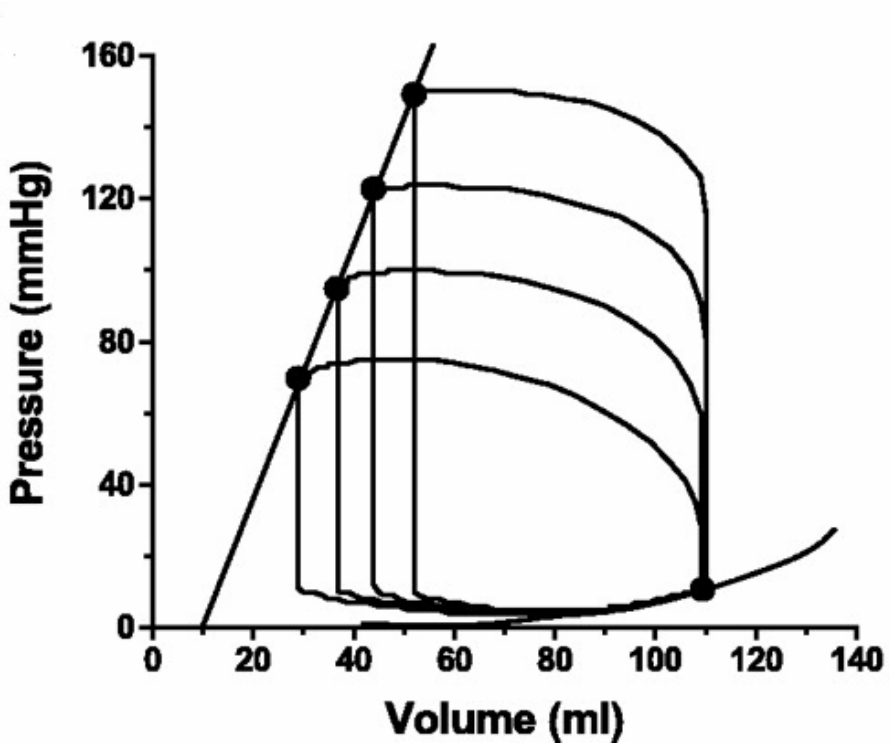


Figure 5 Pressure volume loops of the left ventricle illustrating the response to alterations in afterload (Burkhoff, Mirsky et al. 2005).

2.4.12 Contractility

The contractility (inotropic state) of the left ventricle relates to the strength of contraction independent of loading conditions. At a constant preload and afterload, increased contractility produces an increase in stroke volume and cardiac output. There are a number of indices of contractility that have been used to assess cardiac function (Little 2001; Carabello 2002).

Measurements of pressure-volume loops are useful in the assessment of the contractility of the intact ventricle. Contractility can be assessed using the slope and volume intercept of the ESPVR. An increase in the contractility of the left ventricle is manifest as an increase in the slope of the ESPVR (Starling 1993; Little 2001).

The use of pressure-volume loops for the assessment of left ventricular contractility has a number of theoretic and practical limitations including the need for invasive measurement, and the difficulty in obtaining accurate measurement of left ventricular volume and the ESPVR (Nichols and O'Rourke 1998; Little 2001).

Preload recruitable stroke work is the relationship between left ventricular stroke work and end-diastolic volume and is a measure of contractility (Glower, Spratt et al. 1985; Karunanithi and Feneley 2000).

Ejection fraction is the stroke volume divided by the end-diastolic volume, and therefore represents the fraction of end-diastolic volume ejected during systole (Opie 1998; Carabello 2000; Katz 2001). Ejection fraction is the most commonly used index of left ventricular contractility and may be measured either invasively or non-invasively. Ejection fraction is useful clinically as it can distinguish between systolic and diastolic dysfunction and predicts clinical outcome (Cohn, Gorlin et al. 1974).

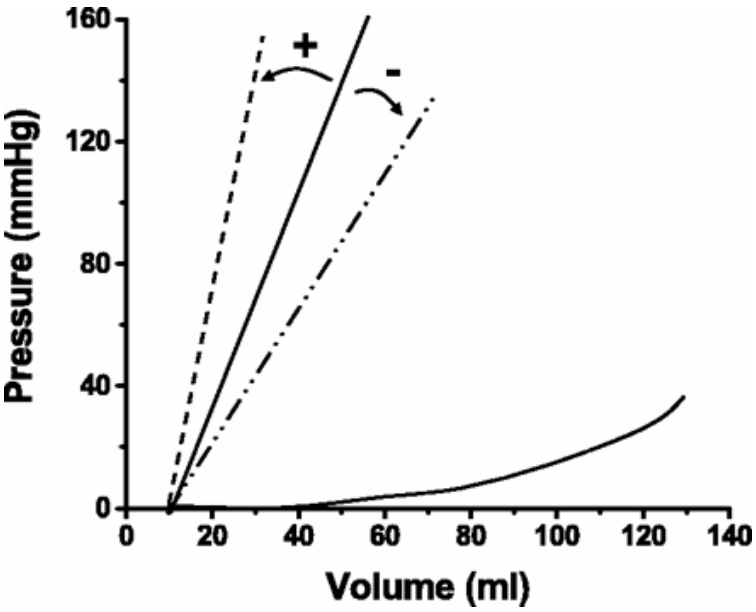


Figure 6 An increase in contractility is represented by an increase in the slope of the ESPVR (Burkhoff, Mirsky et al. 2005).

2.4.13 Myocardial wall tension

The left ventricular pressure and geometry determine the stress or tension in the left ventricular wall. The tension in the ventricular wall may be determined using the law of Laplace. For a thick walled sphere:

Equation 13 $\tau = (P.R) / (2.h)$ (Ross, Covell et al. 1966; Carabello 2000; Westerhof, Stergiopoulos et al. 2005)

The law of Laplace has implications in left ventricular hypertrophy (thickening) and left ventricular dilatation, and in heart failure (Grossman, Jones et al. 1975; Cohn, Ferrari et al. 2000; Mann 2004).

Left ventricular hypertrophy is a compensatory mechanism in chronic pressure loading and acts to reduce wall stress. The thickened left ventricular myocardium is more susceptible to ischaemia, especially at the subendocardial layers. The thickened ventricular myocardium is also stiffer and may impair filling in diastole.

Left ventricular dilatation is a compensatory mechanism that occurs in chronic volume loading and in systolic failure. Dilatation increases the wall stress at a given pressure and results in excessive energy utilisation, especially in the dilated, failing ventricle.

2.5 MECHANICAL PROPERTIES OF THE AORTA

The mechanical properties of the arterial wall influence the physiologic performance of the cardiovascular system and the development and progression of

cardiovascular disease. Arteries, like other biologic tissues, exhibit non-linear elasticity with increasing stiffness at increasing strain (Roy 1880; Bergel 1961a).

The non-linear elasticity of the aorta and large elastic arteries is central to their physiologic functions (Berne and Levy 1977; Boudoulas and Wooley 1996; Nichols and O'Rourke 1998); the smoothing out of pulsatile ventricular contraction to the more steady flow seen in the peripheral circulation; the maintenance of diastolic blood pressure and coronary perfusion, and the stability to rupture over a wide range of inflation pressures. The non-linear elasticity of the arterial wall is a result of the geometric arrangement of the connective tissue elements in the arterial wall (Burton 1954; Roach and Burton 1957; Wolinsky and Glagov 1964; Wolinsky and Glagov 1967).

2.5.1 Function of the aorta

The aorta is the major conduit that distributes oxygenated blood from the left ventricle to the organs and tissues of the body (Gray 1858; Gabella 1995). The aorta absorbs the pulsatile output of the left ventricle and converts it into the smoother type of flow seen in the peripheral circulation, and acts to maintain blood flow during diastole (Berne and Levy 1977; Nichols and O'Rourke 1998; Li 2000; Li 2004; Isselbacher 2005).

During ventricular systole, the thoracic aorta and large elastic arteries are distended by blood from the left ventricle, absorbing pulsations and cushioning the rise in systolic pressure to optimise ventricular-vascular coupling. Elastic recoil of the aorta in diastole maintains diastolic blood pressure and coronary perfusion.

2.5.2 Anatomy of the aorta

The anatomy of the human aorta is well described in standard textbooks of anatomy and cardiovascular surgery (Gray 1858; Gabella 1995; Baue, Geha et al. 1996; Cohn and Edmunds 2003).

The aorta is divided anatomically by the diaphragm into the thoracic aorta and abdominal aorta. The thoracic aorta is further divided into the ascending aorta, arch, and descending aorta.

The ascending aorta commences at the aortic root and enlarges as the three sinuses of Valsalva. The aortic root supports the bases of the tri-leaflet aortic valve, and each leaflet is associated with a sinus of Valsalva. The right and left coronary arteries arise from the right and left sinuses of Valsalva to run on the surface of the heart before giving branches that supply the myocardium.

The tubular segment of the ascending aorta commences at the sinotubular junction and extends to the arch of the aorta. The ascending aorta lies just right of the midline with its proximal portion within the pericardium.

The arch of the aorta arches backward within the thoracic cavity to the left of the trachea and oesophagus to lie on the left side of the vertebral column. The pulmonary trunk and bifurcation, and the right pulmonary artery all lie inferior to the arch of the aorta. The right innominate artery (brachiocephalic artery), left common carotid, and left subclavian artery arise from the convexity of the arch to supply the upper limbs, neck, and head.

The junction of the arch of the aorta and descending aorta is the aortic isthmus. This point is vulnerable to trauma as the ascending and arch of aorta are relatively mobile, whereas the descending thoracic aorta is relatively fixed by the left subclavian artery, the

ligamentum arteriosum, the paired intercostal arteries, and the parietal pleura. The descending thoracic aorta initially lies to the left of the vertebral column, and descends in the thoracic cavity to lie anterior to the vertebral column and posterior to the oesophagus.

The paired intercostal arteries arise from the descending thoracic aorta to supply the chest and abdominal walls, and the diaphragm.

The descending thoracic aorta passes through the diaphragm via the aortic hiatus to become the abdominal aorta. The abdominal aorta gives branches to the abdominal viscera (mesenteric and renal arteries) and terminates at the level of the 4^{th} lumbar vertebra by dividing into the right and left common iliac arteries that supply the pelvis and lower limbs.

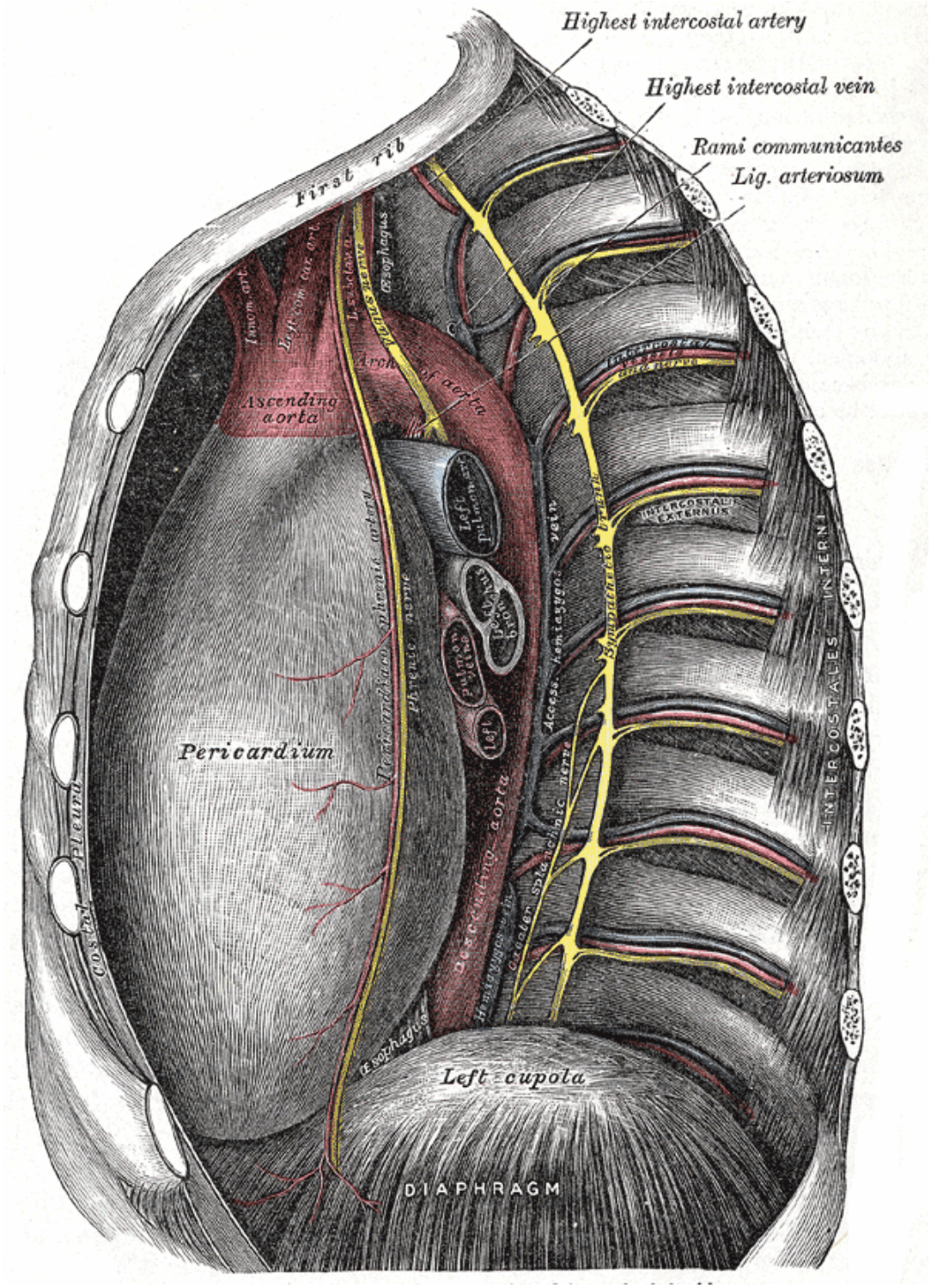


Figure 7 Anatomy of the left hemithorax illustrating the course of the thoracic aorta (Gray 1918).

2.5.3 Histology of the aorta

The aorta is composed of three concentric layers or tunica; the intima, media, and adventitia (Stehbens 1979; Silver, Christiansen et al. 1989).

Tunica Intima

Vascular endothelial cells are flat, elongated, polygonal cells that are orientated in the direction of flow (Flaherty, Pierce et al. 1972; Ferrans 1980). They form a continuous monolayer of cells that provide an anti-thrombogenic interface between the blood and the vessel wall.

Vascular endothelial cells lie on a basement membrane composed of non-fibrillar collagen, such as type IV collagen, laminin, fibronectin, and other extracellular matrix molecules (Silver, Christiansen et al. 1989). The internal elastic lamina separates the tunica intima and media.

Tunica media

The mechanical properties of the aorta are determined primarily by the tunica media (Dobrin 1983; Nichols and O'Rourke 1998). Wolinsky and Glagov (1964) described the architecture of the tunica media as an orderly array of lamellar units consisting of smooth muscle, elastin and collagen. At physiologic pressures elastic lamellae are arranged as a series of concentric rings with uniform thickness and radial spacing. Within the inter-lamellar spaces are smooth muscle cells and collagen fibres orientated helically.

The lamellar unit model of the arterial wall was modified by Clark and Glagov (1985). They showed that elastic tissue between concentric layers of smooth muscle consists of two layers of elastin fibres, each associated with adjacent muscle layers. This

system of “musculo-elastic fascicles” allows for uniform distribution of tensile stress across the arterial wall (Dobrin 1983; Dobrin 1999).

Adventitia

The tunica adventitia is composed of loose connective tissue, primarily collagen fibres with some elastin fibres, fibroblasts and blood vessels (vasa vasorum) (Stehbens 1979; Silver, Christiansen et al. 1989). It is separated from the media by the external elastic lamina, and in the thoracic aorta it merges with surrounding loose connective tissue.

2.5.4 Elastin and collagen content of the aorta

There is a decrease in elastin content and increase in collagen content in the aorta with increasing distance from the heart (Harkness, Harkness et al. 1957; Apter 1966; Fischer and Llaurado 1966). The elastin to collagen ratio falls from approximately 2.0 in the ascending aorta to approximately 0.5 in the abdominal aorta (Milnor 1989).

Elastin is a highly extensible structural protein with an elastic modulus comparable to that of rubber (Aaron and Gosline 1980). Collagen is relatively inextensible with an elastic modulus that is much greater than that of elastin (Burton 1954; Fung 1981; Armentano, Levenson et al. 1991; Barra, Armentano et al. 1993; Armentano, Barra et al. 1995).

As a result of the alterations in elastin and collagen content, there as an increase in elastic modulus (stiffness) along the aorta with increasing distance from the heart (Bergel 1961a; Gow 1972; Nichols and McDonald 1972) as well as an increase in pulse wave velocity (Nichols and McDonald 1972).

2.5.5 Mechanical properties of the arterial wall

The theoretical principles underlying the mechanical properties of the arterial wall are well described in textbooks of arterial haemodynamics and biomedical engineering (Gow 1972; Patel and Vaishnav 1972; Patel and Vaishnav 1980; Fung 1981; Milnor 1989; Park and Lakes 1992; Nichols and O'Rourke 1998). The mechanical properties of biologic tissues and biomaterials are important determinants of their physiologic function and stability. Elasticity is the ability of a material to return to its original shape and dimensions after deformation. Elasticity is usually limited to a level of deformation beyond which, further deformation will produce a permanent deformation or set.

For a material that undergoes a mechanical deformation, the stress is defined as the force per unit area that produces the deformation.

Equation 14 $\text{Stress } (S) = F / A$

Where, $S = \text{Stress } (Nm^{-2})$

$F = \text{Force } (N)$

$A = \text{Cross-sectional area } (m^2)$

Tensile stresses elongate a material whereas compressive stresses compress a material. A stress component parallel to the plane on which it acts is a shearing stress.

The deformation of a material in response to a stress is called strain.

Equation 15 $\text{Strain } (\varepsilon) = (L_1 - L_0) / L_0$

Where, $\varepsilon = \text{strain}$

$L_0 = \text{initial length (m)}$

$L_1 = \text{deformed length (m)}$

The deformation resulting from the strains described above are termed tensile, compressive, and shear strains.

Elongation of a material by a tensile stress causes a reduction in the transverse dimension. Poisson's ratio is the negative ratio of the transverse strain to the longitudinal strain for tensile loading of a material.

Equation 16 $-\sigma_{yx} = \varepsilon_{yy} / \varepsilon_{xx}$

Where, σ = Poisson's ratio

ε_{yy} = transverse strain

ε_{xx} = longitudinal strain

If a material is homogenous, and the Poisson's ratio is the same in all directions, the material is said to be isotropic. Anisotropic materials (such as the arterial wall) are not homogenous and have different valves of σ in different directions i.e. the elastic properties are dependant on the direction in which the force is applied. The value of Poisson's ratio is positive for all known isotropic materials and lies in the range of 0.0 – 0.5. Poisson's ratio is in the range 0.25 – 0.4 for most metals, 0.48 for rubber and rubbery substances, and close to 0.5 for the arterial wall. For an isotropic material with a Poisson's ratio of 0.5, the volume will remain constant with elongation.

Elastic modulus and Poisson's ratio

The elastic properties of a material can be expressed as an elastic modulus that is the ratio between stress and strain. Young's modulus (E) is the ratio of a tensile stress to the resulting elongation (longitudinal strain). A material with a high Young's modulus is stiffer than one with a low Young's modulus. All elastic moduli have the dimensions of stress

(force per unit area), as strain is a dimensionless ratio. Poisson's ratio (σ) and Young's modulus of elasticity (E) can be used to define the elastic properties of blood vessels.

Stress-Strain diagram

The relationship between stress and strain may be represented graphically. There is a linear relationship between applied stress and resulting strain for a purely elastic material. The slope of the stress-strain relationship is the Young's modulus.

The arterial wall (like most soft biologic tissues) shows a non-linear stress-strain relationship, so that the elastic modulus increases with loading (as the strain increases). The non-linear elasticity of the arterial wall results from the lamellar arrangement of collagen and elastin fibres (Burton 1954; Roach and Burton 1957; Wolinsky and Glagov 1964; Wolinsky and Glagov 1967). There is a strain dependant transfer of load from compliant elastin fibres to rigid collagen fibres with distension under physiologic pressures.

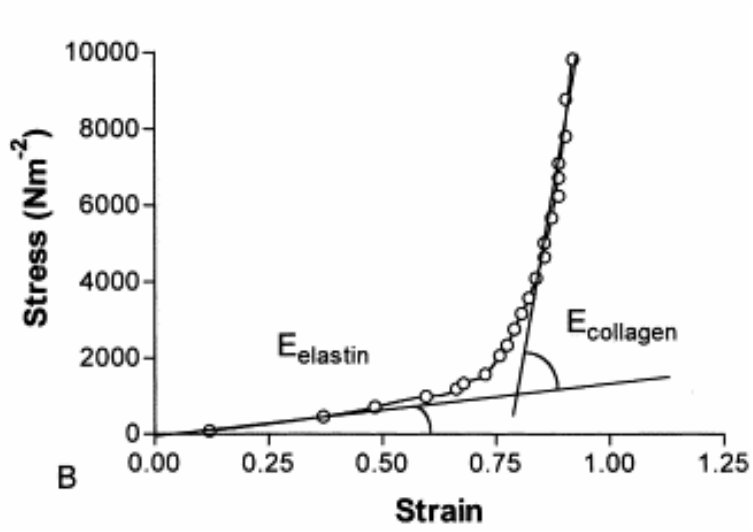


Figure 8 Stress-strain diagram of the human descending thoracic aorta showing the transfer of load from elastin fibers at low strains to collagen fibers at high strains. $E_{elastin}$ is Young's modulus of elastin and $E_{collagen}$ is Young's modulus of collagen (Groenink, Langerak et al. 1999).

The elastic modulus (at a particular strain) is the tangent to the stress-strain curve at that point. The incremental elastic modulus (E_{inc}) (Bergel 1961a; Milnor 1989) is an approximation of elastic modulus, and is calculated from the change in stress (ΔS), the average length (L_m), and the change in length (ΔL).

Equation 17 $E_{inc} = (\Delta S. L_m) / (\Delta L)$

Where, Einc = Incremental elastic modulus

ΔS = change in stress

Lm = average length

ΔL = change in length

2.5.6 Cylindrical stress and strain

The mechanical engineering principles described above can be applied to an intact artery stressed by a distending pressure. For a very thin-walled cylinder, the circumferential tension is related to the distending pressure and radius by the law of Laplace.

Equation 18 $T = P.R$ (Milnor 1989; Nichols and O'Rourke 1998)

Where, T = wall tension (dynes/cm)

P = distending pressure (dynes/cm^2)

R = radius (cm)

For an artery with wall thickness (h), the circumferential stress (τ) is given by:

Equation 19 $\tau = P.R / h$ (Milnor 1989; Nichols and O'Rourke 1998)

Where, h = wall thickness (cm)

2.5.7 Pressure-strain elastic modulus

The pressure-strain elastic modulus (E_p) (Peterson, Jensen et al. 1960) is an expression of arterial stiffness that does not require measurement of wall thickness for its calculation. Wall thickness is technically difficult to measure, and often cannot be measured in in-vivo studies (Nichols and O'Rourke 1998).

Equation 20 $E_p = D_d (P_s – P_d) / (D_s - D_d)$

Where, D_s = systolic arterial diameter

D_d = diastolic arterial diameter

P_s = systolic arterial pressure

P_d = diastolic arterial pressure

The pressure-strain elastic modulus is defined for specific pressures and will vary at different pressures for the same artery as a result of the nonlinear pressure-diameter relation of the arterial wall.

The stiffness index (β) (Kawasaki, Sasayama et al. 1987) is another measure of arterial stiffness that does not require measurement of wall thickness.

Equation 21 $\beta = [D_d \ln (P_s / P_d)] / (D_s – D_d)$

2.5.8 Viscoelasticity

The stress-strain relationship of a perfectly elastic material is independent of the rate at which the stress is applied. The blood vessel wall (like other biologic tissues) displays viscoelastic behaviour, where the stress-strain relationship is dependant on the rate at which the stress is applied, and the stiffness increases as the rate of extension increases (Fung 1981; Milnor 1989; Silver, Christiansen et al. 1989; Nichols and O'Rourke 1998). Viscoelastic materials (and tissues) display creep, stress relaxation, and hysteresis.

A measure of viscoelasticity can be obtained by applying a sinusoidal stress or pressure to the arterial wall. For a viscoelastic material the strain will also be sinusoidal but will lag the stress by a phase angle. The phase lag between the sinusoidal stress and strain curves is a measure of viscoelasticity (Milnor 1989; Nichols and O'Rourke 1998).

2.5.9 Arterial elasticity

Studies of arterial elasticity have been carried out in-vitro on arterial strips, arterial rings, and pressurised cylindrical segments. In-vivo studies of arterial elasticity have been carried out in experimental animals and humans using a number of techniques. Measurement of the elastic properties of the aorta and arterial tree is essential to the understanding the physiology and pathophysiology of the cardiovascular system, as well as for the design of vascular prosthesis.

The parameters that have been used to quantify arterial elastic properties include characteristic impedance (Z_o), pulse wave velocity (c), Young's modulus (E), circumferential elastic modulus (E_o), pressure-strain elastic modulus (E_p), stiffness index (β), and percentage variation in diameter (PVD) or radial pulsation (Milnor 1989; Silver, Christiansen et al. 1989; Nichols and O'Rourke 1998; O'Rourke, Staessen et al. 2002). These parameters all vary with distending pressure (as a result of the non-linear elasticity of the arterial wall), distance of the vessel from the heart, aging, and the presence of disease states.

Pressure-strain elastic modulus and radial pulsation have been used to compare arterial stiffness data from different studies (Milnor 1989; Nichols and O'Rourke 1998; O'Rourke, Staessen et al. 2002). There is a large variation in the values of radial pulsation and pressure-strain elastic modulus in the literature relating to the method used to measure

arterial diameter. Early invasive techniques (e.g. using strain gauges to measure arterial diameter) produced arterial stiffness measurements that were higher than those produced using non-invasive techniques (e.g. angiography) (Silver, Christiansen et al. 1989; Nichols and O'Rourke 1998).

Invasive techniques may impose constraint on the arterial wall and induce vasospasm and ischaemia secondary to surgical dissection (Silver, Christiansen et al. 1989; Stefanadis, Vlachopoulos et al. 1995; Angouras, Sokolis et al. 2000). Current techniques used to measure arterial elastic properties (e.g. sonomicrometers) require minimal or no contact with the arterial wall (Silver, Christiansen et al. 1989; Nichols and O'Rourke 1998).

2.5.10 Uniaxial and biaxial Testing

Uniaxial tensile testing is a simple method for the measurement of the mechanical properties of arterial strips or rings. A uniaxial force is applied to the material while the force and resulting specimen elongation (displacement) are measured to generate a force-displacement curve (Park and Lakes 1992). A stress-strain curve is generated by converting force into stress, and displacement into strain (Park and Lakes 1992). Stress is calculated by dividing the force by the specimen cross-sectional area, and strain is calculated by dividing the final length by the initial length (gauge length) of the specimen in the testing apparatus.

Roy (1880) performed uniaxial tensile tests (as well as in-vitro pressure-volume tests) and described the non-linear elasticity of the arterial wall as well as the increase in stiffness of the human aorta with aging. A number of investigations have used static and dynamic uniaxial tensile tests to describe the mechanical properties of arteries (Cohen, Litwin et al. 1972; Pynadath and Mukherjee 1977; Hayashi 1982; Mohan and Melvin 1982;

Cox 1983; Dunn and Silver 1983; Yin, Spurgeon et al. 1983; Bashey, Cox et al. 1989; Matsuda, Nosaka et al. 1989; Adham, Gournier et al. 1996; Angouras, Sokolis et al. 2000).

There are a number of possible sources of errors in data from arterial strips and rings relating to specimen preparation. Strips need to be immersed and tested in a solution that simulates the physiologic environment, as strips exposed to air lose moisture resulting in altered material properties. Arteries are under longitudinal tension in-vivo and will retract when cut (Learoyd and Taylor 1966; McDonald 1974). The free edges of the specimen produce "edge effects" that may produce minor alterations to mechanical testing data (Nichols and O'Rourke 1998).

Careful specimen cutting is necessary as the excised retracted artery is markedly anisotropic (Patel, Janicki et al. 1969; Dobrin 1986) and the mechanical properties will depend on the orientation of the strip. Arterial strips are ideally cut in the form of a dumbbell in accordance with mechanical engineering principles to prevent rupture at the site of engagement of machine gauges where there is an uncontrolled stress concentration (AS1145-1989 1989; D638-00 2001). The rupture load, which is an indicator of material strength, is only valid when rupture occurs in the middle of the test specimen.

Despite these limitations, the use of strips and rings for uniaxial tensile testing is beneficial in that these tests are simple and provide valuable data about the mechanical properties of the arterial wall and vascular prostheses. These tests however, do not provide information about the mechanical properties of the intact vessel (McDonald 1974; Cox 1983).

A number of investigations have used biaxial tensile tests to describe the mechanical properties of the arterial wall. In biaxial tensile tests, forces are applied in both the circumferential and longitudinal directions (Patel, Tucker et al. 1970; Mohan and

Melvin 1983; Vande Geest, Sacks et al. 2004). Biaxial tensile tests do not provide information about the mechanical properties of the intact artery, as there is an absence of the radial wall stress present in the intact artery.

2.5.11 In-vitro pressure–diameter testing

In-vitro pressure diameter testing is a technique for the measurement of the mechanical properties of the intact artery. Excised vessels are attached to a testing apparatus via two tubes and are inflated and deflated with fluid while pressure and diameter are measured. As arteries will retract longitudinally when excised (Learoyd and Taylor 1966; McDonald 1974), arterial segments used for in-vitro pressure diameter testing are ideally mounted on the testing apparatus at their in-vivo length. Many investigators have used in-vitro pressure diameter tests to describe the mechanical properties of the arterial wall (Bergel 1961a; Bergel 1961b; Learoyd and Taylor 1966; Carew, Vaishnav et al. 1968; Vaishnav, Young et al. 1972; Cox 1974; Cox 1983; Dobrin 1986; Wells, Langille et al. 1998a; Wells, Langille et al. 1999).

In vitro pressure-diameter testing of excised arterial segments provides accurate and detailed data on the mechanical properties of the arterial wall. Benefits of in-vitro pressure testing include the ability to characterise the mechanical properties of the excised segments for a wide pressure range using both static and dynamic sinusoidal displacements. The pressure contour may also be varied to simulate the pressure wave contour in-vivo in the normal and diseased states.

Limitations of in-vitro pressure diameter testing relate to the dissection and excision of the arterial segment, as well as the restraint imposed on the arterial wall with certain methods used to measure diameter (McDonald 1974; Silver, Christiansen et al. 1989;

Stefanadis, Vlachopoulos et al. 1995; Angouras, Sokolis et al. 2000). Excision of the aortic segment alters its mechanical properties because of disruption of the perivascular connective tissues, anatomic structures (eg ligamentum arteriosum) and arterial branches (eg intercostal vessels) that normally tether the aorta in-vivo (Patel and Fry 1966; McDonald 1974).

2.5.12 In-vivo methods

A number of investigators have studied the mechanical properties of intact arteries in-vivo. Arterial pressure and diameter have been measured in-vivo and used to calculate elastic modulus.

Intravascular pressure is readily measured using catheter tip pressure transducers eg Millar catheter tip transducers (Millar instruments, Inc., Houston, Texas) (Nichols and O'Rourke 1998). Arterial diameter has been measured in-vivo using a number of methods and devices, including, strain gauges, angiography, vascular ultrasound, and sonomicrometers.

Invasive measurements using strain gauges

Strain gauge cantilevers or callipers to measure external arterial diameter (Peterson, Jensen et al. 1960; Greenfield and Patel 1962; Patel and Fry 1964; Gow and Taylor 1968; Dobrin and Rovick 1969). Murgo (1971) developed an intravascular strain gauge device to measure internal arterial diameter.

Angiographic measurements

A number of investigators (Arndt, Stegall et al. 1971; Gozna, Marble et al. 1973; Merillon, Motte et al. 1978) have used angiography to measure internal arterial diameter.

Ultrasonic methods

Ultrasonic methods have been developed to measure the mechanical properties of the aorta and other systemic arteries. These techniques include transit-time measurements and vascular ultrasound.

Transit-time measurements

A pair of ultrasonic crystals (sonomicrometers) positioned to face each other across the vascular diameter can be used to measure the pulsatile external diameter of an artery (Pagani, Schwartz et al. 1975; Bertram 1977; Pagani, Baig et al. 1978; Pagani, Mirsky et al. 1979; Gentile, Chuong et al. 1988; Latson, Hunter et al. 1988; Armentano, Levenson et al. 1991; Barra, Armentano et al. 1993; White, Kavanaugh et al. 1994; Armentano, Barra et al. 1995; Lansac, Lim et al. 2002). One of the piezoelectric crystals produces an ultrasonic pulse that is transmitted through the vessel diameter and received by the second crystal. The distance between the two crystals (i.e. the external arterial diameter) is calculated from the transit time of the ultrasonic pulse between the two crystals. Sonomicrometers provide a reliable and continuous measure of external arterial diameter and have a resolution of about 1.0 um. Pressure is usually measured at the site of placement of the sonomicrometers using an intravascular pressure transducer.

Sonomicrometers require fixation to the external wall of the artery and therefore impose some constraint on the arterial wall. This constraint is minimal when compared to that produced by earlier strain gauge techniques. Surgical exposure of the artery for placement of sonomicrometers may result in damage to the vasa vasorum and ischaemia of the arterial wall, producing an acute or chronic increase in arterial stiffness (Stefanadis,

Vlachopoulos et al. 1995; Angouras, Sokolis et al. 2000). Gentle dissection of an artery may be sufficient to increase its stiffness.

Vascular ultrasound

Pulsatile diameter of peripheral arteries has be measured non-invasively using vascular ultrasound by a number of investigators (Hokanson, Mozersky et al. 1972; Hoeks, Ruissen et al. 1985; Hoeks, Brands et al. 1990; Boutouyrie, Laurent et al. 1992; Lanne, Sonesson et al. 1992; Benetos, Laurent et al. 1993; Pedersen, Aslaksen et al. 1993; Sonesson, Hansen et al. 1993; Lanne, Hansen et al. 1994; Sonesson, Lanne et al. 1994; Mangell, Lanne et al. 1996; Graf, Gariepy et al. 1999; Sonesson, Sandgren et al. 1999; Studinger, Lenard et al. 2000; Studinger, Lenard et al. 2003). Use of ultrasonic echo methods to measure the mechanical properties of central arteries may result in error as the pressure is often not measured at the same site as the diameter measurement (O'Rourke, Staessen et al. 2002). The non-invasive nature of ultrasonic measurement means that there is no mechanical constraint imposed on the arterial wall, and there is no alteration of mechanical properties resulting from dissection and trauma to the vasa vasorum.

Magnetic resonance imaging

Non-invasive measurement of the pulsatile diameter of the aorta and large central arteries has been achieved using magnetic resonance imaging (Honda, Yano et al. 1994; Matsumoto, Honda et al. 1996; Hundley, Kitzman et al. 2001).

2.6 CARDIOVASCULAR AGING

2.6.1 Epidemiology

The population of western industrialised nations such as the United States and Australia is aging. In the United States there are about 35 million people who are 65 years of age or older, and this figure is expected to double by 2030 to represent almost 25% of the population (Lakatta and Boluyt 2000; Lakatta and Levy 2003a). By 2030, it is expected that there will be 10 million people 85 years of age or older in the United States (Lakatta and Boluyt 2000; Lakatta and Levy 2003a).

Advancing age is the major risk factor for cardiovascular diseases such as coronary artery disease, hypertension, heart failure, and cerebrovascular disease. The incidence and prevalence of these diseases increases with advancing age (Lakatta and Boluyt 2000; Lakatta and Levy 2003a).

In the western industrialised nations, better therapeutic interventions (coronary care units, bypass surgery, thrombolysis) and preventative strategies (cessation of smoking and blood pressure management) have reduced mortality from cardiovascular disease and delayed primary cardiovascular events (Goldman and Cook 1984; Cooper, Cutler et al. 2000; Gaziano 2005). The reduction in age-adjusted cardiovascular mortality rates has produced an improvement in life expectancy and has increased the number of patients with heart failure (Gaziano 2005).

2.6.2 Structural changes in the large elastic arteries with aging

The large elastic arteries show a progressive increase in arterial diameter and wall thickness with aging (Gould 1960; Learoyd and Taylor 1966; Nakashima and Tanikawa

1971; Gerstenblith, Frederiksen et al. 1977; Nichols, O'Rourke et al. 1985; Towfiq, Weir et al. 1986; Kawasaki, Sasayama et al. 1987; Virmani, Avolio et al. 1991; Lanne, Sonesson et al. 1992; Pedersen, Aslaksen et al. 1993; Sonesson, Hansen et al. 1993; Lanne, Hansen et al. 1994; Pearson, Guo et al. 1994; Sonesson, Lanne et al. 1994; Gabella 1995; Vasan, Larson et al. 1995a; Nichols and O'Rourke 1998; Lakatta and Boluyt 2000; Lakatta and Levy 2003a). The ascending aorta dilates, elongates, and becomes more tortuous with aging (Gould 1960; Pomerance 1983; Schoen 1994). The ascending aorta dilates to a greater degree than descending thoracic and abdominal aorta (Virmani, Avolio et al. 1991).

The histologic changes that alter the structure and function of the large elastic arteries with aging are most prominent in the tunica media, but also involve the tunica intima (Virmani, Avolio et al. 1991; Nichols and O'Rourke 1998; Lakatta and Boluyt 2000; Lakatta and Levy 2003a). These changes occur independently of atherosclerosis and are present in populations with a low incidence of atherosclerosis (Virmani, Avolio et al. 1991).

Atherosclerosis is a focal disease predominantly affecting the arterial intima and produces ischaemia of distal organs or tissues through luminal narrowing, thrombosis and thrombo-embolism. In comparison, the alterations seen with aging in the large elastic arteries are diffuse, predominantly affect the media, and produce an increase in the stiffness and diameter of these arteries (Nichols and O'Rourke 2005).

Tunica Intima

There is an increase in the thickness of the tunica intima of the large elastic arteries with aging (Virmani, Avolio et al. 1991). The endothelium undergoes hyperplasia with thickening of the subendothelial connective tissue layer.

Tunica Media

In the tunica media there is progressive fragmentation of elastin fibres and disruption of elastic lamellae. This is associated with calcium deposition, an increase in collagen and ground substance content, and cystic medial necrosis (Carlson, Lillehei et al. 1970; Schlatmann and Becker 1977; Pomerance 1983; Lakatta, Mitchell et al. 1987; Virmani, Avolio et al. 1991; Lakatta, Gerstenblith et al. 1997; Nichols and O'Rourke 1998).

These alterations are thought to be due to the fatiguing effects of repeated cyclic stress (with arterial pulsation) on the relatively inert elastin fibres in the arterial media. Damage to elastin fibres is associated with collagenous remodelling and calcification (Nichols and O'Rourke 1998).

2.6.3 Arterial stiffness and pulse wave velocity

There is a progressive increase in the stiffness and pulse wave velocity of the large elastic arteries with aging (Nakashima and Tanikawa 1971; Gozna, Marble et al. 1974; Merillon, Motte et al. 1978; Langewouters 1982; Avolio, Chen et al. 1983; Avolio, Deng et al. 1985; Lanne, Sonesson et al. 1992; Sonesson, Hansen et al. 1993; van der Heijden-Spek, Staessen et al. 2000; Hundley, Kitzman et al. 2001). There is little change in the stiffness and pulse wave velocity of the peripheral muscular arteries with aging (Avolio, Chen et al. 1983; Boutouyrie, Laurent et al. 1992; Benetos, Laurent et al. 1993; Bortolotto, Hanon et al. 1999; van der Heijden-Spek, Staessen et al. 2000). The increase in pulse wave velocity of the large elastic arteries is progressive from childhood with a greater than two-fold increase in aortic pulse wave velocity between the second and eighth decades (Avolio, Chen et al. 1983; Vaitkevicius, Fleg et al. 1993).

The findings of arterial stiffening and increased pulse wave velocity with aging have been demonstrated in both Western populations as well as Eastern populations with a low incidence of atherosclerosis, indicating indicate that arterial stiffening occurs independently of atherosclerosis (Avolio, Chen et al. 1983; Avolio, Deng et al. 1985).

2.6.4 Arterial pressure and wave reflection

There is a progressive rise in aortic and left ventricular systolic pressure with aging as a result of stiffening of the large elastic arteries (Nichols, O'Rourke et al. 1985; Nichols, Nicolini et al. 1992). Stiffening of the large elastic arteries results in a greater peak pressure at the time of peak flow as well as early return of wave reflections from peripheral sites to augment pressure in the ascending aorta during late systole (Nichols, Nicolini et al. 1992; Nichols and O'Rourke 1998).

In adolescent humans, wave reflection is beneficial in that the reflected wave returns to the ascending aorta in diastole, thereby augmenting diastolic pressure and increasing coronary blood flow to the left ventricle without increasing left ventricular afterload (Nichols and O'Rourke 1998). As a result of the increase in arterial stiffness and pulse wave velocity with aging, there is early return of the reflected wave to the ascending aorta during ventricular ejection that augments systolic pressure and increases ventricular afterload (Nichols, Nicolini et al. 1992; Nichols and O'Rourke 1998).

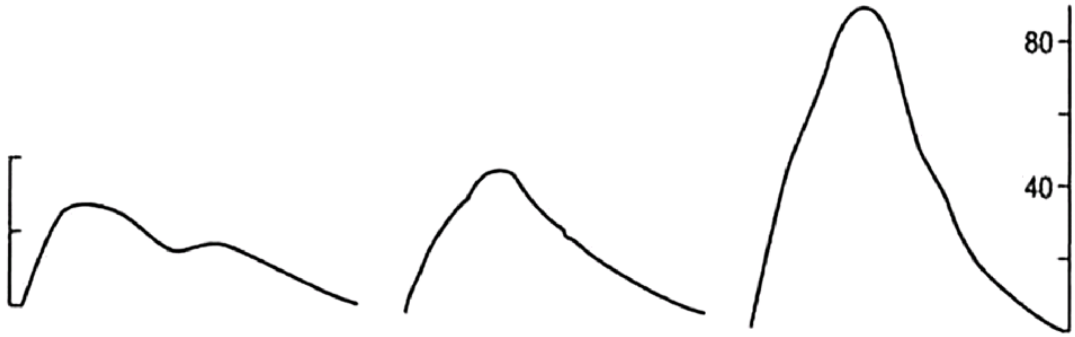


Figure 9 Alterations in the contour of the ascending aortic pressure wave with aging in humans (Nichols and O'Rourke 2005)**.**

The increase in stiffness and pulse wave velocity of the large elastic arteries is responsible for the changes in the contour of the arterial pressure wave with aging (Nichols, O'Rourke et al. 1985; Kelly, Hayward et al. 1989; Nichols and O'Rourke 1998). In humans, the ascending aortic pressure wave contour has been classified into patterns that are each associated with a certain age group, and illustrate the progressive alterations in large artery stiffness, pulse wave velocity, and wave reflection with aging (Murgo, Westerhof et al. 1980; Nichols, Nicolini et al. 1992).

The augmentation index is a measure of the systolic augmentation of the pressure wave by reflected waves. There is a progressive rise of augmentation index in the ascending aorta with aging up to about age 60 then plateaus (McEniery, Yasmin et al. 2005; Nichols and O'Rourke 2005).

Equation 22 Augmentation index = $(P_s - P_i)/(P_s - P_d)$

Where, P_s = systolic pressure

P_d = diastolic pressure

P_i = pressure at the inflection point (occurring at peak blood flow velocity)

Amplification of the pulse pressure and change in contour of the pressure wave as it travels peripherally diminishes with aging (O'Rourke, Blazek et al. 1968). In elderly humans there is little or no amplification of the pressure wave with transmission, and the contour of the pressure wave in the peripheral arteries resembles that in the ascending aorta. The alterations in transmission of the pressure wave with aging result from the increase in arterial stiffness and pulse wave velocity.

2.6.5 Ascending aortic impedance

There are significant changes in the ascending aortic impedance spectrum in humans with aging (Murgo, Westerhof et al. 1980; Merillon, Motte et al. 1982a; Merillon, Motte et al. 1982b; Nichols, O'Rourke et al. 1985). These changes include an increase in characteristic impedance, and a rightward shift of impedance curves to higher frequencies. The increase in the values of ascending aortic impedance modulus at low frequencies occur as a result of early wave reflection, and illustrate the loss of optimal coupling of the left ventricle to the arterial system (Nichols and O'Rourke 1998).

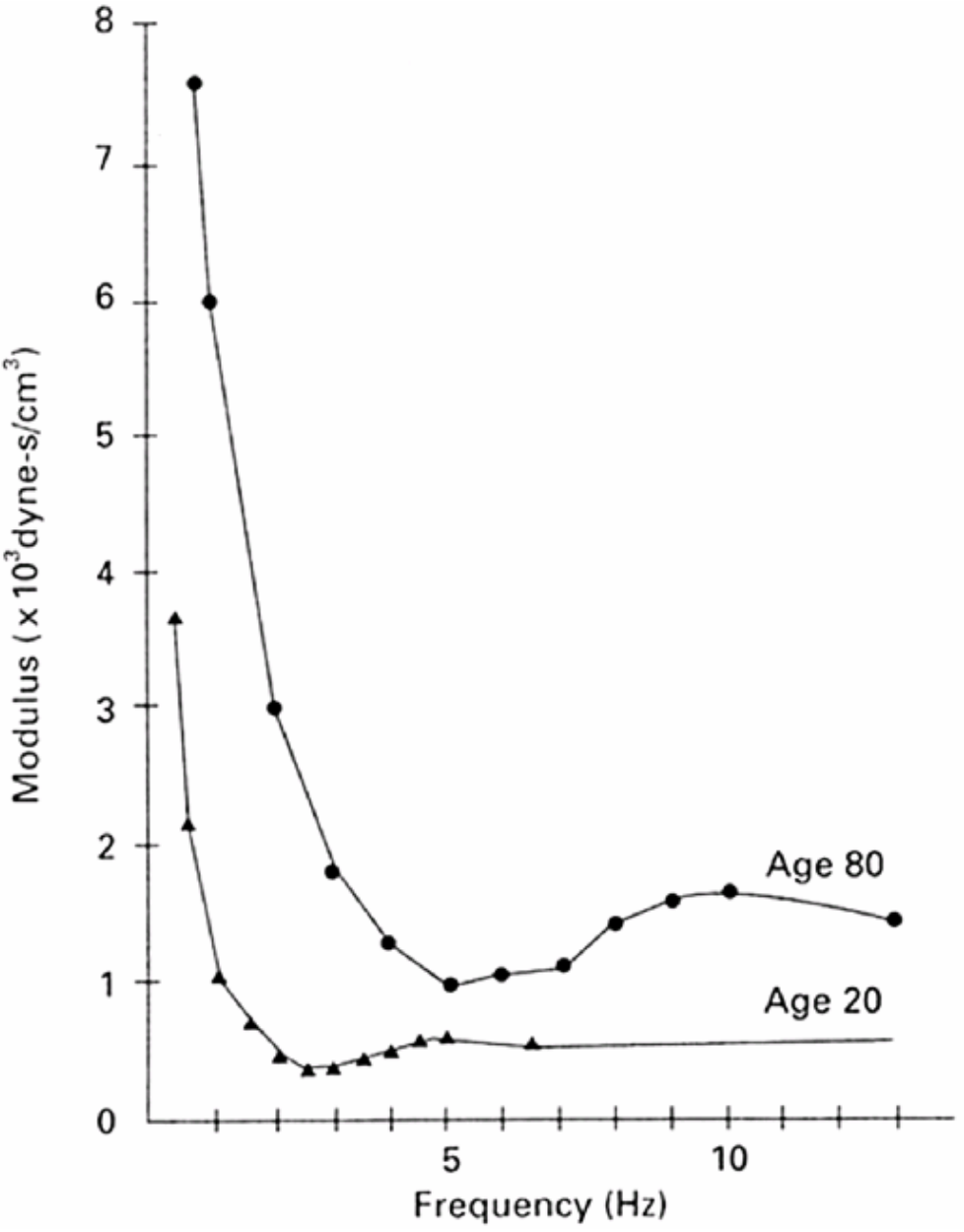


Figure 10 Alterations in ascending aortic impedance modulus with aging in humans (Nichols and O'Rourke 2005)

2.6.6 Brachial artery pressure

As the large elastic arteries stiffen and dilate with aging, systolic arterial pressure increases, diastolic arterial pressure decreases, and pulse pressure increases (Avolio, Chen

et al. 1983; Avolio, Deng et al. 1985; Nichols, Nicolini et al. 1992; Franklin, Gustin et al. 1997; Lakatta and Levy 2003a; O'Rourke and Nichols 2005).

There is a progressive increase in brachial artery systolic arterial pressure from age 30 (Kannel, Gordon et al. 1971; Kannel, Dawber et al. 1980; Kannel, Wolf et al. 1981; Burt, Whelton et al. 1995; Franklin, Gustin et al. 1997). In contrast, brachial artery diastolic pressure rises until 50 years of age then progressively declines. With the increase in systolic pressure and decrease in diastolic pressure, there is a progressive increase in brachial artery pulse pressure with aging.

Measurement of brachial artery pressure, however, underestimates the rise in aortic systolic and pulse pressure, and the increase in ventricular load with age (Nichols and O'Rourke 1998; Vlachopoulos and O'Rourke 2000).

Hypertension is a common cardiovascular condition that affects approximately 50 million patients in the United States and up to 1 billion patients worldwide (Burt, Whelton et al. 1995; Chobanian, Bakris et al. 2003). There is an age-related increase in the prevalence and incidence of hypertension that primarily results from the increase in systolic pressure with aging (Burt, Whelton et al. 1995; Franklin, Gustin et al. 1997).

Isolated systolic hypertension is defined as systolic pressure greater than or equal to 140mmHg with a diastolic pressure of less than 90mmHg (Chobanian, Bakris et al. 2003). Isolated systolic hypertension is the commonest form of hypertension in the elderly and worsens with increasing age (Franklin, Jacobs et al. 2001a). The rise in systolic blood pressure and pulse pressure with age has generally been regarded as benign until recent times (Black 2004). Epidemiologic studies and clinical trials have showed that systolic pressure is a more accurate predictor of cardiovascular risk than diastolic blood pressure.

The Framingham study showed that systolic pressure was a better predictor of coronary heart disease, stroke, and cardiovascular disease (Kannel, Gordon et al. 1971; Kannel, Wolf et al. 1981; Kannel 2000a; Kannel 2000b). Three clinical trials demonstrated that isolated systolic hypertension in patients 60 years or older is associated with a greater risk of heart failure, stroke, and myocardial infarction, and that treatment of isolated systolic hypertension with pharmacologic agents reduces the risk of developing these conditions (SHEP 1991; Staessen, Fagard et al. 1997; Staessen, Wang et al. 1999; Wang, Staessen et al. 2000).

A number of studies have shown that pulse pressure is a more accurate predictor of cardiovascular risk (especially coronary risk) and cerebrovascular risk than systolic pressure or diastolic pressure (Benetos, Safar et al. 1997; Mitchell, Moye et al. 1997; Benetos, Rudnichi et al. 1998; Chae, Pfeffer et al. 1999; Domanski, Davis et al. 1999; Franklin, Khan et al. 1999; Vaccarino, Holford et al. 2000; Safar 2000a; Safar, Blacher et al. 2000b; Franklin, Larson et al. 2001b; Safar, Blacher et al. 2002). Furthermore, a reduction in diastolic pressure is associated with an increased risk of coronary heart disease; possibly due to a reduction in coronary blood flow (Madhavan, Ooi et al. 1994; Benetos, Safar et al. 1997; Franklin, Khan et al. 1999; Franklin, Larson et al. 2001b).

Large artery stiffening and the increase in pulse pressure with age produce microvascular disease in the brain and kidney that results in cerebrovascular accident, dementia, and renal failure (O'Rourke and Safar 2005). The kidneys and brain are particularly susceptible to damage of their microvasculature as they are normally exposed to high volume pulsatile flow (O'Rourke and Safar 2005). Loss of the cushioning function of the aorta and large elastic arteries exposes they microvasculature of these organs to

increased cyclic stress and the development of microvascular disease (O'Rourke and Safar 2005).

2.6.7 Cardiac structure and function

There are a number of changes in cardiac structure and function with aging, and these changes are largely attributable to stiffening and dilatation of the large elastic arteries and the consequent increase in left ventricular afterload (Nichols, O'Rourke et al. 1985; Lakatta, Gerstenblith et al. 1997; Nichols and O'Rourke 1998; Lakatta and Boluyt 2000; Lakatta and Levy 2003a; Lakatta and Levy 2003b).

2.6.8 Cardiac structure

There is a decrease in the number of myocardial cells with aging, with hypertrophy of remaining myocardial cells (Olivetti, Melissari et al. 1991). As a result of myocardial cell hypertrophy, there is a preservation or increase of left ventricular mass with aging (Gerstenblith, Frederiksen et al. 1977; Gardin, Savage et al. 1987; Pearson, Gudipati et al. 1991a). There is an increase in the amount of myocardial collagen and in the fibrous connective tissue matrix with aging (Lakatta and Levy 2003b).

2.6.9 Left ventricular diastolic function

There is a progressive reduction in the early left ventricular diastolic filling rate with aging (Schulman, Lakatta et al. 1992; Swinne, Shapiro et al. 1992; Villari, Vassalli et al. 1997; Schulman 1999). Despite the reduction in early left ventricular diastolic filling, the left ventricular end-diastolic volume index is maintained with aging at rest, as there is

increased filling in late diastole (Lakatta and Levy 2003b). Enlargement and hypertrophy of the left atrium with aging helps maintain left ventricular filling (Lakatta and Levy 2003b).

Factors contributing to the reduction in early left ventricular diastolic filling include the prolongation of the relaxation phase of cardiac muscle, and the increase in myocardial stiffness due to hypertrophy and fibrosis (Lakatta, Gerstenblith et al. 1975; Weber, Anversa et al. 1992; Nichols and O'Rourke 1998; Lakatta and Levy 2003a; Lakatta and Levy 2003b).

2.6.10 Left ventricular systolic function

Left ventricular ejection fraction (and systolic function) at rest is preserved with aging (Fleg, O'Connor et al. 1995; Nichols and O'Rourke 1998; Lakatta and Levy 2003b).

2.6.11 Heart rate and cardiac output

There is no alteration in heart rate at rest (in the supine position) with aging (Fleg, O'Connor et al. 1995; Lakatta and Levy 2003b). Resting cardiac index and stroke volume are unchanged or reduced with aging.

2.6.12 Exercise

There is a marked decline in cardiovascular function during exercise with aging in normal subjects (Fleg, Schulman et al. 1993; Vaitkevicius, Fleg et al. 1993; Fleg, O'Connor et al. 1995; Lakatta, Gerstenblith et al. 1997; Lakatta and Boluyt 2000; Hundley, Kitzman et al. 2001; Lakatta and Levy 2003a; Lakatta and Levy 2003b). There is a decline in maximal oxygen consumption, maximal cardiac output, maximal heart rate and ejection fraction during exhaustive exercise in the elderly. The decline in maximal cardiac output is

secondary to the decline in maximal heart rate, as the stroke volume ejected during exercise is unchanged with aging (Lakatta and Boluyt 2000; Lakatta and Levy 2003b).

2.6.13 B adrenergic stimulation

There is a decline in the responsiveness of the cardiovascular system to β-adrenergic stimulation with aging i.e. there is a reduction in the inotropic, chronotropic, and vasodilator response to β-adrenergic stimulation (Lakatta and Boluyt 2000). This is largely due to a decline in the efficiency of post-synaptic β-adrenergic stimulation with aging (Lakatta and Boluyt 2000; Lakatta and Levy 2003b).

2.6.14 Left ventricular load and ventricular-vascular interaction

Stiffening and dilatation of the large elastic arteries with aging produces a progressive increase in left ventricular load, increased left ventricular myocardial oxygen demand, and ultimately left ventricular failure (Nichols, O'Rourke et al. 1986; O'Rourke, Avolio et al. 1986; Katz 1990; Girerd, Laurent et al. 1991; Kelly, Tunin et al. 1992; Westerhof and O'Rourke 1995; Katz 1998; Nichols and O'Rourke 1998). The effects of aging on the large elastic arteries are largely responsible for the development of isolated systolic hypertension, left ventricular hypertrophy and ultimately left ventricular failure in the elderly (Merillon, Motte et al. 1982a; Merillon, Motte et al. 1982b; Nichols, O'Rourke et al. 1985; O'Rourke, Avolio et al. 1986; Girerd, Laurent et al. 1991; Nichols, Nicolini et al. 1992; Westerhof and O'Rourke 1995; Nichols and O'Rourke 1998; Chae, Pfeffer et al. 1999; Hundley, Kitzman et al. 2001; Morita, Asou et al. 2002).

Changes in ascending aortic impedance show that there is a progressive deterioration in ventricular-vascular interaction with aging (Nichols, O'Rourke et al. 1985;

O'Rourke, Avolio et al. 1986; Westerhof and O'Rourke 1995; Nichols and O'Rourke 1998; O'Rourke and Nichols 2005). With aging, the peak energy of the left ventricular ejection wave occurs at frequencies where the ascending aortic impedance modulus is high. The deterioration in ventricular-vascular interaction is also illustrated by the progressive augmentation of ascending aortic and left ventricular systolic pressure with aging (O'Rourke, Avolio et al. 1986; Westerhof and O'Rourke 1995; Nichols and O'Rourke 1998). Measurement of brachial artery systolic and pulse pressure underestimates the change in central arterial pressure and the decline in ventricular-vascular interaction with age (Franklin, Gustin et al. 1997; Nichols and O'Rourke 1998; Vlachopoulos and O'Rourke 2000; O'Rourke and Nichols 2005).

2.7 HEART FAILURE

Heart failure dramatically increases in prevalence with aging (Kannel and Belanger 1991; Ho, Pinsky et al. 1993; AHA 2005). The pathogenesis of heart failure in the elderly is multifactorial; however, the adverse effects of aging on the cardiovascular system are central to the development of heart failure in the elderly.

Stiffening of the aorta and large elastic arteries produces isolated systolic hypertension and a chronic increase in left ventricular load, resulting in left ventricular hypertrophy, interstitial fibrosis, relative coronary insufficiency, and exacerbation of coronary artery disease (Nichols, O'Rourke et al. 1986; Nichols, Nicolini et al. 1992; Watanabe, Ohtsuka et al. 1993; Ohtsuka, Kakihana et al. 1994; Westerhof and O'Rourke 1995; Kass, Saeki et al. 1996; Nichols and O'Rourke 1998; Franklin, Khan et al. 1999; Morita, Asou et al. 2002; Lakatta and Levy 2003a; Lakatta and Levy 2003b; Safar and Smulyan 2004; Weber, Auer et al. 2004). These changes may be superimposed on other

causes of heart failure in the elderly e.g. valvular heart disease (Lakatta and Levy 2003a; Lakatta and Levy 2003b). The link between increased cardiac load and the development of heart failure has been described by Katz (1990; 1998).

2.7.1 Definition

Heart failure may be defined as the pathophysiologic state where the cardiac output is not sufficient to meet the metabolic needs of the organs and tissues of the body (Colucci and Braunwald 2001). Heart failure may result from an abnormality of systolic function where there is an impairment to ventricular ejection of blood (systolic dysfunction), or from an abnormality of diastolic function where there is an impairment to ventricular filling (diastolic dysfunction) (Gaasch 1994; Colucci and Braunwald 2001; Hunt, Abraham et al. 2005). Systolic dysfunction and diastolic dysfunction commonly coexist in patients with heart failure.

2.7.2 Epidemiology

Heart failure is a major public health issue in western industrialised nations such as the United States and Australia (Braunwald 1997). There are about 5 million patients with heart failure in the United States, with about new 550,000 patients each year (AHA 2005). The number of heart failure patients in Australia has been estimated at 300,000, with about 30,000 new cases being diagnosed annually (NHF/CSANZ 2002).

Heart failure is primarily a disease of the elderly, with the prevalence of heart failure rising with aging (Kannel, Castelli et al. 1972; Lloyd-Jones, Larson et al. 2002). In the United States, heart failure occurs in 1-2% of people aged 45-50 years; 2-6% of people aged 55-64; 4-6% of people aged 65-74; and 10% of people aged 75 years or more (AHA

2005). In the United States, approximately 80% of patients hospitalised with heart failure are aged 65 years or older (Haldeman, Croft et al. 1999).

In the United States, heart failure is responsible for 6.5 million hospital days each year, and is the leading cause of admission and readmission in patients aged 65 years or older (Gooding and Jette 1985; Massie and Shah 1997; Rich and Nease 1999; Jessup and Brozena 2003). In 2002 heart failure accounted for approximately one million hospital discharges in the United States (AHA 2005). In 2001 and 2002, heart failure was the principle diagnosis in 41,878 hospital admissions in Australia, and accounted for 0.7% of all admissions (AIHW 2004). Patients aged 70 years or older accounted for over two thirds of all hospitalizations for heart failure in Australia (AIHW 2004).

The economic burden of treating heart failure in Western industrialised countries is considerable. In the United States, the total estimated cost of treating heart failure in 2005 is approximately 27.9 billion U.S. dollars (AHA 2005).

Heart failure is a significant cause of morbidity and mortality. Approximately 265,000 patients die each year from heart failure in the United States with heart failure as a primary or contributing cause (AHA 2005). During 2001/2, heart failure contributed to 2% of all deaths in Australia (AIHW 2004).

Heart failure is the only cardiovascular disorder that is increasing in incidence and prevalence in western industrialised countries (AIHW 2004; AHA 2005). The incidence of heart failure is expected to rise markedly in the future due to aging of the population and improved survival of patients with cardiovascular diseases (hypertension and coronary artery disease) (Kelly 1997; Chobanian, Bakris et al. 2003).

2.7.3 Systolic dysfunction and diastolic dysfunction

Left ventricular failure may result from systolic dysfunction or diastolic dysfunction (Levy, Larson et al. 1996; Hunt, Abraham et al. 2005). Left ventricular systolic dysfunction occurs when there is a reduction in left ventricular ejection secondary to impaired myocardial contractility (Little 2001; NHF/CSANZ 2002; Bristow and Lowes 2005; Hunt, Abraham et al. 2005; Zile, Baicu et al. 2005). A left ventricular ejection fraction of 0.45 or less is usually indicative of impaired left ventricular systolic function (Little 2001).

In systolic heart failure, the left ventricle is dilated with a rightward shift of its pressure-volume relation and a decrease in the slope of the ESPVR (Zile and Brutsaert 2002; Gaasch and Zile 2004). The diastolic portion of the pressure-volume loop lies along the same diastolic pressure-volume relation i.e. there is no change in the stiffness of the left ventricle (Zile and Brutsaert 2002; Gaasch and Zile 2004).

Left ventricular diastolic dysfunction occurs when there is a reduction in left ventricular diastolic filling at normal diastolic pressures, despite normal ventricular contraction (Zile and Brutsaert 2002). Left ventricular diastolic dysfunction may result from increased myocardial stiffness and/or impaired ventricular relaxation (Zile and Brutsaert 2002). The diagnosis of diastolic heart failure is based on clinical evidence of heart failure in a patient with a normal left ventricular ejection fraction with no echocardiographic features of valvular disease (Zile and Brutsaert 2002; Gaasch and Zile 2004; Hunt, Abraham et al. 2005).

In diastolic heart failure, there is an upward and leftward shift of the diastolic pressure-volume relation of the left ventricle so that a higher diastolic pressure is required to achieve the same diastolic volume (Zile and Brutsaert 2002; Gaasch and Zile 2004).

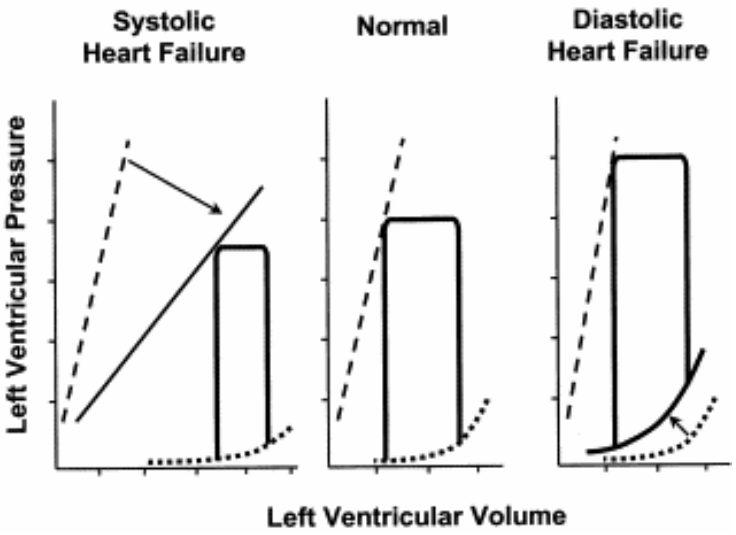


Figure 11 Left ventricular pressure volume loops in patients with systolic heart failure, normal patients, and patients with diastolic heart failure (Zile, Baicu et al. 2005).

2.7.4 Aetiology of heart failure

The fundamental cause of heart failure in the elderly is stiffening of the large elastic arteries and the consequent isolated systolic hypertension and increase in left ventricular load (Nichols, O'Rourke et al. 1985; O'Rourke, Avolio et al. 1986; Westerhof and O'Rourke 1995; Nichols and O'Rourke 2005). Hypertension is the most common antecedent of heart failure (Kannel, Castelli et al. 1972; Levy, Larson et al. 1996). In the Framingham heart study, 91% of people that developed heart failure had a history of hypertension (Levy, Larson et al. 1996).

Arterial stiffening and isolated systolic hypertension, increase left ventricular load to produce left ventricular hypertrophy and diastolic dysfunction (Girerd, Laurent et al. 1991; Levy, Larson et al. 1996; Vasan and Levy 1996; Hundley, Kitzman et al. 2001; Morita, Asou et al. 2002; Kawaguchi, Hay et al. 2003).

Hypertension is also an important risk factor for coronary artery disease (Kannel, Gordon et al. 1971; Stamler, Stamler et al. 1993; Kannel 1996; Benetos, Safar et al. 1997; Franklin, Khan et al. 1999; Franklin, Larson et al. 2001b). Isolated systolic hypertension and increased ventricular load act to increase myocardial oxygen demand, reduce coronary blood flow reserve, and also accelerate coronary artery disease to produce systolic dysfunction (Marcus, Harrison et al. 1987; Houghton, Carr et al. 1992; Kelly, Tunin et al. 1992; Watanabe, Ohtsuka et al. 1993; Ohtsuka, Kakihana et al. 1994; Kass, Saeki et al. 1996; Benetos, Safar et al. 1997; Franklin, Khan et al. 1999; Safar and Smulyan 2004).

2.7.5 Aetiology of systolic dysfunction

Coronary artery disease (ischaemic heart disease and prior myocardial infarction) is the principle cause of systolic dysfunction and accounts for approximately two-thirds of patients with systolic dysfunction (NHF/CSANZ 2002; Gheorghiade and Bonow 2004). Hypertension is an important risk factor for coronary atherosclerosis and coronary events (Kannel, Gordon et al. 1971; Marcus, Harrison et al. 1987; Houghton, Carr et al. 1992; Stamler, Stamler et al. 1993; Kannel 1996; Benetos, Safar et al. 1997; Franklin, Khan et al. 1999; Franklin, Larson et al. 2001b).

Relative coronary insufficiency, myocardial ischaemia, and myocardial infarction are complications of coronary artery disease that are exacerbated by isolated systolic hypertension and increased left ventricular load secondary to aortic stiffening (Watanabe, Ohtsuka et al. 1993; Kass, Saeki et al. 1996; Franklin, Khan et al. 1999; Nishijima, Nakayama et al. 2001; Safar and Smulyan 2004; Weber, Auer et al. 2004).

Less common causes of systolic dysfunction include valvular heart disease, alcoholic cardiomyopathy, inflammatory cardiomyopathy, chronic arrhythmia, drug-

induced cardiomyopathy, and non-ischaemic idiopathic dilated cardiomyopathy (NHF/CSANZ 2002).

2.7.6 Aetiology of diastolic dysfunction

The Framingham and Olmsted County studies indicate that about half of the patients with heart failure had predominantly diastolic dysfunction (Senni, Tribouilloy et al. 1998; Vasan, Larson et al. 1999). The prevalence of diastolic dysfunction increase with aging, and the alterations in the cardiovascular system with aging are central to the pathogenesis of diastolic dysfunction (Brutsaert, Sys et al. 1993; Vasan, Benjamin et al. 1995b; Senni, Tribouilloy et al. 1998; Lakatta and Boluyt 2000; Gottdiener, McClelland et al. 2002; Zile and Brutsaert 2002; Lakatta and Levy 2003a; Lakatta and Levy 2003b).

Hypertension is the most common risk factor for diastolic dysfunction (Levy, Larson et al. 1996; Vasan and Levy 1996; Kitzman 2002; NHF/CSANZ 2002). Isolated systolic hypertension increases left ventricular load, to produce left ventricular hypertrophy and an increase in myocardial connective tissue to produce diastolic dysfunction (Gerstenblith, Frederiksen et al. 1977; Olivetti, Melissari et al. 1991; Pearson, Gudipati et al. 1991b; Hundley, Kitzman et al. 2001; Kawaguchi, Hay et al. 2003). Aortic stiffening and isolated systolic hypertension produce abnormalities in ventricular relaxation and diastolic filling that contribute to diastolic dysfunction (Pearson, Gudipati et al. 1991b; Leite-Moreira, Correia-Pinto et al. 1999).

Coronary artery disease is less common in patients with diastolic dysfunction than systolic dysfunction, but produces diastolic dysfunction through ventricular remodelling and myocardial fibrosis that follow myocardial infarction (Mirsky, Cohn et al. 1974; Vasan and Levy 1996).

Less common causes of diastolic dysfunction include valvular heart disease (especially aortic stenosis), hypertrophic cardiomyopathy, and restrictive cardiomyopathy (idiopathic or secondary to infiltrative disease) (Vasan and Levy 1996; NHF/CSANZ 2002).

2.7.7 Pathophysiology of left ventricular dysfunction

Left ventricular dysfunction is a progressive disorder that is initiated by injury to the myocardium and/or by an abnormal haemodynamic load (NHF/CSANZ 2002; Hunt, Abraham et al. 2005). In response to compromised ventricular function, a number of adaptive responses are activated to maintain cardiac function. These include activation of the Frank-Starling mechanism, activation of neurohumoral systems, and alterations in myocardial structure and geometry (ventricular remodelling) (Schrier and Abraham 1999; Colucci and Braunwald 2001; NHF/CSANZ 2002). The ability of these compensatory mechanisms to maintain cardiac function is limited, and when maintained chronically, these compensatory mechanisms become detrimental and contribute to cardiac failure (Colucci and Braunwald 2001; NHF/CSANZ 2002; Hunt, Abraham et al. 2005).

2.7.8 Ventricular remodelling

Remodelling is a progressive process that attempts to decrease ventricular wall stress by increasing ventricular wall thickness (left ventricular hypertrophy) (Cohn, Ferrari et al. 2000). According to the Law of LaPlace, the left ventricular pressure and geometry (radius and wall thickness) determine the stress in the left ventricular wall (see section 2.4.13 Myocardial wall tension). Left ventricular hypertrophy develops in a morphologic pattern that reduces ventricular wall stress towards normal (Colucci and Braunwald 2001).

The morphologic pattern of remodelling is dependant on the nature of the abnormal haemodynamic load i.e. whether it is predominantly a pressure load or volume load (Grossman, Jones et al. 1975). Chronic pressure overload most commonly occurs in patients with hypertension and aortic stenosis and produces concentric left ventricular hypertrophy (with an increase in the ratio of wall thickness/radius) (Lorell and Carabello 2000). Chronic volume overload is a common consequence of aortic or mitral incompetence and produces eccentric ventricular hypertrophy (cavity dilatation with a decrease in the ratio of wall thickness/chamber dimension) (Lorell and Carabello 2000).

Left ventricular hypertrophy is an independent risk factor for cardiovascular morbidity and mortality (Levy, Garrison et al. 1990; Haider, Larson et al. 1998). Left ventricular hypertrophy is associated with increased myocardial oxygen demand, reduced coronary blood flow reserve, and myocardial ischaemia even in the absence of significant coronary artery disease (Kozakova, Palombo et al. 1997; Kozakova, Galetta et al. 2000). Ventricular dilatation may be complicated by the development of mitral regurgitation (secondary to enlargement of the mitral valve annulus) and arrhythmias that further impair cardiac function (Boltwood, Tei et al. 1983; Wilson, Schwartz et al. 1983; Maskin, Siskind et al. 1984; Kono, Sabbah et al. 1992; Hunt, Abraham et al. 2005). Chronic elevation of left ventricular filling pressure results in increasing left atrial pressure followed by atrial dilatation and atrial fibrillation (Ravelli and Allessie 1997; Maisel and Stevenson 2003; Cha, Redfield et al. 2004).

A ventricle subjected to an abnormal haemodynamic load may fail to maintain compensation and heart failure may supervene. Treatment of hypertension limits left ventricular hypertrophy, reduces coronary heart disease events, and reduces heart failure.

(Dahlof, Lindholm et al. 1991; SHEP 1991; Devereux, Agabiti-Rosei et al. 1996; Kostis, Davis et al. 1997).

2.7.9 Left ventricular load

In systolic heart failure the ventricle acts as a pressure source where ventricular ejection is dependant on the pressure generated (afterload) (Westerhof and O'Rourke 1995). Large increases in ventricular ejection result from small decreases in pressure generated. The dependency of ventricular ejection on afterload explains the efficacy of afterload reduction in systolic heart failure (see Section 2.7.13).

The dependence of ventricular ejection on pressure generated in systolic heart failure has been illustrated through the use of pressure volume loops and pump function curves (Westerhof and O'Rourke 1995; Zile and Brutsaert 2002).

2.7.10 Symptoms and signs

Symptoms of heart failure include exertional dyspnoea, orthopnea, paroxysmal nocturnal dyspnoea, cough, fatigue, weakness, peripheral oedema, and symptoms of right heart failure (abdominal pain, anorexia, nausea) (NHF/CSANZ 2002).

Clinical examination may be unremarkable or reveal tachypnea, elevation of the jugular venous pulse, lateral displacement of the apex beat, basal lung crepitations, hepatomegaly, peripheral oedema, and auscultatory evidence of valvular disease (NHF/CSANZ 2002).

Patients with evidence of cardiac remodelling may be asymptomatic for long periods prior to the development of symptoms (Hunt, Abraham et al. 2005). Furthermore,

there is often no relationship between the severity of symptoms and severity of impairment (Wilson, Rayos et al. 1995; Wilson, Hanamanthu et al. 1999).

2.7.11 Classification

Heart failure patients are classified based on the severity of symptoms using the New York heart association (NYHA) grading system (NHF/CSANZ 2002; Hunt, Abraham et al. 2005). The NYHA classification however is limited in that it is a subjective assessment that does not account for risk factors and structural abnormalities that predispose to heart failure.

The American College of Cardiology and the American Heart Association have developed a new staging system that emphasizes the progressive nature of the disease (Hunt, Abraham et al. 2005). Heart failure is a progressive disorder that begins with established risk factors and structural abnormalities (such as aortic stiffening and dilatation) and progresses to more advanced stages. Treatment at an early stage may be used to prevent the development, or delay the progression of heart failure (Arnold, Yusuf et al. 2003; Hunt, Abraham et al. 2005).

2.7.12 Diagnosis

Symptoms and signs of heart failure lack sensitivity and specificity and are not sufficient to make a diagnosis in the absence of imaging (NHF/CSANZ 2002; Hunt, Abraham et al. 2005). The most useful investigation for the diagnosis of heart failure is echocardiography (Hunt, Abraham et al. 2005). Echocardiography distinguishes between systolic and diastolic dysfunction, identifies structural abnormalities producing or contributing to heart failure (e.g. valvular disease), and quantifies the severity of systolic

functional impairment (NHF/CSANZ 2002; Hunt, Abraham et al. 2005). Other useful investigations include chest radiography, electrocardiography, coronary angiography and cardiac catheterisation, Radionuclide ventriculography and endomyocardial biopsy (NHF/CSANZ 2002; Hunt, Abraham et al. 2005).

2.7.13 Pharmacologic treatment of chronic heart failure

A number of pharmacologic agents with differing mechanisms of action are currently used for the treatment of chronic heart failure (Hunt, Abraham et al. 2005). These include:

1. Agents that inhibit activated neurohumoral systems (the renin angiotensin system and the adrenergic system).
2. Vasodilators (hydralazine and nitrates)
3. Diuretics.
4. Digitalis

Most large clinical trials of pharmacologic agents of heart failure have been conducted in patients with systolic heart failure, however; clinical trials in patients with diastolic heart failure are now being undertaken (Cleland, Tendera et al. 1999; Swedberg, Pfeffer et al. 1999; Yusuf, Pfeffer et al. 2003; Hunt, Abraham et al. 2005).

The reduction of left ventricular load is the most effective way to treat heart failure as evidenced from vasodilating agents when central aortic pressure is considered (Nichols and O'Rourke 2005). Both systolic heart failure and diastolic dysfunction benefit from reduction in left ventricular load. The effectiveness of load reduction in systolic heart failure is based on the fact that the left ventricle acts as pressure source in systolic dysfunction and that small reductions in load may produce large increases in ventricular

ejection (Westerhof and O'Rourke 1995). Load reduction is also beneficial in diastolic heart failure as the reduction of left ventricular load is associated with earlier and more complete ventricular relaxation and regression of left ventricular hypertrophy (Gillebert, Leite-Moreira et al. 1997; Klingbeil, Schneider et al. 2003).

The effectiveness of vasodilating agents in heart failure results from a reduction in the amplitude of the reflected wave, as well as a delay in return of the reflected wave from the periphery (Westerhof and O'Rourke 1995; Safar and London 2000; Nichols and O'Rourke 2005; Pauca, Kon et al. 2005).

Neurohumoral inhibitors

Activation of the renin-angiotensin and adrenergic systems are compensatory responses to heart failure that are deleterious in the long term (Eichhorn and Bristow 1996; Colucci and Braunwald 2001). Clinical trials have shown that pharmacologic agents that inhibit the renin-angiotensin and adrenergic systems improve the natural history of heart failure (see below).

Inhibition of the renin-angiotensin system

The renin-angiotensin system is chronically activated in patients with chronic heart failure (Francis, Goldsmith et al. 1984; Eichhorn and Bristow 1996). Angiotensin II is the product of activation of this system, and its physiologic effects contribute to the progression of heart failure. These effects include vasoconstriction, sodium retention, myocyte hypertrophy, myocardial and vascular fibroblast proliferation, and myocyte apoptosis (Ooi and Colussi 2001; Mann 2004).

The renin-angiotensin system may be inhibited at the level of conversion of Angiotensin I to Angiotensin II, and by antagonism of Angiotensin II receptors. Angiotensin converting enzyme (ACE) is a nonspecific dipeptidase that converts inactive Angiotensin I to active Angiotensin II, as well as inactivating bradykinin (Ooi and Colussi 2001; Mann 2004).

ACE inhibitors act by inhibiting ACE and produce a reduction in plasma and tissue levels of angiotensin II, as well as increased plasma and tissue levels of bradykinin. ACE inhibitors only produce partial inhibition of angiotensin II production as alternate enzyme pathways also generate angiotensin II in humans (e.g. chymase) (Ooi and Colussi 2001; Mann 2004).

There are a number of receptors that bind angiotensin II, and these include the angiotensin 1 and angiotensin 2 receptors. Most of the adverse effects of angiotensin II in heart failure are mediated by the angiotensin 1 receptor. Angiotensin receptor blockers (ARBs) are high affinity antagonists of AT1 receptors (Ooi and Colussi 2001; Mann 2004).

Beneficial effects of ACE inhibitors and ARBs in heart failure

ACE inhibitors and ARBs counter the detrimental effects of activation of the renin-angiotensin system in heart failure (Eichhorn and Bristow 1996). Clinical studies of ACE inhibitors and ARBs show benefits that cannot be readily explained using conventional measures of arterial pressure in the upper limb (Yusuf, Sleight et al. 2000; Dahlof, Devereux et al. 2002). The beneficial benefits of ACE inhibitors and ARBs on ventricular remodelling and clinical outcome have therefore been attributed to inhibition of the direct effects of angiotensin II on the myocardium (Mann 2004; Bristow, Linas et al. 2005).

Whilst the beneficial effects of ACE inhibitors and ARBs may result partly from direct effects on the myocardium, their most significant beneficial effect has a haemodynamic basis; a reduction in ventricular load. The reduction in ventricular load resulting from arterial dilatation produced by vasodilators (including ACE inhibitors, ARBs, nitrates, and vasodilating beta-blockers) is underestimated by conventional clinical measurement of brachial arterial pressure using the cuff sphygmomanometer (Kelly, Gibbs et al. 1990; London, Asmar et al. 2004; Hirata, Vlachopoulos et al. 2005). Measurement of central aortic pressure shows larger reductions in left ventricular load produced by these agents.

ACE inhibitors (and other vasodilators) act by producing vasodilation of peripheral arteries, a delay in the reflection of the pressure wave, and a reduction in systolic augmentation of ascending aortic pressure by the reflected pressure wave (Yaginuma, Avolio et al. 1986; Kelly, Gibbs et al. 1990; Chen, Ting et al. 1995; Ting, Chen et al. 1995; Jiang, O'Rourke et al. 2002; London, Asmar et al. 2004; Hirata, Vlachopoulos et al. 2005; Nichols and O'Rourke 2005; Pauca, Kon et al. 2005). Afterload reduction is therefore the major beneficial effect of ACE inhibitors and ARBs in the treatment of heart failure.

Clinical effects of ACE inhibitors in heart failure

ACE inhibitors are the most effective pharmacologic agents for the treatment of heart failure (Hunt, Abraham et al. 2005). Large scale clinical trials in patients with systolic heart failure have demonstrated the effectiveness of ACE inhibitors in patients with heart failure. ACE inhibitors have been shown to prolong survival, decrease hospitalisation, improve functional class and exercise capacity in symptomatic heart failure patients (CONSENSUS 1987; Cohn, Johnson et al. 1991; SOLVD 1991; SOLVD 1992).ACE

inhibitors prevents or reverses progressive left ventricular remodelling and increases ejection fraction in patients with asymptomatic or symptomatic systolic heart failure (Konstam, Rousseau et al. 1992; Konstam, Kronenberg et al. 1993).

ACE inhibitors reduce mortality and reduce left ventricular dilatation in patients with systolic heart failure following myocardial infarction (Pfeffer, Braunwald et al. 1992; St. John Sutton, Pfeffer et al. 1994; Cleland, Erhardt et al. 1997).

ACE inhibitors have been shown to reduce the risk of developing heart failure in patients at high risk of cardiovascular disease but without left ventricular dysfunction (Yusuf, Sleight et al. 2000; Arnold, Yusuf et al. 2003).

Clinical effects of ARBs in heart failure

ARBs are as effective as ACE inhibitors in reducing mortality in patients with heart failure (Pitt, Segal et al. 1997; Pitt, Poole-Wilson et al. 2000; Cohn, Tognoni et al. 2001; Granger, McMurray et al. 2003). ARBs prolong survival, reduce hospitalisation, improve exercise capacity and symptoms, reduce ventricular volumes, and increase left ventricular ejection fraction in heart failure patients (Lang, Elkayam et al. 1997; Pitt, Poole-Wilson et al. 2000; Cohn, Tognoni et al. 2001; Wong, Staszewsky et al. 2002).

In patients with impaired left ventricular function post myocardial infarction, ARBs are as effective in reducing mortality as ACE inhibitors (Pfeffer, McMurray et al. 2003).

Beta-blockers

Beta-blockers inhibit the chronic activation of the adrenergic system that occurs in heart failure (Eichhorn and Bristow 1996; Bristow 2000; Colucci and Braunwald 2001). Beta blockers have diverse pharmacologic effects; however, they are all competitive

antagonists of the beta 1 adrenergic receptors. Only the second generation beta-1 selective beta-blockers or the third generation vasodilator beta-blockers are useful for the treatment of heart failure (Eichhorn and Bristow 1997; Bristow 2000).

Both second and third generation beta blockers improve ventricular function, reduce myocardial oxygen demand and wall tension, and reverse ventricular remodelling after an initial period of myocardial depression (Eichhorn and Bristow 1996). The beneficial effects may take months to develop.

Clinical effects of beta blockers in heart failure

Large clinical trials have shown that three beta blockers have been shown to reduce total mortality in patients with mild to moderate heart failure already receiving ACE inhibitors:

1. Carvedilol (beta-1, beta-2, and alpha-1 antagonist) (Packer, Bristow et al. 1996)
2. Bisoprolol (beta-1 selective antagonist) (CIBIS-II 1999)
3. Metoprolol extended release (beta-1 selective antagonist) (MERIT-HF 1999)

Carvedilol also improves survival in patients with severe heart failure (ejection fraction less than 25% and moderate to severe symptoms) (Packer, Coats et al. 2001). The beneficial effects and increased tolerability of carvedilol in patients with advanced heart failure may result from its vasodilating properties (Bristow 2000). In patients with left ventricular dysfunction following myocardial infarction, carvedilol reduces mortality and recurrence of myocardial infarction (CAPRICORN 2001).

Metoprolol CR/XL, bisoprolol, and carvedilol also reduce hospitalisation and improve symptoms in patients with heart failure (Packer, Bristow et al. 1996; CIBIS-II 1999; MERIT-HF 1999; Packer, Coats et al. 2001).

Limitations of pharmacologic treatment of heart failure

Pharmacologic agents such as ACE inhibitors, ARBs, beta blockers, and vasodilators have been effective in reducing mortality in patients with heart failure (Levy, Kenchaiah et al. 2002; Roger, Weston et al. 2004). In the Framingham study, 1-year and 5-year mortality declined from 30% to 28%, and 70% to 59%, respectively in males (Levy, Kenchaiah et al. 2002). In the Olmsted County study, 1-year mortality and 5-year mortality declined from 30% to 21%, and 65% to 50% in males(Roger, Weston et al. 2004). Despite the improvement in survival produced by these agents, the prognosis for patients with heart failure remains poor (Levy, Kenchaiah et al. 2002; Roger, Weston et al. 2004). Furthermore, it seems that pharmacologic agents have reached their therapeutic limit with newer pharmacologic agents failing to produce improved survival (Bristow, Linas et al. 2005).

Afterload reduction remains the most effective treatment of heart failure and since pharmacologic agents have reached their therapeutic limit, new strategies to reduce load are currently being developed, including inhibitors of collagen cross-linking, and mechanical devices (mechanical circulatory support).

The effectiveness of ACE inhibitors in preventing the development of heart failure illustrates the importance of idea of heart failure as a progressive disease that can be arrested or delayed at an early stage through effective treatment (Yusuf, Sleight et al. 2000; Hunt, Abraham et al. 2005). Pharmacologic agents or surgical devices that treat aortic stiffening and dilatation and isolated systolic hypertension, can be expected to arrest or delay the development of heart failure in the elderly.

2.7.14 Heart transplantation

Heart transplantation is an effective treatment for advanced heart failure with 1- and 5-year survival rates of approximately 85% and 70% (AHA 2005). The use of heart transplantation is however restricted by a severe shortage of donors that limits the annual number of cases performed to only 2000 in the United States (AHA 2005). Cardiac transplantation is not available to patients aged 70 years or older, although most programs do not consider patients 65 years or older (Steinman, Becker et al. 2001). Heart transplantation is therefore not a therapeutic option for the increasing number of elderly patients with heart failure.

2.7.15 Mechanical circulatory support

Mechanical circulatory support (MCS) is a surgical treatment of severe heart failure. Mechanical methods that support the heart and circulation may be divided into those that are used in the short term and those that are used in the long term (Cohn and Edmunds 2003; Mann 2004). Short term MCS methods are used for the treatment of acute reversible heart failure, as occurs following myocardial infarction or cardiotomy. Long-term MCS methods provide long-term reduction of left ventricular load for the treatment of patients with severe heart failure.

Intra-aortic balloon pump

The IABP is the most commonly used device for short term MCS, but can also be used for longer term MCS. The IABP is an intravascular, catheter-based device with a balloon that is advanced to lie in the descending thoracic aorta between the left subclavian artery and the renal arteries (Moulopoulos, Topaz et al. 1962; Cohn and Edmunds 2003;

Mann 2004). The balloon may be inserted into the common femoral artery, iliac artery, axillary artery, or ascending thoracic aorta (Kantrowitz, Tjonneland et al. 1968; Perler, McCabe et al. 1983; McBride, Miller et al. 1989; Pinkard, Utley et al. 1993; Meyns, Nishimura et al. 2000).

Inflation and deflation of the balloon occurs rhythmically with the cardiac cycle, with inflation occurring during diastole and deflation occurring during systole (Weber and Janicki 1974; Nichols and O'Rourke 2005). The IABP indirectly supports the left ventricle by unloading the left ventricle during systole, and by augmenting coronary blood flow in diastole (Powell, Daggett et al. 1970; Weber and Janicki 1974). Balloon deflation during systole reduces ascending aortic and left ventricular pressure therefore reduces left ventricular load, left ventricular stroke work, and myocardial oxygen consumption, and increases left ventricular ejection. Balloon deflation during diastole increases ascending aortic diastolic pressure and augments coronary blood flow and myocardial oxygen supply.

The IABP is used for MCS in surgical and nonsurgical patients for the treatment of cardiogenic shock, low output heart failure, or myocardial ischaemia. Clinical indications for the insertion of an IABP include the following (Creswell, Rosenbloom et al. 1992; Kang, Edwards et al. 2001; Baskett, Ghali et al. 2002; Cohn and Edmunds 2003):

1. Myocardial ischaemia refractory to medical therapy.
2. Prophylactic placement in patients with critical coronary artery disease (usually left main) or severe left ventricular dysfunction prior to coronary artery surgery.
3. Cardiogenic shock refractory to medical therapy following myocardial infarction.
4. Intra-operative implantation in patients failing to wean from cardiopulmonary bypass.
5. Postoperative low cardiac output state unresponsive to inotropic agents.

6. Acute deterioration of myocardial function to provide short-term mechanical circulatory support (as a bridge to recovery or as a bridge to transplantation).

Absolute contraindications for the use of the IABP include aortic regurgitation and aortic dissection (Bojar 2005). Despite the effectiveness of the IABP for the treatment of heart failure and myocardial ischaemia, there are a number of limitations to its use (Kantrowitz, Wasfie et al. 1986; Mann 2004; Bojar 2005):

1. The IABP does not completely unload the failing heart, and only supports the failing heart rather than acting as a flow source.
2. The presence of cardiac arrhythmia may result in suboptimal timing of inflation and deflation of the balloon.
3. The balloon may rupture requiring urgent removal.
4. The presence of absolute contraindications precludes its use.
5. IABP use is associated with recognised complications.

Recognised complications of the IABP include limb ischaemia, infection, bleeding, cerebral embolism, stroke, paraplegia, mesenteric and renal ischaemia, aortic dissection, and thrombocytopenia (Kantrowitz, Wasfie et al. 1986; Baskett, Ghali et al. 2002; Cohn and Edmunds 2003; Bojar 2005).

Para-aortic counter-pulsation devices

A number of devices and procedures, including aortomyoplasty and para-aortic balloon counterpulsation devices have been developed to produce systolic unloading and diastolic augmentation using chronic counterpulsation (Neilson and Chiu 1986; Chachques, Grandjean et al. 1990; Pattison, Cumming et al. 1991; Cabrera Fischer, Christen et al. 1999;

Trainini, Barisani et al. 1999; Trainini, Cabrera Fischer et al. 2002; Cabrera Fischer, de Forteza et al. 2004).

Para-aortic counterpulsation devices consist of a balloon cuff placed around the ascending or descending aorta that deflates in systole and inflates in diastole. Animal and human studies have shown that deflation during systole reduces systolic pressure and afterload and inflation during diastole augments coronary blood flow (Cabrera Fischer, de Forteza et al. 2004). In aortomyoplasty the latissimus dorsi muscle is wrapped around the ascending or descending thoracic aorta and is electrically conditioned to contract in diastole and relax in systole to produce long-term counterpulsation (Neilson and Chiu 1986; Chachques, Grandjean et al. 1990; Pattison, Cumming et al. 1991; Cabrera Fischer, Christen et al. 1999; Trainini, Barisani et al. 1999; Trainini, Cabrera Fischer et al. 2002).

Both para-aortic counterpulsation and aortomyoplasty are beneficial in that they are non-blood contacting with a reduced incidence of thromboembolic complications compared to the IABP. Both techniques have a number of limitations, however, that restrict their clinical use (Neilson and Chiu 1986; Cabrera Fischer, de Forteza et al. 2004):

1. Both techniques are very invasive and require widespread dissection and implantation of foreign material that increases the risk of infection.
2. Both techniques utilise active (rather than passive) mechanisms that are prone to mechanical failure- these include the pressure generating mechanism and balloon for the para-aortic counterpulsation devices, and the muscle stimulating mechanism for aortomyoplasty.
3. Both techniques do not completely unload the failing heart, and only support the failing heart rather than acting as a flow source.

Aortomyoplasty has a number of additional limitations that have restricted its clinical use including:

1. The loss of biomechanical performance during transformation of the latissimus dorsi muscle.
2. Ischaemia of the distal latissimus dorsi
3. The delay in circulatory assistance due to conditioning
4. The relative inefficient transfer of power from muscle to the arterial system.

Clinical experience with para-aortic counterpulsation devices and aortomyoplasty is limited and both technologies should still be considered experimental.

Mechanical devices

Ventricular assist devices function by unloading the failing ventricle while maintaining cardiac output in patients with severe heart failure. They may be used to support the left ventricle and/or the right ventricle in the short or long term. Current indications for the use of ventricular assist devices include the following (Knight 1999; Anastasiadis 2003; Cohn and Edmunds 2003; Dec 2004):

1. Bridge to recovery: support of the failing ventricle until recovery occurs e.g. postcardiotomy syndrome or acute myocarditis (Farrar 2000; Acker 2001; Pennington, Smedira et al. 2001).
2. Bridge to transplantation: support of the failing ventricle and maintenance of end-organ function until a donor heart becomes available (Farrar 2000; Deng, Loebe et al. 2001; El-Banayosy, Korfer et al. 2001; Morgan, John et al. 2004).
3. Destination therapy: long term support of the failing ventricle (Rose, Gelijns et al. 2001; Dembitsky, Tector et al. 2004).

Ventricular assist devices may be broadly divided into the following categories (Knight 1999; Anastasiadis 2003; Cohn and Edmunds 2003):

1. Extracorporeal devices:

   Provide short term MCS to support the failing ventricle until recovery occurs.

   a. ABIOMED BVS 5000 (ABIOMED Cardiovascular Inc., Danvers, MA). Extracorporeal pulsatile pump providing univentricular or biventricular support and approved by the Federal Drug Administration (FDA) in the United States for postcardiotomy recovery (Jett and Lazzara 2000).

2. Implantable pulsatile devices:

   Provide long term MCS as a bridge to transplant or destination therapy.

   a. HeartMate left ventricular assist system (LVAS) (Thoratec Corporation, Pleasanton, CA). Implantable pulsatile devices providing left ventricular support and approved by the FDA as a bridge to transplant (HeartMate Implantable Pulsatile and HeartMate Vented Electric) (Morgan, John et al. 2004) and as destination therapy (HeartMate Vented Electric) (Rose, Gelijns et al. 2001; Dembitsky, Tector et al. 2004).

   b. Novacor LVAS (World Heart Corporation, Oakland, CA). Implantable pulsatile device providing left ventricular support; approved by the FDA as a bridge to transplant (Deng, Loebe et al. 2001; Robbins, Kown et al. 2001) and currently being trialed as destination therapy (FDA interventional device exemption G99288; RELIANT-Randomized Evaluation of the Novacor LVAS In A Non-Transplant Population).

3. Paracorporeal pulsatile devices:

Provide intermediate to long term MCS as a bridge to recovery or bridge to transplant.

a. Thoratec ventricular assist device (VAD) (Thoratec Laboratories Corp., Pleasanton, CA). External pulsatile device providing left, right, or bi-ventricular support and approved by the FDA for postcardiotomy recovery or as a bridge to transplant (El-Banayosy, Korfer et al. 1999; El-Banayosy, Arusoglu et al. 2000; Farrar 2000).

4. Axial flow pumps:

Provide long term MCS as a bridge to transplant or destination therapy.

a. Jarvik 2000 (Jarvik Heart Inc., New York, NY). Implantable axial flow, non-pulsatile device providing left ventricular support; currently being trialed as a bridge to transplant (Frazier, Myers et al. 2001; Frazier, Myers et al. 2002; Frazier, Myers et al. 2004).

b. MicroMed-Debakey VAD (MicrpMed Technology Inc., Houston, TX). Implantable axial flow, non-pulsatile device providing left ventricular support; currently being trialed as a bridge to transplant (Wieselthaler, Schima et al. 2000; Goldstein 2003).

c. Heartmate II LVAD (Thoratec Corporation, Pleasanton, CA). Implantable axial flow, non-pulsatile device providing left ventricular support (Griffith, Kormos et al. 2001; Frazier, Delgado et al. 2004).

5. Totally implantable devices:

Currently in preclinical or initial clinical testing.

a. Arrow LionHeart LVD-2000 (Mehta, PaeJr et al. 2001; El-Banayosy, Arusoglu et al. 2003).

b. Novacor II (World Heart Corporation, Oakland, CA) (Robbins, Kown et al. 2001).

c. VentrAssist LVAS (Ventracor Limited, Chatswood, NSW, Australia) (James, Meer et al. 2003).

6. Total artificial heart

Provide long term MCS

a. CardioWest total artificial heart (TAH) (Syncardia Systems Incorporated, Tucson, AZ). Implantable pulsatile device providing biventricular support and approved by the FDA as a bridge to transplantation (Arabia, Copeland et al. 1999; Copeland, Smith et al. 2001; Copeland, Smith et al. 2004a; Copeland, Smith et al. 2004b).

b. The AbioCor implantable replacement heart (ABIOMED Incorporated, Danvers, MA). Totally implantable pulsatile device providing biventricular support and being trialed as destination therapy (Dowling, Gray et al. 2003; Dowling, Gray et al. 2004; Samuels, Holmes et al. 2005).

Ventricular assist devices, ventricular assist systems, and total artificial hearts are effective as a bridge to transplantation in patients with severe, end-stage heat failure (El-Banayosy, Korfer et al. 1999; El-Banayosy, Arusoglu et al. 2000; Deng, Loebe et al. 2001; Robbins, Kown et al. 2001; Morgan, John et al. 2004; Copeland, Smith et al. 2004a; Copeland, Smith et al. 2004b). The REMATCH trial established the superiority of mechanical devices to medical management for the treatment of end-stage heart failure, and these devices are currently being used or trialed for destination therapy (Dembitsky, Tector et al. 2004; Dowling, Gray et al. 2004). Despite these successes, mechanical devices have a number of limitations:

1. Mechanical devices do not treat the underlying cause of heart failure in the elderly-aortic dilatation and stiffness.
2. Survival rates in patients treated with these devices remains unacceptably high (Dembitsky, Tector et al. 2004).
3. Mechanical devices are only effective in established heart failure and may not be used to prevent the development of heart failure.
4. Mechanical devices are invasive and involve a major surgical procedure for implantation including median sternotomy (or left thoracotomy in the case of the Jarvik 2000); cardiopulmonary bypass; anastomosis to at least the left ventricle and aorta; and often creation of an abdominal or subcutaneous pocket (Cohn and Edmunds 2003).
5. The combination of an extensive procedure, large amount of prosthetic material, blood-device interface, as well as extracorporeal components results in a high rate of serious infection for mechanical devices (El-Banayosy, Korfer et al. 1999; Deng, Loebe et al. 2001; El-Banayosy, Korfer et al. 2001; Robbins, Kown et al. 2001; Dembitsky, Tector et al. 2004; Morgan, John et al. 2004; Copeland, Smith et al. 2004b).
6. Mechanical devices involve a blood-device interface with a high incidence of thromboembolic complications (Deng, Loebe et al. 2001; El-Banayosy, Korfer et al. 2001; Robbins, Kown et al. 2001; Copeland, Smith et al. 2004b). The HeartMate LVAS has a lower rate of thromboembolic complication than other mechanical devices (Dembitsky, Tector et al. 2004; Morgan, John et al. 2004).
7. Mechanical devices are active devices and consist of complex components that may fatigue, rupture, or fail (Deng, Loebe et al. 2001; El-Banayosy, Korfer et al. 2001;

Robbins, Kown et al. 2001; Dembitsky, Tector et al. 2004; Morgan, John et al. 2004; Copeland, Smith et al. 2004b).

8. The cost and availability of mechanical devices limits their use in many patients.
9. Some mechanical devices e.g. HeartMate LVAS and CardioWest TAH cannot be used in small sized patients (Dembitsky, Tector et al. 2004).

New devices currently under development or trial are expected to reduce the rate of mechanical failure and complications and to improve outcome.

2.7.16 Conventional surgical treatments of heart failure

Conventional cardiothoracic procedures are beneficial in patients with heart failure and may be grouped in to three broad areas:

1. Revascularisation for ischaemic heart disease.
2. Valve operations for valvular lesions.
3. Left ventricular reconstruction.

Coronary Artery Bypass Grafting

Coronary artery disease is a common cause of heart failure that results from inadequate perfusion of the myocardium and its subsequent sequelae (Kannel and Belanger 1991). Patients with heart failure and coronary artery disease may have reversible myocardial ischaemia that benefits from revascularisation using coronary artery bypass surgery. Revascularisation of patients with left ventricular systolic dysfunction using coronary artery bypass surgery results in an improvement in survival when compared to medical therapy alone (ECSS 1982; CASS 1983).

Coronary artery bypass surgery can be performed on patients with severe left ventricular systolic dysfunction (ejection fraction less than 30%) with low operative mortality to produce an improvement in survival, functional class and ejection fraction (Coles, Del Campo et al. 1981; Elefteriades, Tolis et al. 1993; Elefteriades, Morales et al. 1997; Topkara, Cheema et al. 2005). The mechanism behind this improvement is due to recruitment of hibernating but viable myocardium and the protection of functioning portions of the myocardium from further ischaemic events (Rahimtoola 1993; Kouchoukos, Blackstone et al. 2003).

Coronary artery bypass surgery can be performed concurrently with other surgical treatments of heart failure e.g. mitral valve reconstruction and ventricular surgical reconstruction (Cohn and Edmunds 2003; Kouchoukos, Blackstone et al. 2003). Whilst it may be a useful surgical treatment of heart failure it does not treat the fundamental cause of heart failure in the elderly – increase load due to aortic stiffening and dilatation. In addition, revascularisation is associated with a poorer outcome in patients with an ejection fraction of less than 20% (Kouchoukos, Blackstone et al. 2003; Topkara, Cheema et al. 2005). The risks associated with coronary artery bypass surgery are increased with aging (Peterson, Jollis et al. 1994; Graham, Ghali et al. 2002).

Mitral valve repair (Geometric mitral reconstruction)

Mitral valve regurgitation is a serious complication of heart failure that arises from alterations in the annular-ventricular apparatus that accompany left ventricular remodelling. Left ventricular remodelling (dilatation) is associated with progressive enlargement of the mitral annulus, reduction in leaflet coaptation, and development of functional mitral regurgitation (Boltwood, Tei et al. 1983; Kono, Sabbah et al. 1992). Ischaemic heart

disease may also contribute to the development of mitral regurgitation through papillary muscle dysfunction (Izumi, Miyatake et al. 1987). Development of "geometric" or functional mitral regurgitation creates further ventricular dilatation, and is associated with a poor clinical outcome (Blondheim, Jacobs et al. 1991).

Reduction of the size of the mitral annulus may be achieved surgically using an undersized annuloplasty ring (geometric mitral reconstruction) (Cohn and Edmunds 2003; Kouchoukos, Blackstone et al. 2003). Geometric mitral reconstruction restores leaflet coaptation and valve competency to unload the left ventricle, and improves functional class, ventricular geometry, ejection fraction and survival (Bolling, Pagani et al. 1998; Chen, Adams et al. 1998; Bishay, McCarthy et al. 2000).

Surgical ventricular reconstruction

Progression of heart failure is accompanied by dilatation and thinning of the left ventricle, leading to increased wall stress and myocardial oxygen consumption via the law of LaPlace. In surgical ventricular reconstruction, akinetic or dyskinetic myocardium produced by myocardial infarction is excised to reduce ventricular radius and myocardial wall stress, restore ventricular geometry, and improve ventricular efficiency. The Dor procedure is a one form of surgical ventricular reconstruction, and involves exclusion of anteroseptal, apical or anterolateral left ventricular scarred segments using an intracardiac patch or direct closure (Athanasuleas, Stanley et al. 2001; Athanasuleas, Buckberg et al. 2004). Concomitant coronary artery bypass surgery and/or mitral valve reconstruction is performed if indicated (Athanasuleas, Stanley et al. 2001; Athanasuleas, Buckberg et al. 2004).

Patients undergoing surgical ventricular reconstruction show improvements in ventricular geometry left ventricular ejection fraction, functional class and long term survival (Athanasuleas, Stanley et al. 2001; Athanasuleas, Buckberg et al. 2004). The STICH (Surgical Treatment for Ischemic Heart Failure) trial is currently underway to evaluate the long term functional benefit of surgical ventricular reconstruction coupled with coronary artery bypass surgery (Cohn and Edmunds 2003; Hunt, Abraham et al. 2005).

Resection of a viable segment of the lateral wall of the left ventricle has been advocated to optimise wall tension in patients with dilated cardiomyopathy (partial left ventriculectomy- the Batista procedure) (Batista, Santos et al. 1996; Batista, Verde et al. 1997; Batista 1999). Clinical results with Batista procedure have been disappointing, and the procedure has fallen into disfavour (McCarthy, McCarthy et al. 1998; Starling, McCarthy et al. 2000).

2.8 AIM

The aim of this thesis is to provide proof of concept for a surgical treatment of stiffening of the ascending aorta with age. A reduction in the stiffness of the ascending aorta is expected to ameliorate the adverse effects of aortic stiffening on cardiovascular function in the elderly. Expected beneficial effects include a reduction in systolic pressure and pulse pressure, an increase in diastolic pressure (and coronary blood flow), and an improvement in ascending aortic impedance, ventricular load, and ventricular-vascular interaction.

The surgical procedure involves wrapping an elastic material around the ascending aorta of elderly patients, to reduce the stiffness of the ascending aorta towards that seen in

youth. The procedure exploits the dilatation of the aorta seen in aging with wrap material reducing the diameter of the aorta to take up the load of pulsatile pressure and flow.

Possible clinical indications may include the treatment of heart failure (by reduction of mechanical load and improved coronary blood flow) and isolated systolic hypertension. The procedure may be a useful adjunct to the medical and surgical treatment of myocardial ischaemia (by reduction of ventricular load, regression of myocardial hypertrophy, and improved coronary blood flow), and the treatment of microvascular disease of the brain and kidney.

Proof of concept is investigated in the following studies in this thesis:

1. The effect of application of the elastic wrap on the stiffness of the normal aorta is investigated using an ovine model (Chapter 3).
2. The effect of application of the elastic wrap on the stiffness of a dilated and stiffened vessel is investigated using an ovine model of aortic dilatation and stiffness (Chapter 4).
3. The effect of application of the elastic wrap on the stiffness of the human aorta and on aortic pressure is investigated using a pulsatile in-vitro pressure model of the aged human ascending aorta (Chapter 5).
4. The effect of wrapping the aged human ascending aorta on pulse pressure is investigated using a multi-branched model of the arterial system (Chapter 6).
5. The effect of chronic implantation of the elastic wrap on the structure of the normal aorta is investigated using an ovine model (Chapter 7).
6. The mechanical properties of the ovine descending thoracic aorta and the elastic wrap material are investigated using uniaxial tensile testing (Chapter 8).

The implications of these studies are discussed individually in each Chapter and then collectively in Chapter 9 (Discussion) and Chapter 10 (Conclusions). The study design in this thesis has been in keeping with the principles of animal experimentation. These broad principles are the refinement of investigative techniques to reduce the impact on animals, and ultimately the replacement of animals with other methods.

Figure 12 A cylindrical segment of the elastic wrap material.

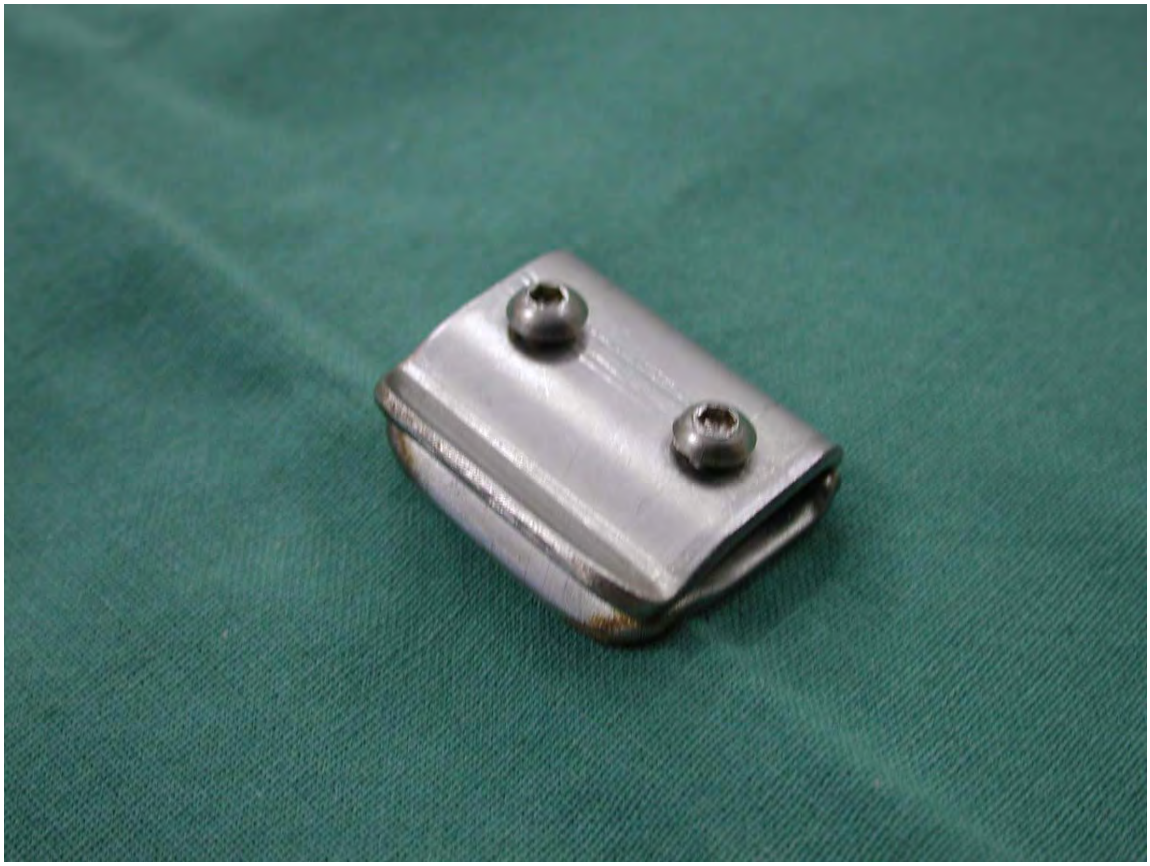


Figure 13 The clamp mechanism used to fix the elastic wrap around the aorta.

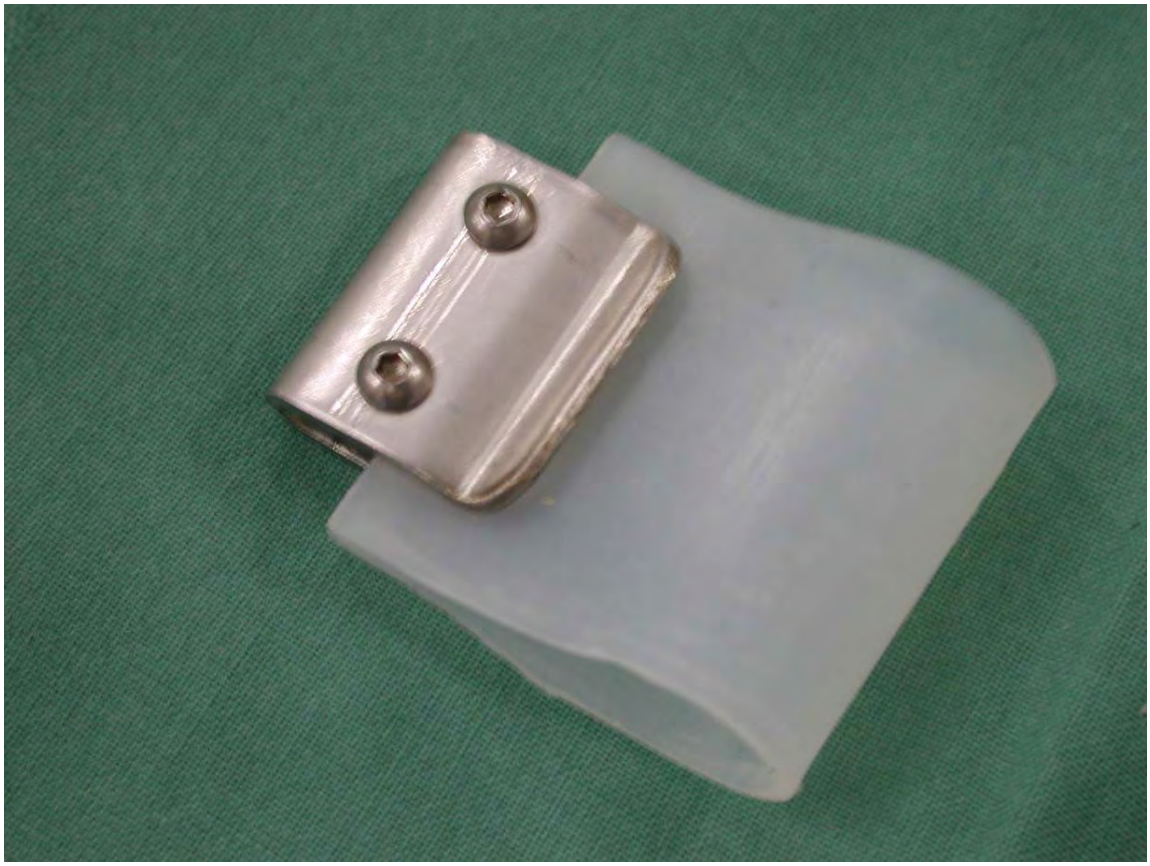


Figure 14 The clamp applied to fix a rectangular segment of the elastic wrap.

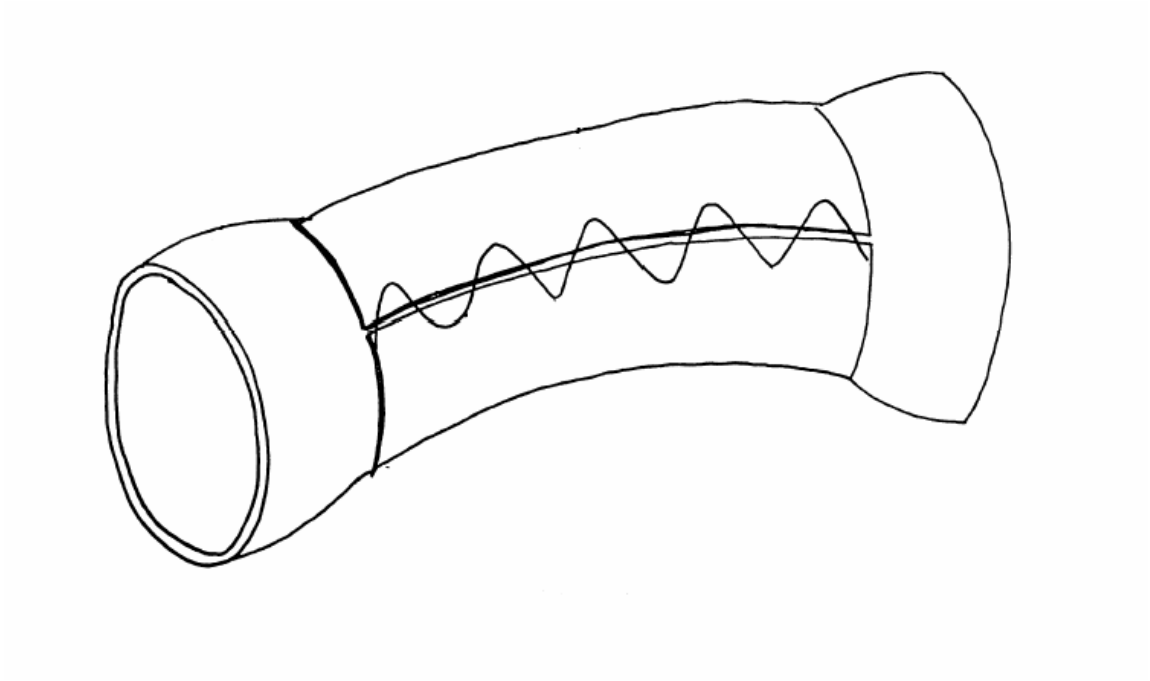


Figure 15 Schematic illustrating a rectangular segment of the elastic wrap placed around the aorta to reduce the diameter of the aorta. The elastic wrap is fixed in place using a continuous suture as opposed to a clamp device. This fixation method was not used in the following studies.

CHAPTER 3: THE EFFECT OF APPLICATION OF AN ELASTIC WRAP ON THE OVINE THORACIC AORTA

3.1 INTRODUCTION

External aortic wraps have been used for both experimental and clinical purposes. Rigid external bands have been applied to the aorta to reduce aortic wall motion and to constrict the aortic lumen to induce hypertension and increase cardiac load in experimental animals (O'Rourke 1967b; Ishihara, Zile et al. 1992; Aoyagi, Mirsky et al. 1992b; Watanabe, Ohtsuka et al. 1993; Ohtsuka, Kakihana et al. 1994; Koide, Nagatsu et al. 1997; Walther, Falk et al. 2000). Latissimus dorsi muscle has been wrapped around the thoracic aorta in experimental animals as well as clinically in humans to actively reduce cardiac load and improve coronary blood flow through counterpulsation (Neilson and Chiu 1986; Chachques, Grandjean et al. 1990; Pattison, Cumming et al. 1991; Cabrera Fischer, Christen et al. 1999; Trainini, Barisani et al. 1999; Trainini, Cabrera Fischer et al. 2002). Ascending aortic aneurysms have been wrapped with stiff noncompliant materials in an effort to prevent further enlargement and to prevent rupture (Robicsek 1982; Carrel, von Segesser et al. 1991; Bauer, Pasic et al. 2002; Arsan, Akgun et al. 2004; Robicsek, Cook et al. 2004; Olearchyk 2004a; Olearchyk 2004b).

The use of an elastic wrap to reduce the diameter of the stiffened and dilated ascending aorta in elderly humans has been proposed as a treatment of aortic stiffening and dilatation. Application of an elastic wrap to reduce the diameter of the aged ascending aorta is expected to restore aortic elasticity and improve ventricular-vascular interaction and has

been suggested as a treatment for isolated systolic hypertension and heart failure in the elderly.

Application of a stiff non-elastic wrap on the normal thoracic aorta has been shown to increase aortic stiffness and to increase cardiac load (Tropea, Schwarzacher et al. 2000). The effect of application of an elastic wrap on the stiffness of the normal aorta has not been previously studied.

The aim of this study was to determine the effect of application of an elastic wrap on the stiffness of the normal ovine thoracic aorta. The relationship between aortic pressure and diameter (stiffness) was studied before and after the application of the elastic wrap on the ovine proximal descending thoracic aorta.

3.2 MATERIALS AND METHODS

Neutered adult male sheep were used in this study (see Appendix 1). Two pilot studies and five definitive studies were conducted. The pilot studies were designed to develop and refine the surgical, anaesthetic and measurement techniques to minimise trauma to the animal. The data from the two pilot studies provided insight into the variation in the data from the definitive studies. Based on prehoc power assessments a sample of 5 animals was deemed adequate to demonstrate a difference in aortic stiffness before and after elastic wrap application.

3.2.1 Anaesthesia

Adult sheep underwent intravenous induction of general anaesthesia (Pentobarbitone sodium; 30mg/kg), which was maintained after endotracheal intubation using inhalational agents (halothane 2-3% in 100% oxygen). Lung ventilation was achieved

using a positive pressure ventilator. Physiologic parameters were monitored during the procedure (see Appendix 1).

3.2.2 Surgery

Femoral arterial line

Exposure of the left femoral artery was made for placement of an arterial sheath for insertion of a 7 French Millar Catheter (Model SPC-771; Millar Instruments, Houston, TX). A 5 cm longitudinal skin incision was made in the left femoral region over the femoral artery. The soft tissue and muscle overlying the femoral artery were divided using electrocautery to expose the vessel. The vessel was isolated between two #1 silk ligatures.

After anticoagulation with intravenous heparin (5000IU) an arterial sheath was inserted into the femoral artery, and secured with the silk sutures.

Thoracotomy

The procedure was performed trough a left thoracotomy incision. At the level of the third intercostal space, a skin incision was made from the ventral portion of the latissimus dorsi ventrally along the cranial margin of the fourth rib for a distance of approximately 20 cm towards the costochondral junction taking care to avoid the internal thoracic artery.

With electrocautery, the cutaneous trunci muscle and the superficial pectoral muscle (transverse part) were incised within the length of the skin incision. The latissimus dorsi muscle was only incised for a few centimetres at its ventral margin. The external and internal intercostal muscles were incised at the cranial margin of the fourth rib, and the pleural space was entered by bluntly perforating the pleura with a Pean forceps. The pleura was incised along the length of the skin incision.

The ribs were retracted to expose the distal arch of aorta, proximal descending thoracic aorta, pericardium, left lung root, and left azygos vein. The upper lobe of the left lung was packed with surgical gauze to facilitate exposure of these structures.

The proximal part of the descending thoracic aorta (lying cranial to the left azygos vein) has no intercostal branches and was dissected free from surrounding structures to facilitate placement of ultrasonic crystals and a segmental elastic wrap. The left azygos vein overlying the aorta was mobilised and ligated and divided between two #1 silk sutures.

3.2.3 Instrumentation

A 7F Millar Catheter was inserted through the femoral artery via the sheath and advanced into the proximal descending thoracic aorta. This catheter was used to measure the arterial pressure waveform in this region before and after application of the elastic wraps. The position of the tip of the catheter was confirmed manually prior to data collection.

One pair of ultrasonic crystals (Model VD5-2; Triton technology, San Diego, Cal) was placed on the external surface of the proximal descending thoracic aorta to measure external aortic diameter. The transit time signal of the ultrasonic signal was converted into distance using a sonomicrometer (Model 200-201; Triton Technology, San Diego, CA). The ultrasonic crystals were used to measure the pulsatile diameter of the aorta before and after application of the elastic wraps.

3.2.4 Elastic material

An elastic silicon polymer was used as the elastic wrap material. The mechanical properties of the material were measured using uniaxial tensile testing (see Chapter 8). The

material was developed by Medtronic (Medtronic, Inc., Minneapolis, MN) to simulate the mechanical properties of the young human ascending aorta (4% stiffness material) and pulmonary artery (12% stiffness material) for the in-vitro testing of prosthetic valves. Two materials of differing stiffness were used in this study:

1. 4% stiffness material: cylindrical lengths of this material show a 4% increase in diameter with each pulsation when exposed to simulated physiologic pressure and flow in an in-vitro set up.
2. 12% stiffness material: cylindrical lengths of this material show a 12% increase in diameter with each pulsation when exposed to simulated physiologic pressure and flow in an in-vitro set up.

The material comes in prefabricated cylindrical lengths. Two cylindrical segments of each elastic material (internal diameter 30mm, length 3cm) were divided along the longitudinal axis at one point to form a rectangular piece of material.

Each piece of material was marked with four sutures, forming lengths of 63cm and 57cm between the sutures. The distance between these sutures indicated the internal circumference of the wrap material when the material was fixed at these sutures with an arterial clamp to form a cylinder. The arterial clamp used to fix the material around the aorta grasped the elastic material external to the sutures. The distances between the sutures were derived by multiplying the desired internal diameter of the wrap by pi (3.14). The two internal diameters of the elastic wrap evaluated in this study were 20mm (circumference 63cm), and 18mm (circumference 57cm).

3.2.5 Experimental protocol

Study design

A repeated measures study design was used to reduce the variation in results and therefore minimise the number of animals required for the study.

Baseline - Normotension

When haemodynamic steady state was achieved, two baseline readings of pressure and diameter in the region of the proximal descending thoracic aorta were taken. The position of the tip of the pressure catheter was at the same level as the ultrasonic crystals. This was confirmed manually prior to haemodynamic measurement.

Aortic wrap - Normotension

Both the 4% stiffness material and 12% stiffness material were used in the study. The two internal diameters of the wrap material evaluated were 20mm and 18mm. The material was applied externally to the segment of the aorta over the ultrasonic crystals to reduce the diameter of the native aorta. The elastic wrap was fixed with an arterial clamp at the points indicated by the sutures, and the readings taken when haemodynamic steady state was achieved.

Two separate readings were taken for the 20mm 4% wrap and for the 18mm 4% wrap. Two separate readings were taken for the 20mm 12% wrap and for the 18mm 12% wrap. Application of wraps was randomised and the surgeon was blinded to the nature of the material (i.e. 4% versus 12% stiffness material) to reduce bias.

Baseline - Hypertension

Hypertension was induced with intravenous infusion of Aramine (Metaraminol Bitartrate). Two readings were taken once the systolic blood pressure had reached 130mmHg and haemodynamic steady state had been achieved.

Aortic wrap - Hypertension

Two separate readings were taken for the 20mm 4% wrap and for the 18mm 4% wrap in the hypertensive condition (as above). Two separate readings were taken for the 20mm 12% wrap and for the 18mm 12% wrap in the hypertensive condition (as above).

Sacrifice

The animal was humanely euthanised at the end of the procedure with a lethal injection of Pentobarbitone Sodium (90mg/kg).

3.2.6 Data analysis

A System 6 mainframe (Model 200-200; Triton Technology, San Diego, CA) was fitted with a sonomicrometer module (Model 200-201; Triton Technology, San Diego, CA) and a dual pressure model (Model 200-204; Triton Technology, San Diego, CA) for the measurement of aortic diameter and pressure. Data was digitised and analysed on a CA recorder (Data integrated scientific systems, Pinckney, Michigan) and was displayed in real time during data collection. Data was sampled simultaneously at a frequency of 500Hz.

During the haemodynamic steady state condition a series of at least 5 beats were digitised and averaged for the calculation of:

1. Mean, systolic, diastolic and pulse pressure values.

2. Maximum and minimum aortic diameter.
3. Heart rate.
4. Pressure-strain elastic modulus.

The pressure strain-elastic modulus (E_p) is a measurement of the elastic properties (stiffness) of the aortic wall and is calculated using the following formula (Peterson, Jensen et al. 1960):

$$E_p = (dP/dD) \times D$$

Where, D_m = minimum aortic diameter

dD = pulsatile change in aortic diameter (maximum diameter minus the minimum diameter).

dP = pulse pressure (systolic aortic pressure minus diastolic aortic pressure)

Haemodynamic data and aortic diameter, area, and stiffness data are presented as mean +/- standard deviation. Data were compared graphically using Microsoft Excel (Office 2000; Microsoft Corporation), and analysed using a one-way analysis of variance (ANOVA) followed by a Tukey Honest significant difference post-hoc test using SPPS for Windows (SPSS Inc, Chicago, Illinois). Statistical significance was set at a level of $p < 0.05$.

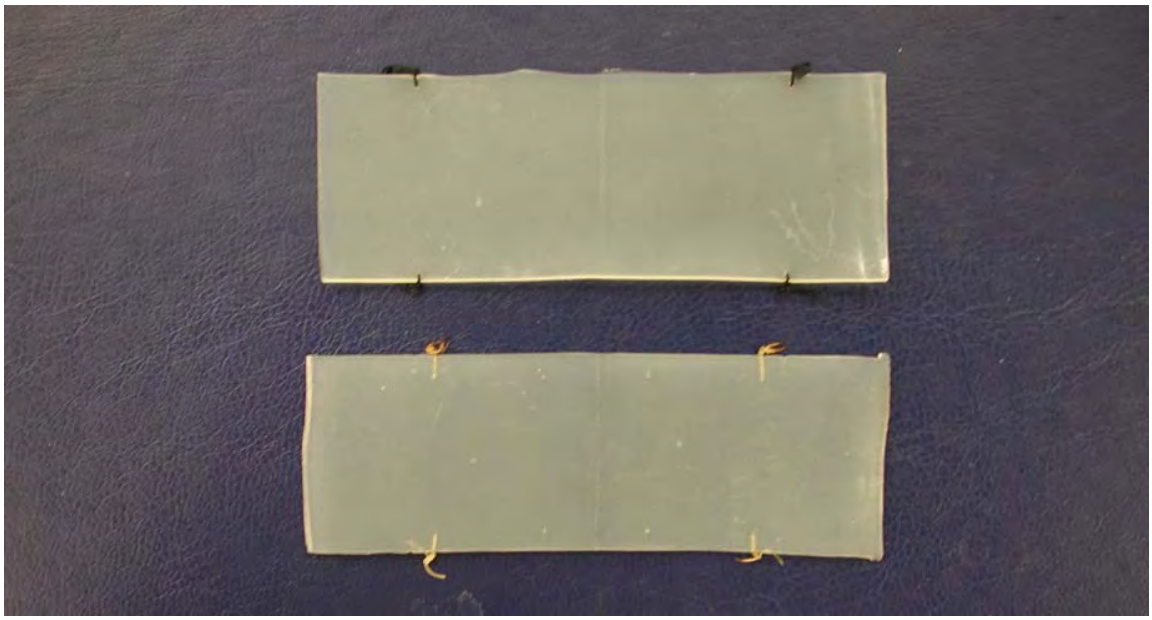


Figure 16 Two rectangular lengths of elastic wrap material with sutures placed to mark post fixation diameter

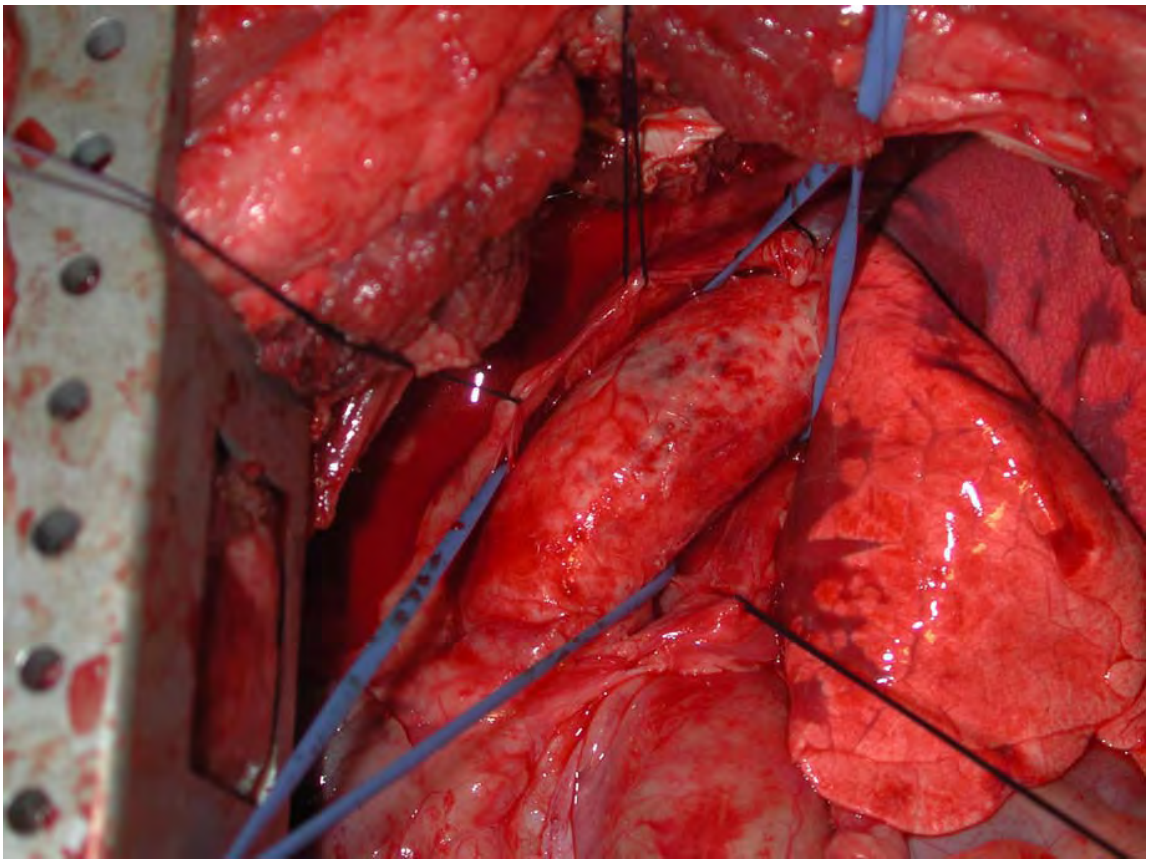


Figure 17 Exposure of the ovine proximal descending thoracic aorta

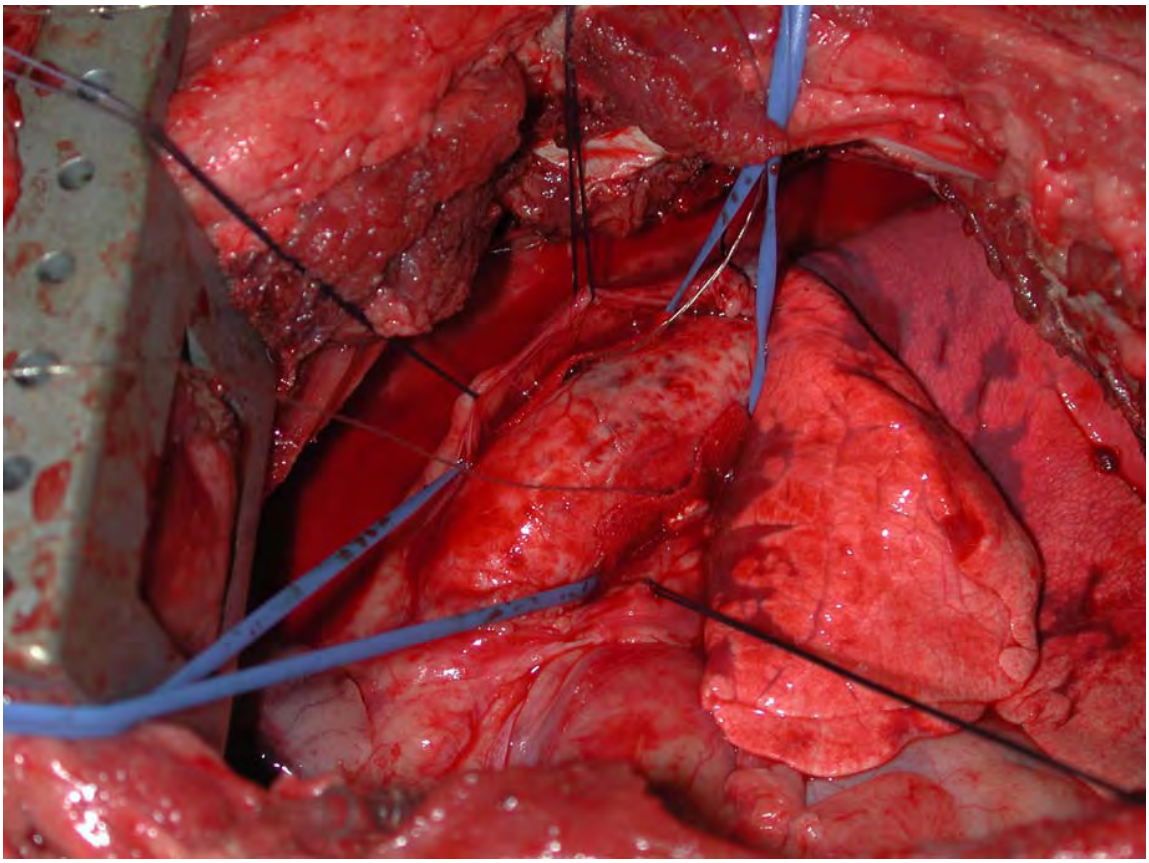


Figure 18 Placement of ultrasonic crystals to measure pulsatile aortic diameter

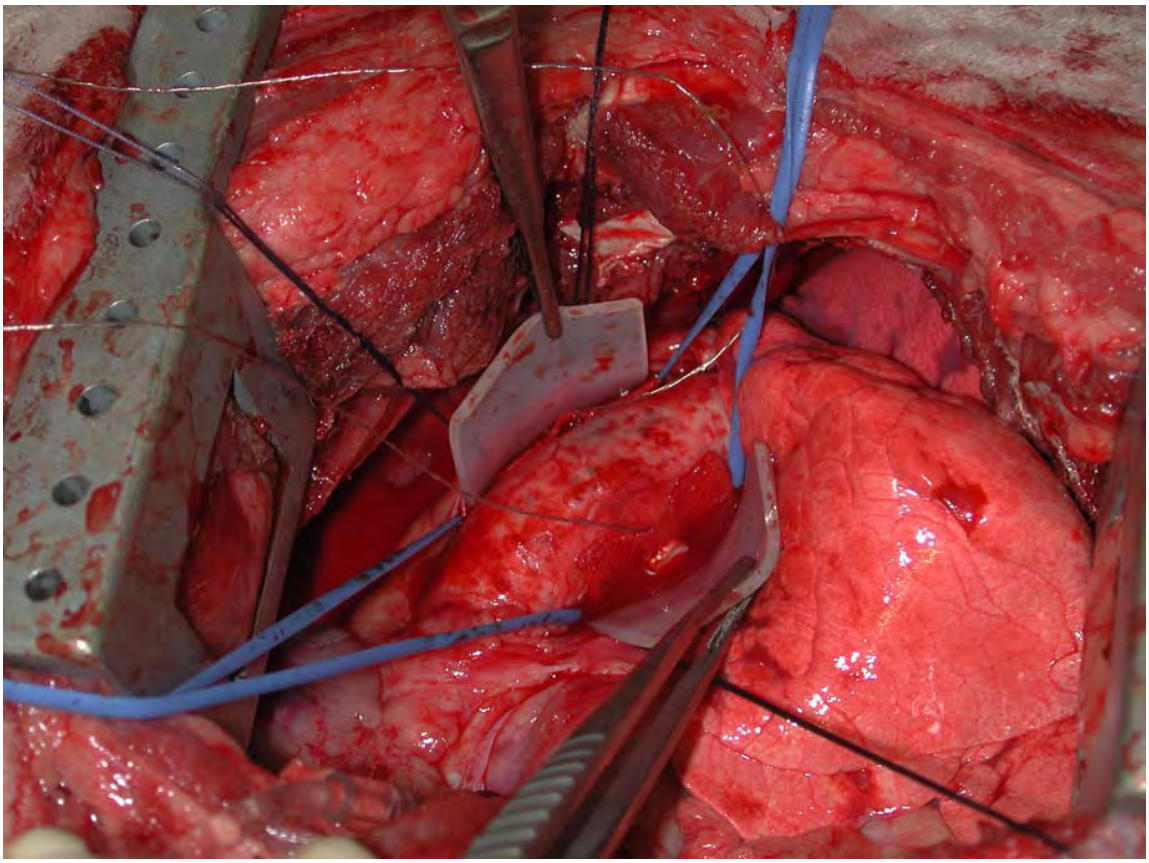


Figure 19 Elastic wrap application over the ultrasonic crystals

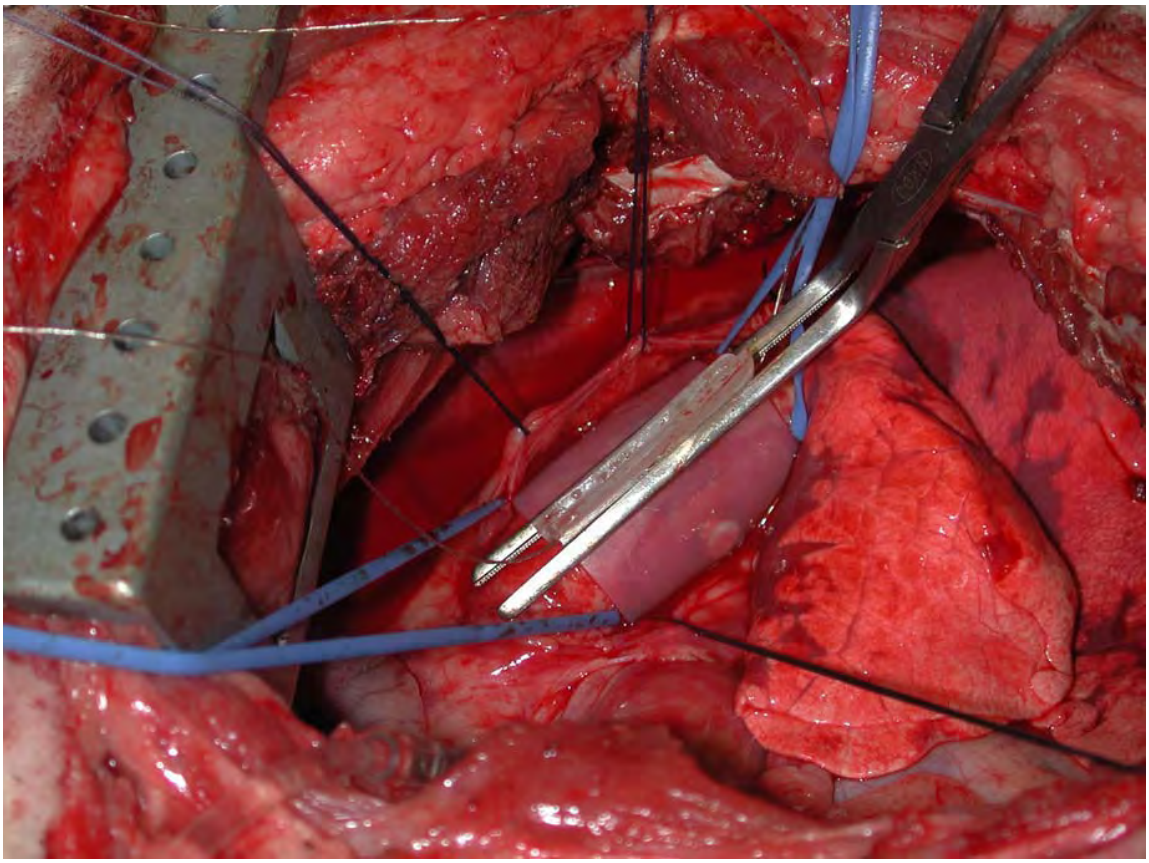


Figure 20 Fixation of the elastic wrap using an arterial clamp

3.3 RESULTS

All animals survived the entire procedure without requiring defibrillation or administration of inotropic or anti-arrhythmic drugs. There was no evidence of cardiovascular compromise, respiratory failure or hypothermia.

3.3.1 Normotension

Haemodynamics

Normotension (N = 5)	Group 1 Baseline	Group 2 12% 20mm	Group 3 12% 18mm	Group 4 4% 20mm	Group 5 4%18mm
HR (bpm.)	91 +/- 23.5	93 +/- 16.7	96 +/- 17.2	97 +/- 18.6	98 +/- 19.6
SBP (mmHg)	101 +/- 19.2	109 +/- 11.3	108 +/- 9.3	106 +/- 12.5	107 +/- 10.2
DBP (mmHg)	85 +/- 19.6	91 +/- 8.8	91 +/- 8.4	89 +/- 10.4	90 +/- 8.5
MBP (mmHg)	92 +/- 18.6	100 +/- 9.6	99 +/- 8.3	97 +/- 11.3	97 +/- 8.8
PP (mmHg)	17 +/- 2.9	18 +/- 4.7	17 +/- 2.8	18 +/- 3.5	17 +/- 2.9

HR = heart rate; SBP = systolic blood pressure; DBP = diastolic blood pressure; MBP = mean blood pressure; PP = pulse pressure. Data presented as mean +/- SD.

Table 4 Alterations in haemodynamic parameters following application of elastic wraps to the ovine proximal descending thoracic aorta in normotension.

Following application of the elastic wraps there were no significant alterations in heart rate, systolic pressure, diastolic pressure, mean pressure, or pulse pressure.

Aortic diameter, area, and stiffness

Normotension (N=5)	Group 1 Baseline	Group 2 12% 20mm	Group3 12% 18mm	Group 4 4% 20mm	Group 5 4% 18mm
Min D (mm)	19.85 +/- 1.77	14.77 +/- 0.55 ***	12.95 +/- 0.97 ***	14.15 +/- 1.20 ***	12.08 +/- 1.24 ***
Max D (mm)	20.95 +/- 1.71	15.22 +/- 0.60 ***	13.37 +/- 1.06 ***	14.51 +/- 1.26 ***	12.39 +/- 1.28 ***
δD (mm)	1.10 +/- 0.27	0.45 +/- .11 ***	0.42 +/- 0.13 ***	0.36 +/- 0.08 ***	0.31 +/- 0.07 ***
%δD	5.59 +/- 1.69	3.06 +/- 0.68 **	3.20 +/- 0.88 ***	2.52 +/- 0.43 ***	2.53 +/- 0.46 ***
Min A (mm^2)	311.31 +/- 54.49	171.43 +/- 12.85 ***	132.23 +/- 20.21 ***	158.02 +/- 26.79 ***	115.49 +/- 23.47 ***
Max A (mm^2)	346.27 +/- 56.26	182.13 +/- 14.58 ***	140.97 +/- 22.95 ***	166.18 +/- 28.88 ***	121.44 +/- 24.79 ***
δA (mm^2)	34.96 +/- 8.28	10.69 +/- 2.76 ***	8.74 +/- 3.34 ***	8.16 +/- 2.34 ***	5.96 +/- 1.68 ***
%δA	11.51 +/- 3.59	6.22 +/- 1.39 **	6.50 +/- 1.83 *	5.10 +/- 0.88 ***	5.13 +/- 0.94 ***
Ep (dyn/cm^2 x e6)	0.42 +/- 0.08	0.84 +/- 0.14 *	0.81 +/- 0.20 *	0.95 +/- 0.10 ***	0.92 +/- 0.09 ***

Min D= minimum aortic diameter; Max D = maximum aortic diameter; δD = pulsatile change in aortic diameter; %δD = percentage pulsatile change in aortic diameter [(δD /Min D x 100)]; Min A = minimum aortic area; Max A = maximum aortic area; δA = pulsatile change in aortic area; %δA = percentage pulsatile change in aortic area [(δA /Min A x 100)]; Ep = pressure-strain elastic modulus [Ep=(PP/δD)×Min D). (* $p < 0.01$, ** $p < 0.005$, *** $p < 0.001$ c/w baseline, data presented as mean +/- SD)

Table 5 Alterations in aortic diameter, area and stiffness following application of elastic wraps to the ovine proximal descending thoracic aorta in normotension.

Following application of the elastic wraps there was a significant reduction in the minimum aortic diameter and area in all wrap groups when compared to baseline. There were no significant differences in minimum aortic diameter and area between wrap groups; however the following patterns were evident. Application of a 4% wrap produced a smaller minimum aortic diameter and area when compared to a similarly sized 12% wrap. Application of an 18mm wrap produced a smaller minimum aortic diameter and area when compared to application of a 20mm wrap.

There was a significant reduction in the percentage pulsatile change in aortic diameter and area in all wrap groups when compared to baseline. There were no significant differences in percentage pulsatile change in aortic diameter and area between wrap groups; however the following patterns were evident. The percentage pulsatile change in aortic diameter and area of the 12% wrap groups was greater than that of the 4% wrap groups. For the 12% material, application of an 18mm wrap produced a slightly greater percentage pulsatile change of aortic diameter and area than application of a 20mm wrap. For the 4% wrap material, the percentage pulsatile change of aortic diameter and area was similar for the 18mm and 20mm wraps.

The aortic stiffness (E_p) of all wrap groups was significantly greater than baseline. There were no significant differences in aortic stiffness between wrap groups; however the following patterns were evident. Aortic stiffness of the 4% wrap groups was greater than aortic stiffness of the 12% wrap groups. For each wrap material, application of an 18mm wrap produced aortic stiffness slightly less than application of a 20mm wrap.

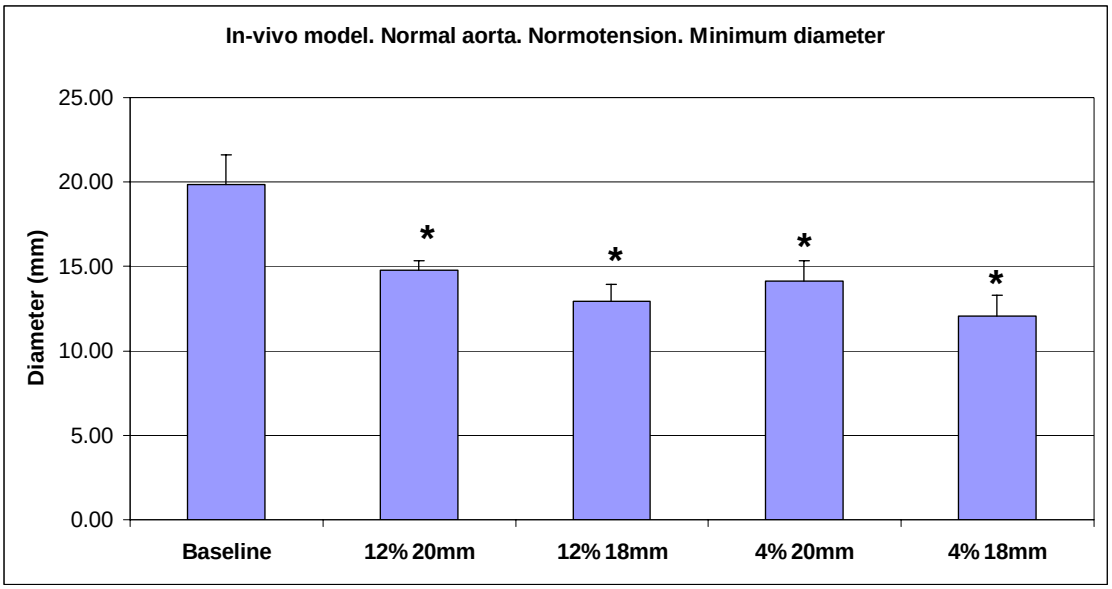


Figure 21 Alterations in minimum aortic diameter following application of elastic wraps in normotension.

* $p < 0.001$ c/w baseline.

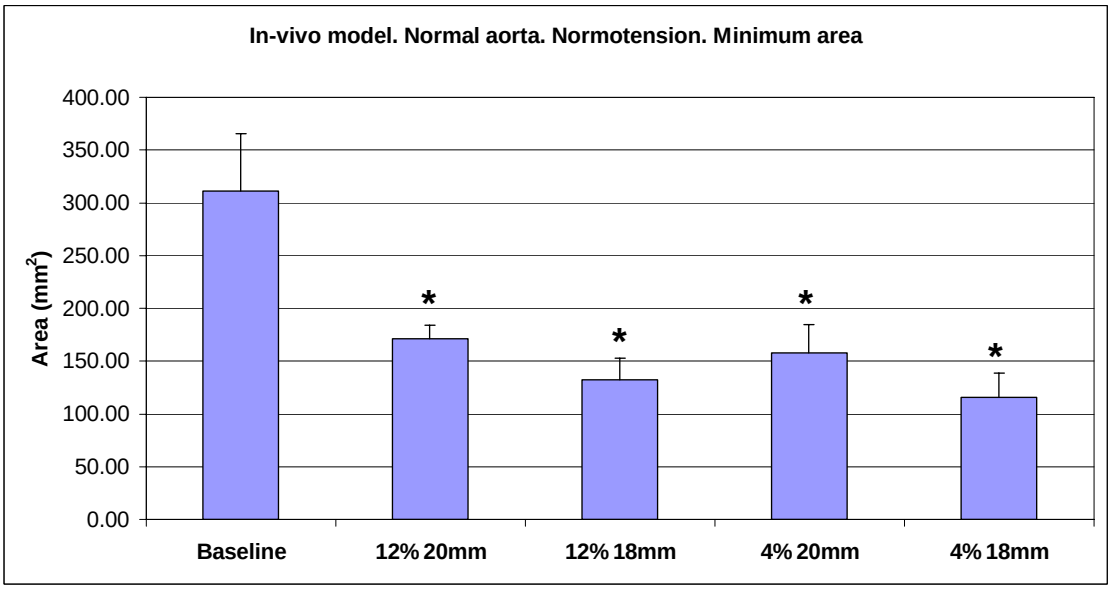


Figure 22 Alterations in minimum aortic area following application of elastic wraps in normotension.

* $p < 0.001$ c/w baseline.

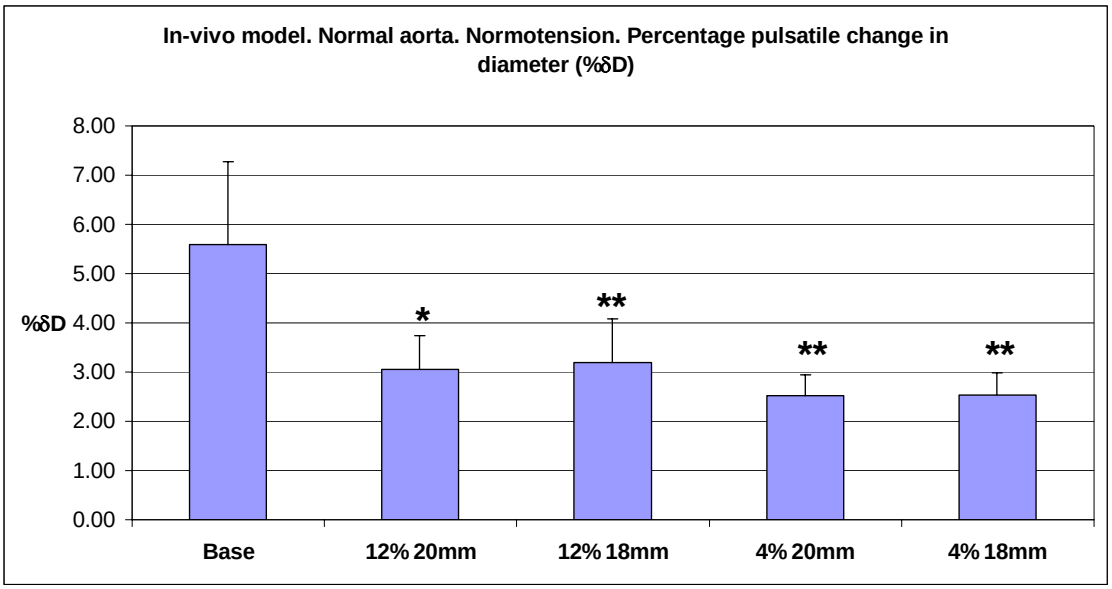


Figure 23 Alterations in percentage pulsatile change in aortic diameter following application of elastic wraps in normotension. * $p < 0.005$, ** $p < 0.001$ c/w baseline.

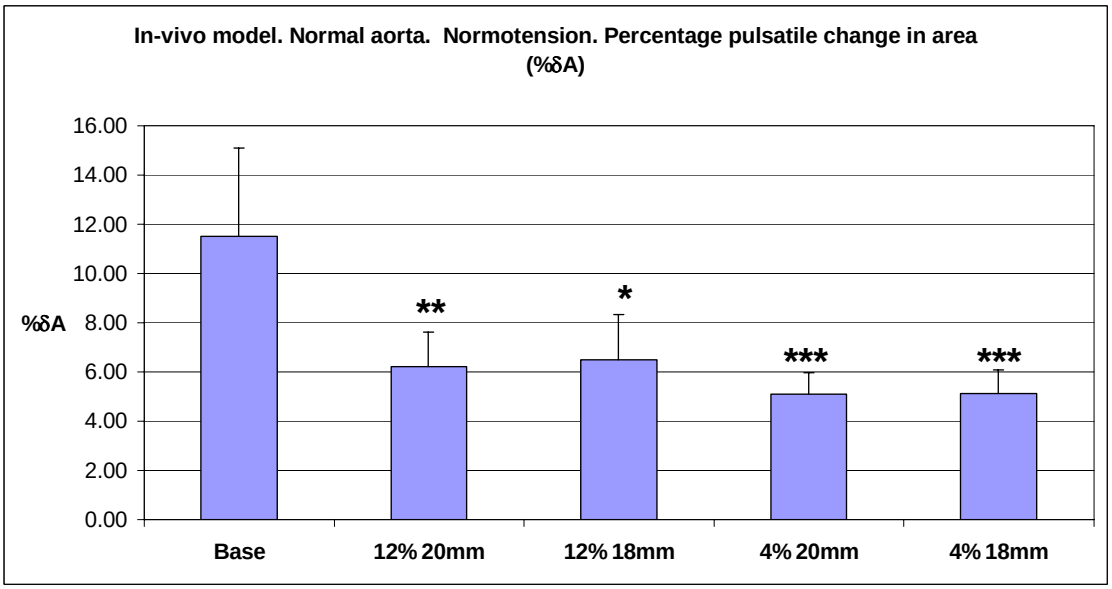


Figure 24 Alterations in percentage pulsatile change in aortic area following application of elastic wraps in normotension. * $p < 0.01$, ** $p < 0.005$, *** $p < 0.001$ c/w baseline.

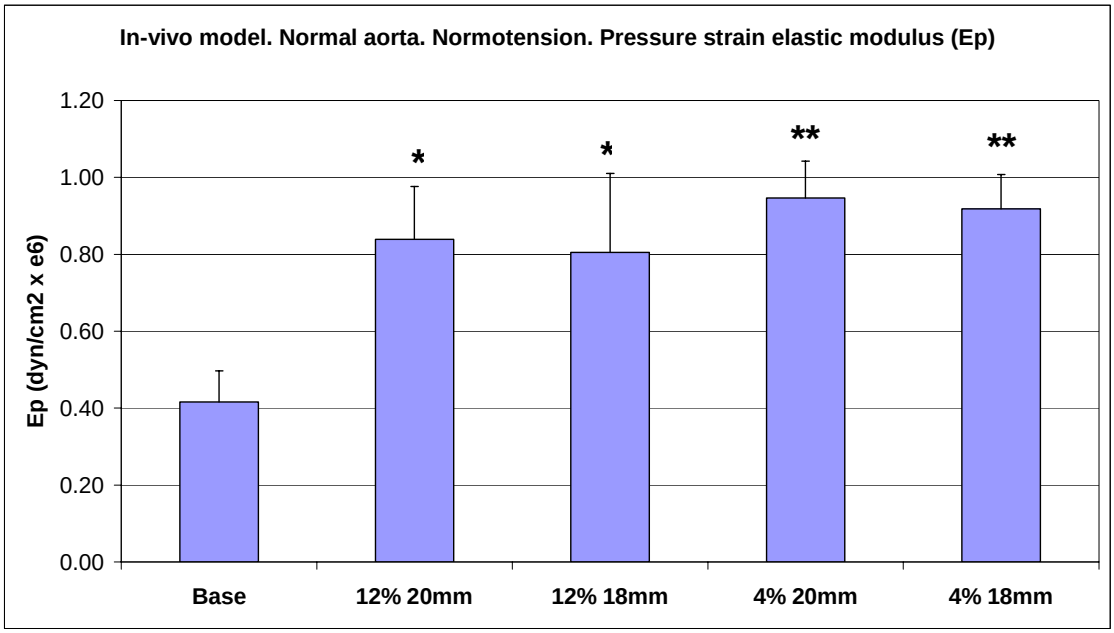


Figure 25 Alterations in pressure strain elastic modulus following application of elastic wraps in normotension.

* p = 0.01, ** p < 0.001 c/w baseline.

3.3.2 Hypertension

Haemodynamics

(N = 5)	Baseline Normotension	Baseline Hypertension	Significance
HR (bpm.)	91 +/- 23.5	114 +/- 18.9	N/S
SBP (mmHg)	101 +/- 19.2	135 +/- 11.3	P < 0.01
DBP (mmHg)	85 +/- 19.6	112 +/- 11.9	P < 0.05
MBP (mmHg)	92 +/- 18.6	122 +/- 12.2	P < 0.01
PP (mmHg)	17 +/- 2.9	23 +/- 3.7	P < 0.05

HR = heart rate; SBP = systolic blood pressure; DBP = diastolic blood pressure; MBP = mean blood pressure; PP = pulse pressure. Data presented as mean +/- SD.

Table 6 Alterations in baseline haemodynamic parameters following intravenous infusion of Aramine.

Hypertension (N = 5)	Group 1 Baseline	Group 2 12% 20mm	Group 3 12% 18mm	Group 4 4% 20mm	Group 5 4%18mm
HR (bpm.)	114 +/- 18.9	108 +/- 11.0	109 +/- 11.0	105 +/- 19.4	104 +/- 21.1
SBP (mmHg)	135 +/- 11.3	139 +/- 9.9	140 +/- 10.5	139 +/- 13.5	139 +/- 15.0
DBP (mmHg)	112 +/- 11.9	116 +/- 8.8	121 +/- 15.6	116 +/- 10.7	116 +/- 15.8
MBP (mmHg)	122 +/- 12.2	127 +/- 8.9	129 +/- 11.8	127 +/- 11.1	126 +/- 15.6
PP (mmHg)	23 +/- 3.7	23 +/- 4.2	24 +/- 3.9	22 +/- 5.7	23 +/- 4.6

HR = heart rate; SBP = systolic blood pressure; DBP = diastolic blood pressure; MBP = mean blood pressure; PP = pulse pressure. Data presented as mean +/- SD.

Table 7 Alterations in haemodynamic parameters following application of elastic wraps to the ovine proximal descending thoracic aorta in hypertension.

Following infusion of Aramine there was a significant increase in systolic pressure, diastolic pressure, mean pressure, and pulse pressure when compared to normotension baseline values. With application of the elastic wraps there were no significant alterations in the haemodynamic values of the wrap groups when compared to baseline hypertension values. There were no significant differences in haemodynamic values between wrap groups.

Aortic diameter, area, and stiffness

(N = 5)	Baseline Normotension	Baseline Hypertension	Significance
Min D (mm)	19.85 +/- 1.77	21.62 +/- 1.13	N/S
Max D (mm)	20.95 +/- 1.71	22.88 +/- 1.26	N/S
δD (mm)	1.10 +/- 0.27	1.26 +/- 0.22	N/S
%δD	5.59 +/- 1.69	5.80 +/- 0.93	N/S
Min A (mm^2)	311.31 +/- 54.49	367.85 +/- 38.94	N/S
Max A (mm^2)	346.27 +/- 56.26	411.93 +/- 45.47	N/S
δA (mm^2)	34.96 +/- 8.28	44.08 +/- 9.33	N/S
%δA	11.51 +/- 3.59	11.94 +/- 1.97	N/S
Ep (dyn/cm^2 x e6)	0.42 +/- 0.08	0.55 +/- 0.13	N/S

Min D= minimum aortic diameter; Max D = maximum aortic diameter; δD = pulsatile change in aortic diameter; %δD = percentage pulsatile change in aortic diameter [(δD /Min D x 100)]; Min A = minimum aortic area; Max A = maximum aortic area; δA = pulsatile change in aortic area; %δA = percentage pulsatile change in aortic area [(δA /Min A x 100)]; Ep = pressure-strain elastic modulus [Ep=(PP/δD)×Min D). Data presented as mean +/- SD)

Table 8 Alterations in baseline haemodynamic parameters following intravenous infusion of Aramine.

Hypertension (N=5)	Group 1 Baseline	Group 2 12% 20mm	Group3 12% 18mm	Group 4 4% 20mm	Group 5 4% 18mm
Min D (mm)	21.62 +/- 1.13	15.31 +/- 1.11 **	13.40 +/- 0.73 **	15.07 +/- 0.90 **	12.21 +/- 1.07 **
Max D (mm)	22.88 +/- 1.26	15.79 +/- 1.22 **	13.86 +/- 0.84 **	15.40 +/- 0.96 **	12.49 +/- 1.15 **
δD (mm)	1.26 +/- 0.22	0.48 +/- .14 **	0.45 +/- 0.12 **	0.34 +/- 0.09 **	0.28 +/- 0.08 **
%δD	5.80 +/- 0.93	3.11 +/- 0.75 **	3.36 +/- 0.70 **	2.23 +/- 0.55 **	2.23 +/- 0.53 **
Min A (mm^2)	367.85 +/- 38.94	184.77 +/- 25.9 **	141.32 +/- 15.32 **	178.69 +/- 20.86 **	117.84 +/- 20.57 **
Max A (mm^2)	411.93 +/- 45.47	196.68 +/- 29.51 **	151.16 +/- 18.41 **	186.83 +/- 22.66 **	123.29 +/- 22.49 **
δA (mm^2)	44.08 +/- 9.33	11.91 +/- 4.25 **	9.84 +/- 3.09 **	8.14 +/- 2.58 **	5.45 +/- 2.05 **
%δA	11.94 +/- 1.97	6.33 +/- 1.55 **	6.84 +/- 1.44 **	4.51 +/- 1.12 **	4.50 +/- 1.07 **
Ep (dyn/cm^2 x e6)	0.55 +/- 0.13	0.99 +/- 0.11 *	0.98 +/- 0.05 *	1.37 +/- 0.19 **	1.44 +/- 0.39 **

Min D= minimum aortic diameter; Max D = maximum aortic diameter; δD = pulsatile change in aortic diameter; %δD = percentage pulsatile change in aortic diameter [(δD /Min D x 100)]; Min A = minimum aortic area; Max A = maximum aortic area; δA = pulsatile change in aortic area; %δA = percentage pulsatile change in aortic area [(δA /Min A x 100)]; Ep = pressure-strain elastic modulus [Ep=(PP/δD)×Min D). (* $p < 0.05$, ** $p < 0.001$ c/w baseline, data presented as mean +/- SD)

Table 9 Alterations in aortic diameter, area and stiffness following application of elastic wraps to the ovine proximal descending thoracic aorta in hypertension.

Following infusion of Aramine there was an increase in minimum and maximum aortic diameter and area when compared to baseline normotension (however, this did not achieve statistical significance). Similarly, the aortic stiffness (E_p) of the hypertension baseline group was greater than the pressure-strain elastic modulus of the normotension baseline group.

Following application of the elastic wraps, there was a significant reduction in minimum aortic diameter and area in all wrap groups when compared to baseline.

Application of a 4% wrap produced a smaller minimum aortic diameter and area when compared to a similarly sized 12% external aortic wrap. Application of an 18mm wrap produced a smaller minimum aortic diameter and area when compared to application of a 20mm wrap.

There was a significant reduction in the percentage pulsatile change in aortic diameter and area following application of the elastic wraps when compared to baseline. There were no significant differences in percentage pulsatile change in aortic diameter and area between wrap groups; however the following patterns were evident. The percentage pulsatile change in aortic diameter and area of the 12% wrap groups was greater than that of the 4% wrap groups. For the 12% material, application of an 18mm wrap produced a slightly greater percentage pulsatile change of aortic diameter and area than application of a 20mm wrap. For the 4% wrap material, the percentage pulsatile change of aortic diameter and area was similar for the 18mm and 20mm wraps.

The aortic stiffness (E_p) of all wrap groups was significantly greater than baseline. The aortic stiffness (E_p) of the 4% wrap groups was greater than the stiffness of the 12% wrap groups. For each wrap material, application of an 18mm wrap produced aortic wall stiffness similar to application of a 20mm wrap.

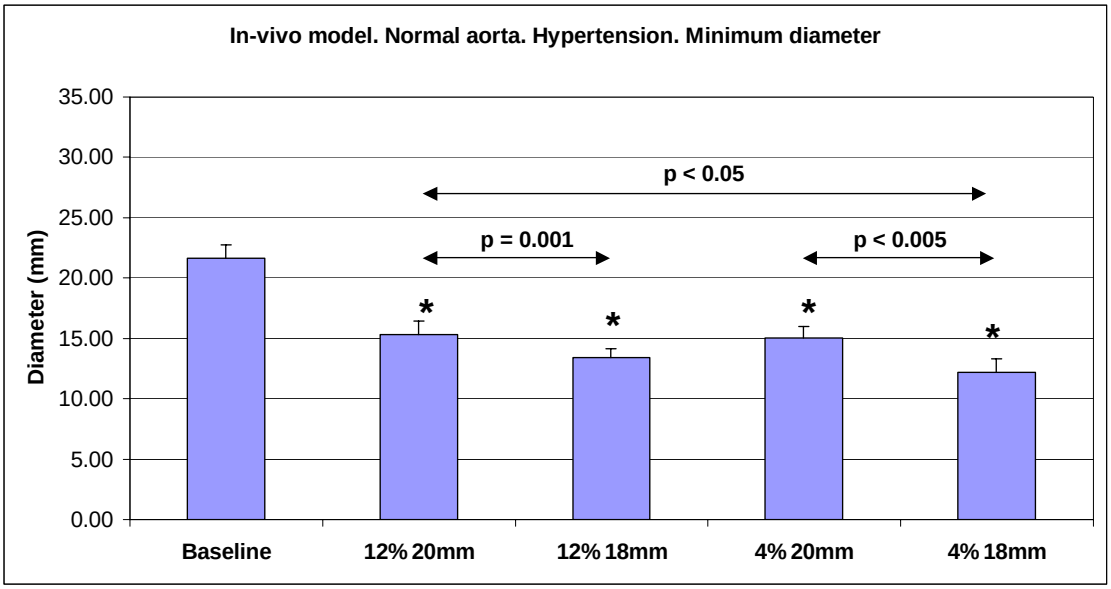


Figure 26 Alterations in minimum aortic diameter following application of elastic wraps in hypertension. * p < 0.001 c/w baseline. Arrows indicate between groups comparison.

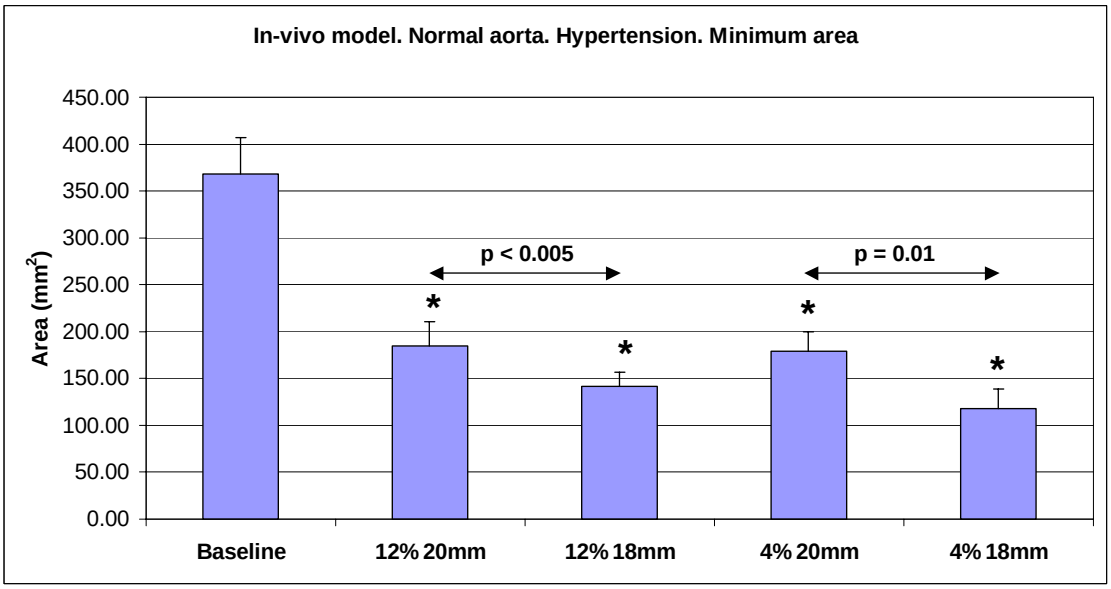


Figure 27 Alterations in minimum aortic area following application of elastic wraps in hypertension. * p < 0.001 c/w baseline. Arrows indicate between groups comparison.

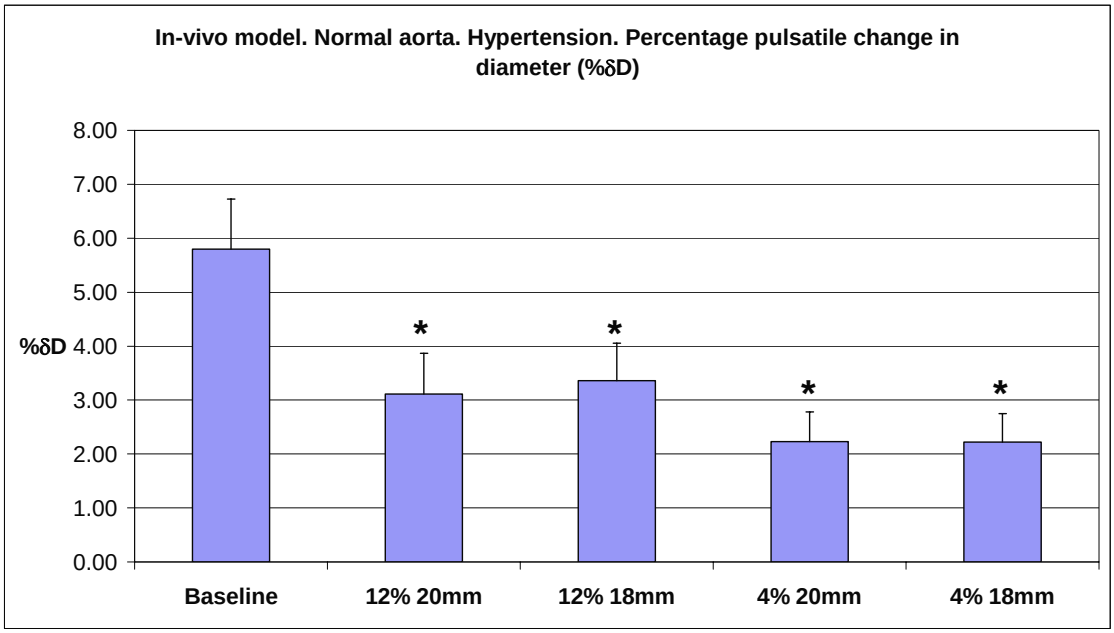


Figure 28 Alterations in percentage pulsatile change in aortic diameter following application of elastic wraps in hypertension. * $p < 0.001$ c/w baseline.

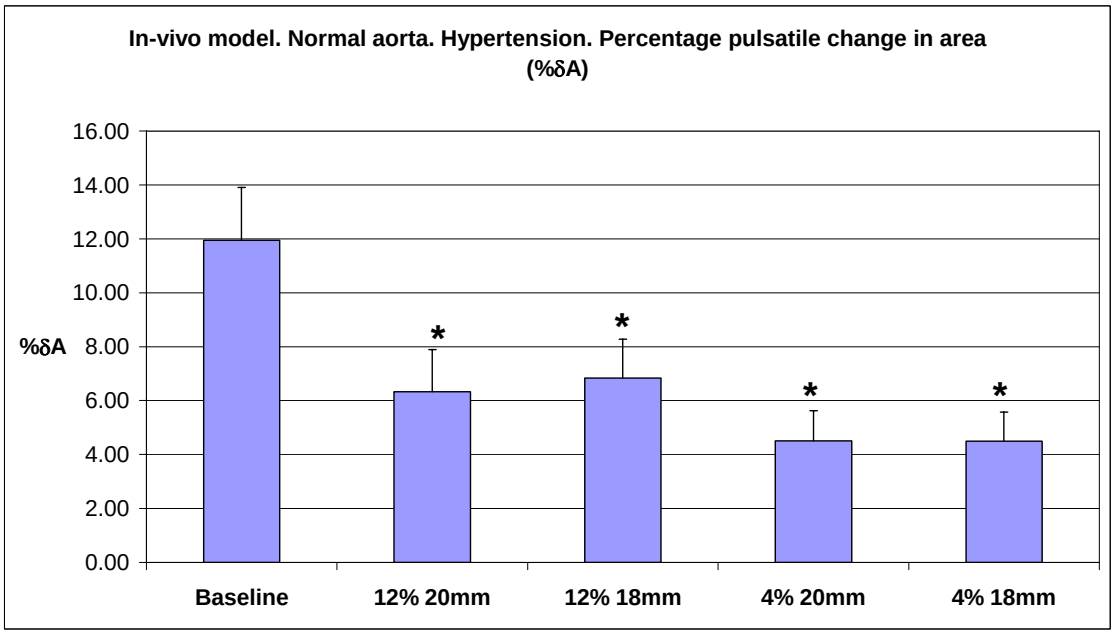


Figure 29 Alterations in percentage pulsatile change in aortic area following application of elastic wraps in hypertension. * $p < 0.001$ c/w baseline.

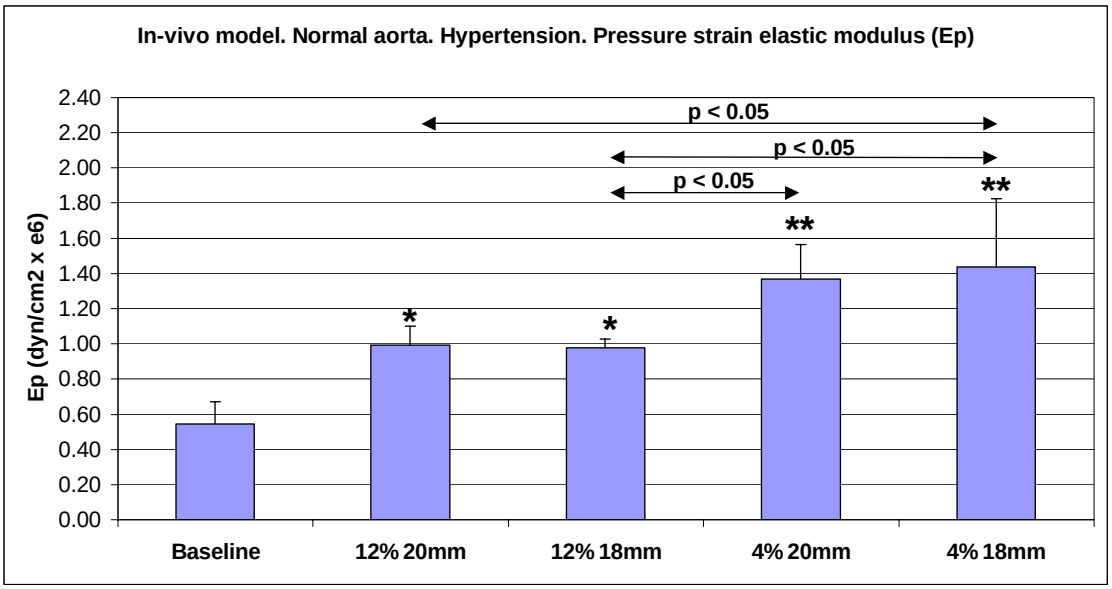


Figure 30 Alterations pressure strain elastic modulus following application of elastic wraps in hypertension.

* $p < 0.05$, ** $p < 0.001$ c/w baseline. Arrows indicate between groups comparison.

3.4 DISCUSSION

3.4.1 Animal model

An animal model was used so that the alterations in aortic stiffness produced by wrap application could be measured in-vivo where the vessel is distended by physiologic pulsatile pressure and flow. The contour of the pressure waveform in the sheep aorta is similar to that seen in the young human subjects (Nichols and O'Rourke 2005). The sheep model has been used extensively as an animal model for cardiovascular research.

Specifically, the sheep model has been used for the:

1. Investigation of arterial pressure and flow and the effect of pharmacologic agents on arterial pressure and flow (Matalon, Nesarajah et al. 1982; Breuhaus and Chimoskey 1983; Matalon, Nesarajah et al. 1983; Nesarajah, Matalon et al. 1983; Breuhaus, Saneii et al. 1985; Huang, Upton et al. 1997; Segers, Steendijk et al. 2001);
2. Investigation of the mechanical properties of the aorta (Mangell, Lanne et al. 1996; Wells, Langille et al. 1998a; Wells, Adamson et al. 1998b; Wells, Langille et al. 1999; Lansac, Lim et al. 2002);
3. Investigation of ventricular-vascular interaction (Aoyagi, Fujii et al. 1992a; Aoyagi, Mirsky et al. 1992b; Aoyagi, Fujii et al. 1993; Cabrera Fischer, Christen et al. 1999; Segers, Steendijk et al. 2001; Cabrera Fischer, de Forteza et al. 2004);
4. Development of prosthetic valves, arterial conduits, and other cardiovascular devices (Boudghene, Sapoval et al. 1996; Power, Raman et al. 1999; Nojiir, Kijima et al. 2000; Soula, Janne d'Othee et al. 2001; Bar-El, Tio et al. 2003; Doll, Kornherr

et al. 2003; Meer, James et al. 2003; Opitz, Schenke-Layland et al. 2004; Ueberrueck, Tautenhahn et al. 2005);

5. Investigation of the mechanical properties, structural alterations, and haemodynamic effects of prosthetic valves and arterial conduits in-vivo (Chanda, Kuribayashi et al. 1997; Zilla, Weissenstein et al. 2000; Puc, Marra et al. 2001; Trantina-Yates, Weissenstein et al. 2001).

The sheep model has also been used as an animal model of heart failure, with heart failure induced by rapid ventricular pacing, induction of myocardial infarction, and aortic banding to increase cardiac load (Llaneras, Nance et al. 1994; Rademaker, Charles et al. 1996; Rademaker, Charles et al. 1997; Rademaker, Cameron et al. 2000; Walther, Falk et al. 2000; Byrne, Raman et al. 2002; Raman, Byrne et al. 2003).

The proximal descending thoracic aorta of the sheep was used as the site to be wrapped in this study, as it is easily accessible through a left thoracotomy incision. The arch of aorta and descending thoracic aorta of sheep are anatomically similar to humans, with the exception that the arch of aorta in sheep has only one branch arising from its convexity (May 1970). This common brachiocephalic artery gives rise to the right and left subclavian arteries and the right and left common carotid arteries. In humans, the arch of aorta gives three branches from its convexity; the brachiocephalic artery, the left common carotid artery, and the left subclavian artery. All other anatomic relations of the aortic arch and descending aorta are similar in sheep and humans.

In sheep, the region from the distal arch of aorta to the end of the proximal descending thoracic aorta is free of arterial branches; however, it is tethered to the bifurcation of the main pulmonary artery by the ligamentum arteriosum (May 1970). Once the ligamentum arteriosum is divided to separate the distal arch of aorta from the

pulmonary artery, the aorta is easily mobilized circumferentially without the need to ligate any branches to facilitate wrap placement, and without disruption of the vasa vasorum. Ligation of intercostal branches or disruption of the vasa vasorum may alter the mechanical properties of the aortic wall by inducing ischaemia or infarction of the aortic media (Stefanadis, Vlachopoulos et al. 1995; Angouras, Sokolis et al. 2000).

The region of the descending thoracic aorta was used for this study, as opposed to the ascending aorta, for the following reasons:

1. The ascending aorta in the sheep is very short and intimately adherent to the pulmonary trunk. The ascending aorta cannot be dissected from the main pulmonary artery in-vivo without injuring these vessels.
2. The endpoint of the study was the alteration in the stiffness of the wrapped vessel, rather than the alteration in the ascending aortic pressure and flow wave, and ventricular-vascular interaction.

The sheep proximal descending thoracic aorta provides an easily accessible large elastic artery subjected to physiologic pressure and flow. It is easily mobilised and dissected free of surrounding structures and tissues, thereby facilitating placement of the elastic wrap as well as placement of external ultrasonic crystals for the measurement of pulsatile aortic diameter. Further, the region of the distal arch of aorta and proximal descending aorta in the sheep resembles the geometry of the ascending aorta in the human (the region that will be wrapped in the human).

3.4.2 Measurement of aortic stiffness

Arterial pressure was measured using an intravascular catheter tip manometer, and aortic diameter was measured using sonomicrometers (Pagani, Schwartz et al. 1975;

Bertram 1977; Pagani, Baig et al. 1978; Pagani, Mirsky et al. 1979; Gentile, Chuong et al. 1988; Latson, Hunter et al. 1988; Armentano, Levenson et al. 1991; Barra, Armentano et al. 1993; White, Kavanaugh et al. 1994; Armentano, Barra et al. 1995; Lansac, Lim et al. 2002). The use of sonomicrometers to measure aortic diameter has a number of advantages over other techniques used to measure arterial diameter:

1. Sonomicrometers impose minimal load or mechanical constraint on the arterial wall and do not significantly affect arterial wall stiffness.
2. Sonomicrometers have a high resolution (0.1mm) for the measurement of arterial diameter.

Aortic stiffness was expressed as the pressure strain elastic modulus (E_p) (Peterson, Jensen et al. 1960). Calculation of pressure-strain elastic modulus does not require measurement of arterial thickness and so can be used as an in-vivo measurement of arterial stiffness. Use of pressure-strain elastic modulus also allows comparison of stiffness data obtained from previous studies.

3.4.3 Induction of hypertension

Infusion of metaraminol produced a reproducible rise in systolic, mean, and diastolic arterial pressure. Metaraminol is an α-1 agonist (as well as β-1 agonist)that produces peripheral arterial vasoconstriction (Hoffman 2001; Kee 2003). The global increases in blood pressure produced by peripheral arterial vasoconstriction differs from the blood pressure changes produced by aortic stiffening and dilatation (increased systolic and mean arterial pressure and decreased diastolic pressure) that are seen in isolated systolic hypertension and aging (Nichols and O'Rourke 2005).

Increases in systolic pressure beyond 140mmHg secondary to infusion of metaraminol are associated with the development of lethal arrhythmias in the sheep (unpublished data). The rise in systolic pressure in this study (greater than 130mmHg) was sufficient to bring aortic wall stress to the ascending limb of the aortic wall stress-strain curve, and so simulate aortic systolic wall stiffness seen in systolic hypertension (Pagani, Baig et al. 1978).

3.4.4 Elastic wrap application

Application of both elastic wraps (12% and 4%) to reduce the diameter of the aorta ,increased the stiffness of the aorta in this study. The increase in aortic stiffness (E_p) produced by elastic wrap application in this study was not as great as the increase in aortic stiffness produced by application of a non-elastic wrap (e.g. Dacron) that has been reported in the literature (Tropea, Schwarzacher et al. 2000). Tropea (2000) showed that application of a non-elastic Dacron wrap to the descending thoracic aorta (in a rabbit model of hypertension) increased aortic stiffness by a factor of 3.3. In the present study, the greatest increase in aortic stiffness was seen with application of the 4% stiffness 18mm diameter wrap, which increased aortic stiffness by a factor of 2.62 in hypertension. Application of the 12% 18mm wrap only increased aortic stiffness by a factor of 1.78 in hypertension.

Application of the stiffer material (4% stiffness material) in this study produced a stiffer aorta than application of the less stiff material (12% stiffness material) (however, this was not significant). The stiffness of the wrap material therefore influences the stiffness of the wrapped vessel.

Whilst the thickness of the aortic wall or combined thickness of the aortic wall and wrap material was not measured, these thicknesses must also play a role in determining the

final stiffness when Young's modulus is considered (see Section 2.5.5). The application of an elastic wrap to the aorta increases thickness and so would increase Young's modulus (and Ep) even if the material has the same distensibility as the wrapped aorta. This may explain the increase in Ep that is produced by application of a wrap material (12% material), despite the material being less stiff than the wrapped aorta.

Application of an elastic wrap to the aorta that reduces the diameter of the aorta may result in the load of pulsatile flow and pressure being borne at least partly by the elastic wrap rather than the aortic wall. The wrap may unload the aortic wall so that the aortic wall stress moves to the more horizontal part of the aortic wall stress-strain curve (Pagani, Baig et al. 1978). The final stiffness of the wrapped artery is then likely to be determined by:

1. The mechanical properties of the arterial wall.
2. The mechanical properties of the wrap material.
3. The distending pressure and contour of the pressure wave.

Although the two diameter reductions of wrap application (18mm and 20mm) did not produce significantly differing stiffness in this study, the extent of diameter reduction may also determine the stiffness of the wrapped aorta.

3.5 CONCLUSIONS

In conclusion, application of an elastic wrap to the normal sheep descending thoracic aorta will increase its stiffness. The increase in aortic stiffness produced by application of an elastic wrap is not as great as the increase in aortic stiffness produced by application of a non-elastic wrap (e.g. Dacron).

The stiffness of the elastic wrap material will influence the stiffness of the wrapped aorta. Application of a less stiff elastic wrap material (12% stiffness) to the normal sheep descending aorta produces a smaller increase in aortic stiffness than application of a more stiff elastic wrap material (4% stiffness).

The stiffness of the wrapped aorta is determined by the mechanical properties of the aortic wall and wrap material, the distending pressure, and possibly by the diameter reduction produced by wrap application. The elastic wrap may act to unload the aortic wall so that the load of pulsatile pressure and flow is partially borne by the elastic wrap material.

Application of an elastic wrap to a stiffened and dilated ascending aorta (as seen in elderly humans) may therefore reduce its stiffness by unloading the aortic wall and bearing the load of pulsatile pressure and flow.

CHAPTER 4: THE EFFECT OF APPLICATION OF AN ELASTIC WRAP IN AN OVINE MODEL OF AORTIC DILATATION AND STIFFNESS

4.1 INTRODUCTION

The aorta and large elastic arteries stiffen and dilate with age as a result of repeated cyclic stress through life (Nichols and O'Rourke 2005). Stiffening and dilatation of the aorta and large elastic arteries produces isolated systolic hypertension and an increase in cardiac load, and is the fundamental cause of heart failure in the elderly (Nichols, Nicolini et al. 1992; Westerhof and O'Rourke 1995; Hundley, Kitzman et al. 2001; Nichols and O'Rourke 2005). Medications currently used to treat isolated systolic hypertension and cardiac failure do not target aortic stiffening and dilatation (Safar and London 2000; Van Bortel, Struijker-Boudier et al. 2001; Bristow, Linas et al. 2005; Hunt, Abraham et al. 2005; Nichols and O'Rourke 2005). Furthermore, there is no effective surgical treatment of aortic dilatation and stiffness.

The use of an elastic wrap to reduce the diameter of the stiffened and dilated ascending aorta in elderly humans has been proposed as a treatment of aortic stiffening and dilatation. Application of an elastic wrap to reduce the diameter of the aged ascending aorta is expected to restore aortic elasticity and improve ventricular-vascular interaction and has been suggested as a treatment for isolated systolic hypertension and heart failure in the elderly.

The aims of this study were to develop an adult sheep model of aortic stiffness and dilatation and to determine the effect of elastic wrap application on the stiffness of this model. The relationship between aortic pressure and diameter (stiffness) was studied before and after the application of the elastic wrap on the model of aortic dilatation and stiffness.

4.2 MATERIALS AND METHODS

Neutered adult male sheep were used in this study (see Appendix 1). Two pilot studies and five definitive studies were used. The pilot studies were designed to develop and refine the surgical, anaesthetic and measurement techniques to minimise trauma to the animal. The data from the two pilot studies provided insight into the variation in the data from the definitive studies. Based on prehoc power assessments a sample of 5 animals was deemed adequate to demonstrate a difference in graft stiffness before and after elastic wrap application.

4.2.1 Anaesthesia

Adult sheep underwent intravenous induction of general anaesthesia (Pentobarbitone sodium; 30mg/kg), which was maintained after endotracheal intubation using inhalational agents (halothane 2-3% in 100% oxygen). Lung ventilation was achieved using a positive pressure ventilator. Physiologic parameters were monitored during the procedure (see Appendix 1).

4.2.2 Surgery

Femoral arterial line

Exposure of the left femoral artery was made for placement of an arterial sheath for insertion of a 7 French Millar Catheter (Model SPC-771; Millar Instruments, Houston, TX). A 5 cm longitudinal skin incision was made in the left femoral region over the femoral artery. The soft tissue and muscle overlying the femoral artery were divided using electrocautery to expose the vessel. The vessel was isolated between two #1 silk ligatures.

After anticoagulation with intravenous heparin (5000IU) an arterial sheath was inserted into the femoral artery, and secured with the silk sutures.

Thoracotomy

The procedure was performed trough a left thoracotomy incision. At the level of the third intercostal space, a skin incision was made from the ventral portion of the latissimus dorsi ventrally along the cranial margin of the fourth rib for a distance of approximately 20 cm towards the costochondral junction taking care to avoid the internal thoracic artery.

With electrocautery, the cutaneous trunci muscle and the superficial pectoral muscle (transverse part) were incised within the length of the skin incision. The latissimus dorsi muscle was only incised for a few centimetres at its ventral margin. The external and internal intercostal muscles were incised at the cranial margin of the fourth rib, and the pleural space was entered by bluntly perforating the pleura with a Pean forceps. The pleura was incised along the length of the skin incision.

The ribs were retracted to expose the distal arch of aorta, proximal descending thoracic aorta, pericardium, left lung root, and left azygos vein. The upper lobe of the left

lung was packed with surgical gauze to facilitate exposure of these structures. The proximal part of the descending thoracic aorta (lying cranial to the left azygos vein) has no intercostal branches and was dissected free from surrounding structures. The left azygos vein overlying the aorta was mobilised and ligated and divided between two #1 silk sutures.

The ligamentum arteriosum was divided using electrocautery and the distal part of the arch of aorta was divided free of surrounding structures. The mobilised segment of aorta was cross-clamped at its proximal and distal ends using two arterial clamps. The mobilised segment of the descending aorta was then resected (approximately 3cm of aorta was resected).

A Dacron aortic graft (22mm diameter; Haemashield, Meadox Medicals Inc, Oakland NJ), of larger diameter than the native aorta, was anastomosed into the intervening segment using continuous proline sutures. The cross clamps were removed to re-establish normal circulation. Cross clamp time was approximately 30 minutes.

4.2.3 Instrumentation

A 7F Millar catheter was inserted through the femoral artery and advanced into the proximal descending thoracic aorta and was be used to measure the arterial pressure waveform in the region of the Dacron graft, before and after the application of the elastic wraps to the Dacron graft. The position of the tip of the catheter was confirmed manually prior to data collection.

One pair of ultrasonic crystals (Model VD5-2; Triton technology, San Diego, Cal) was placed on the external surface of the Dacron graft to measure external diameter. The transit time signal of the ultrasonic signal was converted into distance using a sonomicrometer (Model 200-201; Triton Technology, San Diego, CA). They were used to

measure the pulsatile diameter of the Dacron graft before and after application of the elastic wraps.

4.2.4 Elastic material

An elastic silicon polymer was used as the elastic wrap material. The mechanical properties of the material were measured using uniaxial tensile testing (see Chapter 8). The material was developed by Medtronic (Medtronic, Inc., Minneapolis, MN) to simulate the mechanical properties of the young human ascending aorta (4% stiffness material) and pulmonary artery (12% stiffness material) for the in-vitro testing of prosthetic valves.

Two materials of differing stiffness were used in this study:

1. 4% stiffness material: cylindrical lengths of this material show a 4% increase in diameter with each pulsation when exposed to simulated physiologic pressure and flow in an in-vitro set up.
2. 12% stiffness material: cylindrical lengths of this material show a 12% increase in diameter with each pulsation when exposed to simulated physiologic pressure and flow in an in-vitro set up.

The material comes in prefabricated cylindrical lengths. Two cylindrical segments of each elastic material (internal diameter 30mm, length 3cm) were divided along the longitudinal axis at one point to form a rectangular piece of material.

Each piece of material was marked with four sutures, forming lengths of 63cm and 57cm between the sutures. The distance between these sutures indicated the internal circumference of the wrap material when the material was fixed at these sutures with an arterial clamp to form a cylinder. The arterial clamp used to fix the material around the Dacron graft grasped the elastic material external to the sutures.

The distances between the sutures were derived by multiplying the desired internal diameter of the wrap by pi (3.14). The two internal diameters of the elastic wrap evaluated in this study were 20mm (circumference 63cm), and 18mm (circumference 57cm).

4.2.5 Experimental protocol

Study design

A repeated measures study design was used to reduce the variation in results and therefore minimise the number of animals required for the study.

Dacron graft - normotension

When haemodynamic steady state was achieved two readings of arterial pressure and diameter of the Dacron graft (simulating the stiff and dilated aorta seen in the elderly) were taken. The position of the tip of the pressure catheter was at the same level as the ultrasonic crystals. This was confirmed manually prior to haemodynamic measurement.

Elastic wraps - normotension

Both the 4% stiffness material and 12% stiffness material were used in the study. The two internal diameters of the wrap material evaluated were 20mm and 18mm. The material was applied externally to the Dacron graft over the ultrasonic crystals to reduce the diameter of the Dacron graft. The wrap was fixed with an arterial clamp at the points indicated by the sutures, and the readings taken when haemodynamic steady state was achieved.

Two separate readings were taken for the 20mm 4% wrap and 18mm 4% wrap. Two separate readings were taken for the 20mm 12% wrap and 18mm 12% wrap. Application of

wraps was randomised and the surgeon was blinded to the nature of the material (i.e. 4% versus 12% stiffness material) to reduce bias.

Dacron graft - hypertension

Hypertension was induced with intravenous infusion of Aramine (Metaraminol Bitartrate). Two readings were taken once the systolic blood pressure had reached 130mmHg and haemodynamic steady state had been achieved.

Elastic wraps - hypertension

Two separate readings were taken for the 20mm 4% wrap and 18mm 4% wrap in the hypertensive condition (as above). Two separate readings were taken for the 20mm 12% wrap and 18mm 12% wrap in the hypertensive condition (as above).

Sacrifice

The animal was humanely euthanised at the end of the procedure with a lethal injection of Pentobarbitone Sodium (90mg/kg).

4.2.6 Data analysis

A System 6 mainframe (Model 200-200; Triton Technology, San Diego, CA) was fitted with a sonomicrometer module (Model 200-201; Triton Technology, San Diego, CA) and a dual pressure model (Model 200-204; Triton Technology, San Diego, CA) for the measurement of graft diameter and pressure. Data was digitised and analysed on a CA recorder (Data integrated scientific systems, Pinckney, Michigan) and was displayed in real time during data collection. Data was sampled simultaneously at a frequency of 500Hz.

During the haemodynamic steady state condition a series of at least 5 beats were digitised and averaged for the calculation of:

1. Mean, systolic, diastolic and pulse pressure values.
2. Maximum and minimum graft diameter.
3. Heart rate.
4. Pressure-strain elastic modulus.

The pressure strain-elastic modulus (E_p) is a measurement of the elastic properties (stiffness) of the Dacron graft and is calculated using the following formula (Peterson, Jensen et al. 1960):

$$E_p = (dP/dD) \times D$$

Where, D_m = minimum diameter

dD = pulsatile change in diameter (maximum diameter minus the minimum diameter).

dP = pulse pressure (systolic pressure minus diastolic pressure)

Haemodynamic data and graft diameter, area, and stiffness data are presented as mean +/- standard deviation. Data were compared graphically using Microsoft Excel (Office 2000; Microsoft Corporation), and analysed using a one-way analysis of variance (ANOVA) followed by a Tukey Honest significant difference post-hoc test using SPPS for Windows (SPSS Inc, Chicago, Illinois). Statistical significance was set at a level of $p < 0.05$.

Figure 31 Schematic of the ovine arch and descending thoracic aorta. The proximal descending thoracic aorta has been clamped proximally and distally and resected.

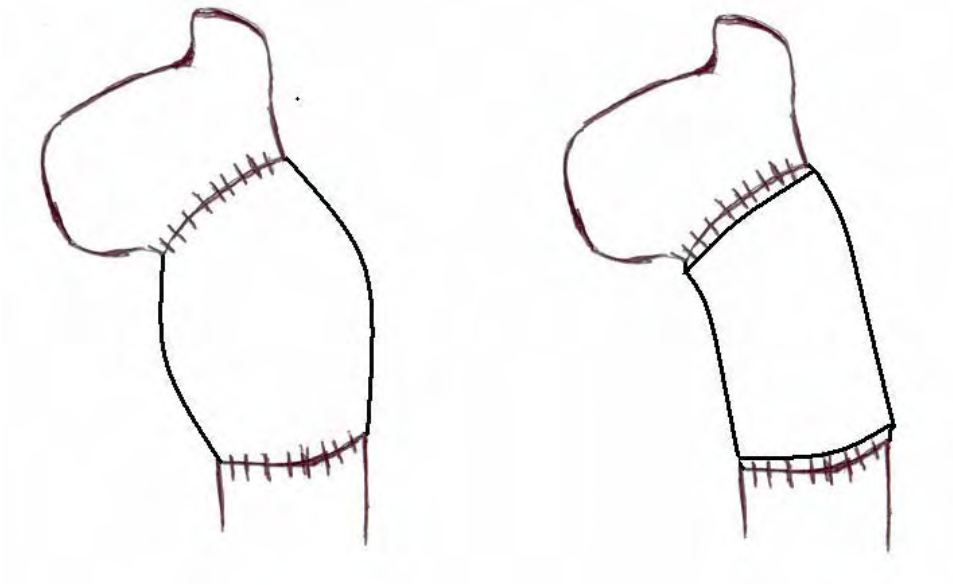


Figure 32 Continuity of the circulation has been re-established by anastomosing an interposition graft (Dacron) with a diameter greater than the diameter of the native aorta. The Dacron graft has been wrapped with an elastic material to reduce its diameter.

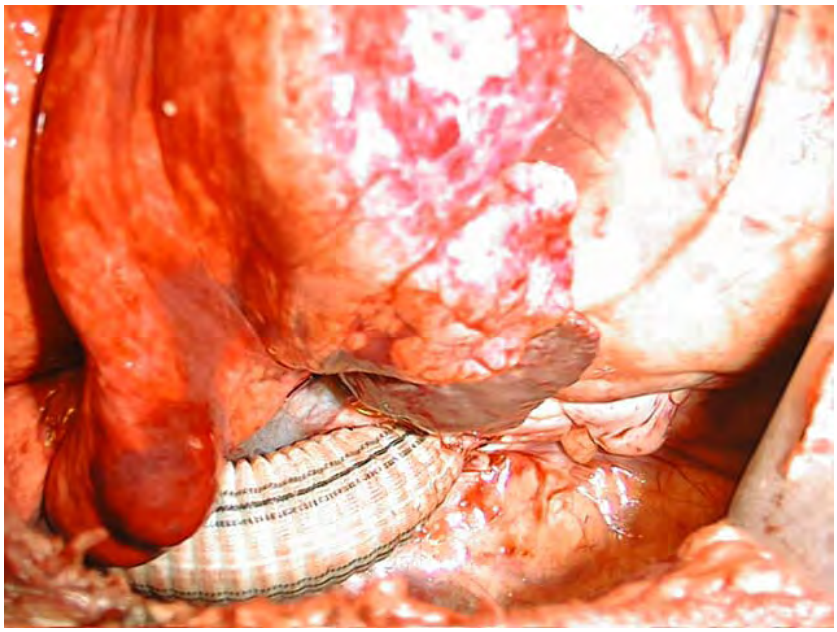


Figure 33 The ovine proximal descending thoracic aorta replaced with an interposition Dacron graft that has a diameter greater than the diameter of the native aorta.

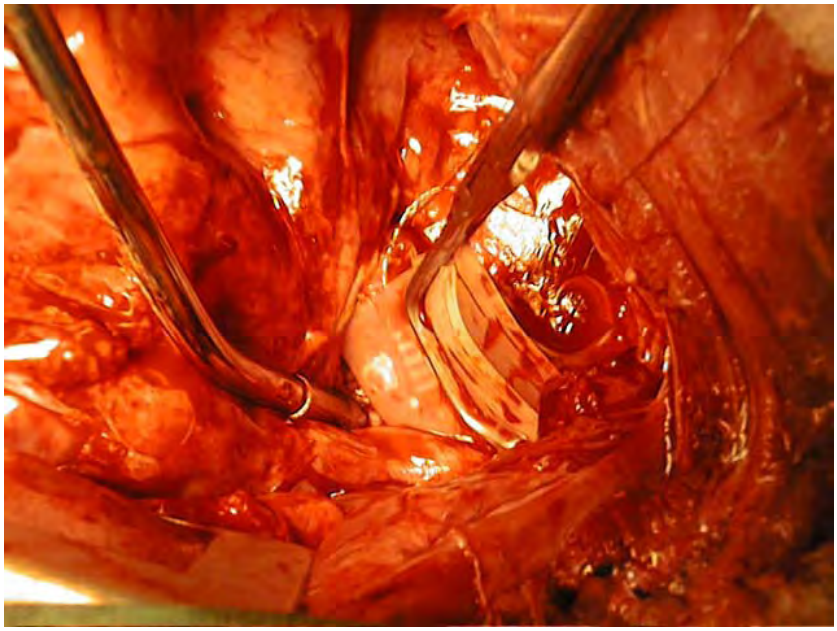


Figure 34 An elastic wrap has been placed around the oversized Dacron graft to reduce the diameter of the Dacron graft.

4.3 RESULTS

All animals survived the entire procedure without requiring defibrillation or administration of inotropic or anti-arrhythmic drugs. There was no evidence of cardiovascular compromise, respiratory failure or hypothermia.

4.3.1 Normotension

Haemodynamics

Normotension (N = 5)	Group 1 Dacron (Base)	Group 2 12% 20mm	Group 3 12% 18mm	Group 4 4% 20mm	Group 5 4%18mm
HR (bpm.)	109 +/- 26.6	102 +/- 22.1	102 +/- 23.2	98 +/- 24.4	99 +/- 23.2
SBP (mmHg)	98 +/- 16.5	91 +/- 18.6	90 +/- 17.7	86 +/- 16.6	88 +/- 15.4
DBP (mmHg)	76 +/- 13.7	70 +/- 15.6	69 +/- 15.1	65 +/- 15.0	67 +/- 14.0
MBP (mmHg)	88 +/- 15.1	81 +/- 16.8	80 +/- 16.1	76 +/- 15.6	76 +/- 16.0
PP (mmHg)	22 +/- 5.9	21 +/- 5.5	20 +/- 4.9	21 +/- 6.0	21 +/- 6.0

HR = heart rate; SBP = systolic blood pressure; DBP = diastolic blood pressure; MBP = mean blood pressure; PP = pulse pressure. Data presented as mean +/- SD.

Table 10 Alterations in haemodynamic parameters following application of elastic wraps to the Dacron graft in normotension.

Following application of the elastic wraps to the Dacron graft there were no significant alterations in heart rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure, or pulse pressure.

Dacron graft diameter, area, and stiffness

Normotension (N=5)	Group 1 Dacron (Baseline)	Group 2 12% 20mm	Group3 12% 18mm	Group 4 4% 20mm	Group 5 4% 18mm
Min D (mm)	22.15 +/- 1.59	16.15 +/- 1.69 **	13.59 +/- 1.86 **	15.16 +/- 1.67 **	12.39 +/- 1.53 **
Max D (mm)	22.27 +/- 1.56	16.48 +/- 1.68 **	13.90 +/- 1.92 **	15.45 +/- 1.68 **	12.67 +/- 1.53 **
δD (mm)	0.12 +/- 0.05	0.33 +/- 0.08 **	0.30 +/- 0.08 *	0.29 +/- 0.05 ##	0.27 +/- 0.03 #
%δD	0.55 +/- 0.25	2.07 +/- 0.57 **	2.22 +/- 0.48 **	1.89 +/- 0.35 **	2.22 +/- 0.36 **
Min A (mm^2)	386.48 +/- 55.06	206.52 +/- 42.84 **	147.22 +/- 42.45 **	182.21 +/- 38.40 **	122.04 +/- 31.13 **
Max A (mm^2)	390.59 +/- 54.46	214.91 +/- 43.44 **	153.88 +/- 44.74 **	189.10 +/- 39.74 **	127.41 +/- 31.89 **
δA (mm^2)	4.11 +/- 1.51	8.40 +/- 2.01 #	6.66 +/- 2.57	6.89 +/- 1.84	5.37 +/- 0.97
%δA	1.10 +/- 0.49	4.18 +/- 1.17 **	4.49 +/- 0.98 **	3.82 +/- 0.72 **	4.49 +/- 0.73 **
Ep (dyn/cm^2 x e6)	6.23 +/- 2.94	1.48 +/- 0.59 **	1.35 +/- 0.64 **	1.58 +/- 0.72 **	1.27 +/- 0.28 **

Min D= minimum graft diameter; Max D = maximum graft diameter; δD = pulsatile change in graft diameter; %δD = percentage pulsatile change in graft diameter [(δD /Min D x 100)]; Min A = minimum graft area; Max A = maximum graft area; δA = pulsatile change in graft area; %δA = percentage pulsatile change in graft area [(δA /Min A x 100)]; Ep = pressure-strain elastic modulus [Ep=(PP/δD)×Min D). (# $p < 0.05$, ## $p < 0.01$, * $p < 0.005$, ** $p < 0.001$ c/w baseline, data presented as mean +/- SD)

Table 11 Alterations in graft diameter, area and stiffness following application of elastic wraps to the Dacron graft in normotension.

Following application of the elastic wraps to the Dacron graft, there was a significant reduction in minimum graft diameter and area in all groups when compared to

baseline graft values. There were no significant differences in minimum graft diameter and area between wrap groups; however the following patterns were evident. Application of a 4% wrap produced a smaller minimum graft diameter and area when compared to a similarly sized 12% wrap. Application of an 18mm wrap produced a smaller minimum graft diameter and area when compared to application of a 20mm wrap.

There was a significant increase in the percentage pulsatile change in graft diameter and area following application of the external elastic wraps when compared to baseline graft values. There were no significant differences in percentage pulsatile change in graft diameter and area between wrap groups; however the following patterns were evident. The percentage pulsatile change in graft diameter and area of the 12% wrap groups was similar to the 4% wrap groups. For each wrap material, application of an 18mm wrap produced a slightly greater percentage pulsatile change in graft diameter and area than application of a 20mm wrap.

The graft stiffness (E_p) of all wrap groups were significantly less than baseline graft values (i.e. application of the elastic wraps reduced the stiffness of the Dacron aortic graft). There were no significant differences in graft stiffness between wrap groups; however the following patterns were evident. The stiffness of the Dacron graft of the 12% wrap groups was similar to the 4% wrap groups (groups 4 and 5). For each wrap material, application of an 18mm wrap reduced graft stiffness slightly more than application of a 20mm wrap did.

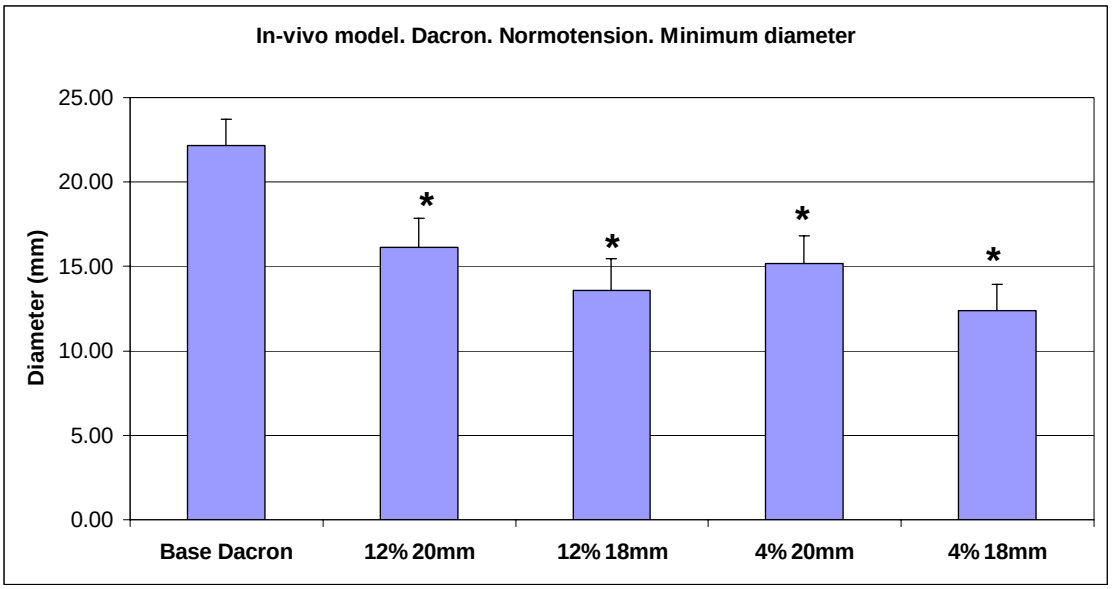


Figure 35 Alterations in minimum graft diameter following application of elastic wraps in normotension. * p < 0.001 c/w baseline.

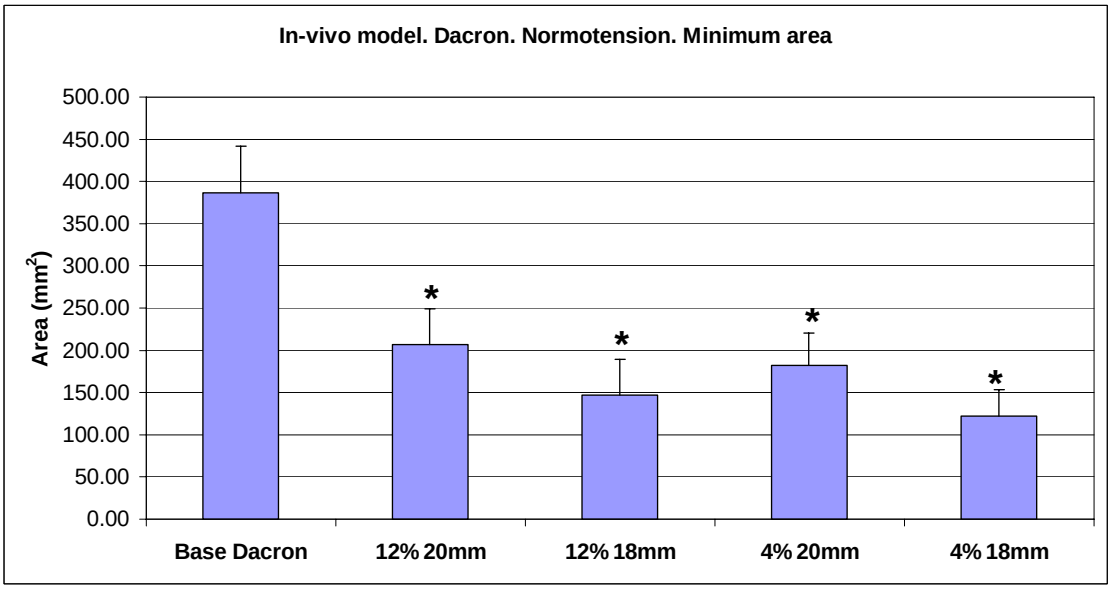


Figure 36 Alterations in minimum graft area following application of elastic wraps in normotension. * p < 0.001 c/w baseline.

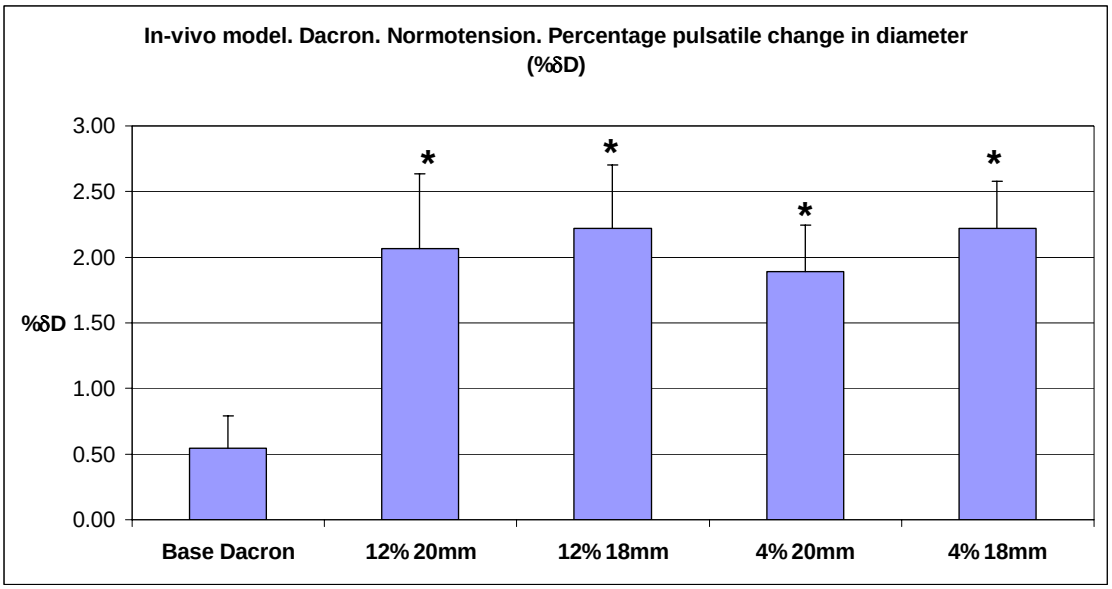


Figure 37 Alterations in percentage pulsatile change in graft diameter following application of elastic wraps in normotension. * $p < 0.001$ c/w baseline.

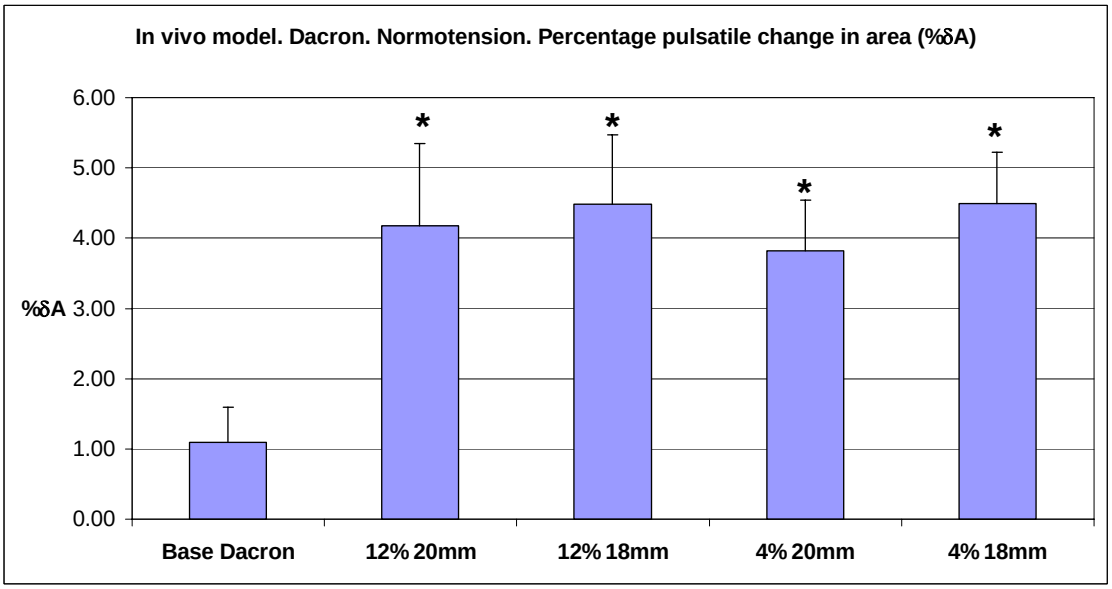


Figure 38 Alterations in percentage pulsatile change in graft area following application of elastic wraps in normotension. * $p < 0.001$ c/w baseline.

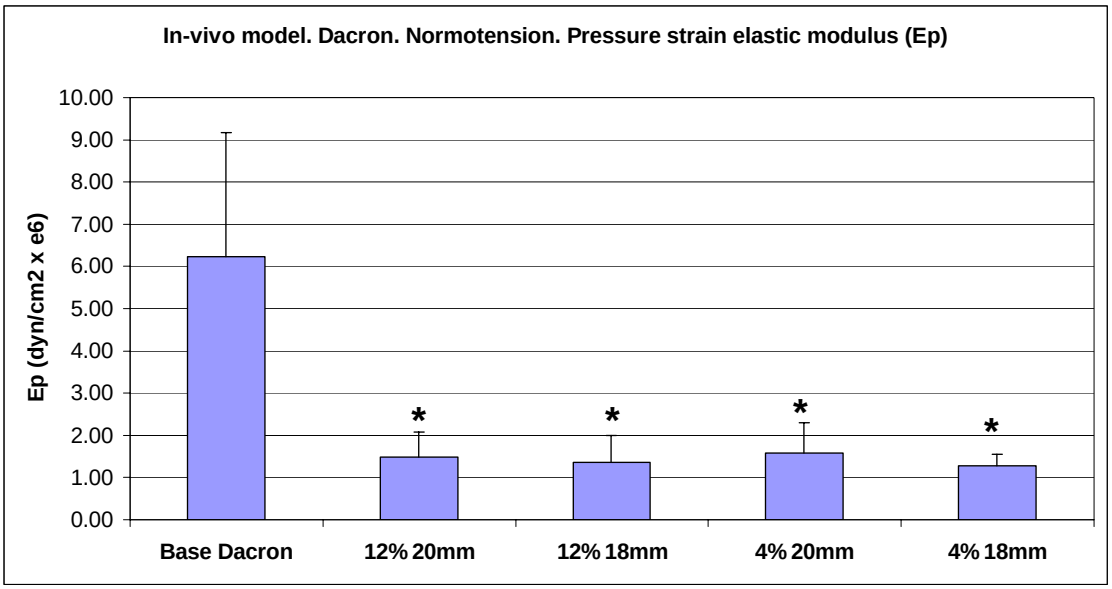


Figure 39 Alterations in pressure strain elastic modulus following application of elastic wraps in normotension. * $p < 0.001$ c/w baseline.

4.3.2 Hypertension

Haemodynamics

(N = 5)	Dacron (Baseline) Normotension	Dacron (Baseline) Hypertension	Significance
HR (bpm.)	109 +/- 26.6	113 +/- 15.1	N/S
SBP (mmHg)	98 +/- 16.5	129 +/- 5.2	P < 0.05
DBP (mmHg)	76 +/- 13.7	103 +/- 7.6	P < 0.05
MBP (mmHg)	88 +/- 15.1	116 +/- 6.0	P < 0.05
PP (mmHg)	22 +/- 5.9	25 +/- 5.4	N/S

HR = heart rate; SBP = systolic blood pressure; DBP = diastolic blood pressure; MBP = mean blood pressure; PP = pulse pressure. Data presented as mean +/- SD.

Table 12 Alterations in baseline haemodynamic parameters following intravenous infusion of Aramine.

Hypertension (N = 5)	Group 1 Dacron(Base)	Group 2 12% 20mm	Group 3 12% 18mm	Group 4 4% 20mm	Group 5 4%18mm
HR (bpm.)	113 +/- 15.1	99 +/- 24.0	109 +/- 16.1	110 +/- 19.3	111 +/- 21.8
SBP (mmHg)	129 +/- 5.2	123 +/- 17.3	127 +/- 15.7	126 +/- 17.9	124 +/- 17.5
DBP (mmHg)	103 +/- 7.6	99 +/- 12.9	102 +/- 12.6	103 +/- 14.3	100 +/- 15.5
MBP (mmHg)	116 +/- 6.0	110 +/- 15.1	114 +/- 13.6	115 +/- 16.1	112 +/- 16.4
PP (mmHg)	25 +/- 5.4	24 +/- 7.4	25 +/- 7.1	23 +/- 5.4	25 +/- 5.1

HR = heart rate; SBP = systolic blood pressure; DBP = diastolic blood pressure; MBP = mean blood pressure; PP = pulse pressure. Data presented as mean +/- SD.

Table 13 Alterations in haemodynamic parameters following application of elastic wraps to the Dacron graft in hypertension.

Following infusion of Aramine there was a significant increase in systolic blood pressure, diastolic blood pressure, and mean arterial pressure. With application of the external elastic wraps there were no significant alterations in the haemodynamic values of the wrap groups when compared to baseline hypertension values.

Dacron graft diameter, area, and stiffness

(N = 5)	Dacron (Baseline) Normotension	Dacron (Baseline) Hypertension	Significance
Min D (mm)	22.15 +/- 1.59	22.41 +/- 1.65	N/S
Max D (mm)	22.27 +/- 1.56	22.50 +/- 1.56	N/S
δD (mm)	0.12 +/- 0.05	0.08 +/- 1.56	N/S
%δD	0.55 +/- 0.25	0.38 +/- 0.11	N/S
Min A (mm^2)	386.48 +/- 55.06	395.96 +/- 57.28	N/S
Max A (mm^2)	390.59 +/- 54.46	398.90 +/- 56.93	N/S
δA (mm^2)	4.11 +/- 1.51	2.94 +/- 0.50	N/S
%δA	1.10 +/- 0.49	0.76 +/- 0.22	N/S
Ep (dyn/cm^2 x e6)	6.23 +/- 2.94	9.23 +/- 2.04	N/S

Min D= minimum graft diameter; Max D = maximum graft diameter; δD = pulsatile change in graft diameter; %δD = percentage pulsatile change in graft diameter [(δD /Min D x 100)]; Min A = minimum graft area; Max A = maximum graft area; δA = pulsatile change in graft area; %δA = percentage pulsatile change in graft area [(δA /Min A x 100)]; Ep = pressure-strain elastic modulus [Ep=(PP/δD)×Min D). Data presented as mean +/- SD)

Table 14 Alterations in baseline haemodynamic parameters following intravenous infusion of Aramine.

Hypertension (N=5)	Group 1 Dacron (Baseline)	Group 2 12% 20mm	Group3 12% 18mm	Group 4 4% 20mm	Group 5 4% 18mm
Min D (mm)	22.41 +/- 1.65	17.20 +/- 1.54 **	15.29 +/- 1.09 **	16.67 +/- 1.74 **	14.52 +/- 2.00 **
Max D (mm)	22.50 +/- 1.56	17.51 +/- 1.68 *	15.60 +/- 1.92 **	16.96 +/- 1.68 **	14.81 +/- 1.53 **
δD (mm)	0.08 +/- 1.56	0.31 +/- 1.68 *	0.31 +/- 1.92 **	0.30 +/- 1.68 *	0.29 +/- 1.53 *
%δD	0.38 +/- 0.11	1.78 +/- 0.58 *	2.06 +/- 0.57 **	1.79 +/- 0.38 *	2.00 +/- 0.39 **
Min A (mm^2)	395.96 +/- 57.28	233.82 +/- 41.39 **	184.25 +/- 26.64 **	219.95 +/- 44.36 **	168.06 +/- 45.26 **
Max A (mm^2)	398.90 +/- 56.93	242.17 +/- 42.33 **	191.87 +/- 27.19 **	227.83 +/- 45.84 **	174.74 +/- 46.64 **
δA (mm^2)	2.94 +/- 0.50	8.34 +/- 2.64 #	7.63 +/- 2.35 ##	7.88 +/- 2.31 ##	6.68 +/- 1.93
%δA	0.76 +/- 0.22	3.60 +/- 1.18 *	4.17 +/- 1.17 **	3.61 +/- 0.77 *	4.04 +/- 0.80 **
Ep (dyn/cm^2 x e6)	9.23 +/- 2.04	1.80 +/- 0.35 *	1.69 +/- 0.39 *	1.78 +/- 0.34 *	1.68 +/- 0.31 *

Min D= minimum graft diameter; Max D = maximum graft diameter; δD = pulsatile change in graft diameter; %δD = percentage pulsatile change in graft diameter [(δD /Min D x 100)]; Min A = minimum graft area; Max A = maximum graft area; δA = pulsatile change in graft area; %δA = percentage pulsatile change in graft area [(δA /Min A x 100)]; Ep = pressure-strain elastic modulus [Ep=(PP/δD)×Min D). (# $p < 0.05$, ## $p < 0.01$, * $p < 0.005$, ** $p < 0.001$ c/w baseline, data presented as mean +/- SD)

Table 15 Alterations in graft diameter, area and stiffness following application of elastic wraps to the Dacron graft in hypertension.

Following infusion of Aramine there was an increase in minimum and maximum Dacron graft diameters and areas when compared to normotension baseline levels (however, this did not achieve statistical significance). Similarly, the pressure-strain elastic

modulus of the hypertension baseline group was greater than the pressure-strain elastic modulus of the normotension baseline level.

Following application of the elastic wraps, there was a significant reduction in minimum graft diameter and area in all wrap groups when compared to baseline graft values. There were no significant differences in minimum graft diameter and area between wrap groups; however the following patterns were evident. Application of a 4% wrap produced a smaller minimum graft diameter and area when compared to a similarly sized 12% elastic wrap. Application of an 18mm wrap produced a smaller minimum graft diameter and area when compared to application of a 20mm wrap.

There was a significant increase in the percentage pulsatile change in graft diameter and area following application of the elastic wraps when compared to baseline graft values. There were no significant differences in percentage pulsatile change in graft diameter and area between wrap groups; however the following patterns were evident. The percentage pulsatile change in graft diameter and area of each 12% was similar to each similarly sized 4% wrap. For both materials, application of an 18mm wrap produced a slightly greater percentage pulsatile change of graft diameter and area than application of a 20mm wrap.

The graft stiffness (E_p) of all wrap groups were significantly less than baseline graft values (i.e. application of the elastic wraps reduced the stiffness of the Dacron aortic graft). There were no significant differences in graft stiffness between wrap groups, however the following patterns were evident. The stiffness of each 12% wrap group was similar to each similarly sized 4% wrap group. For each wrap material, application of an 18mm wrap reduced graft stiffness slightly more than application of a 20mm wrap did.

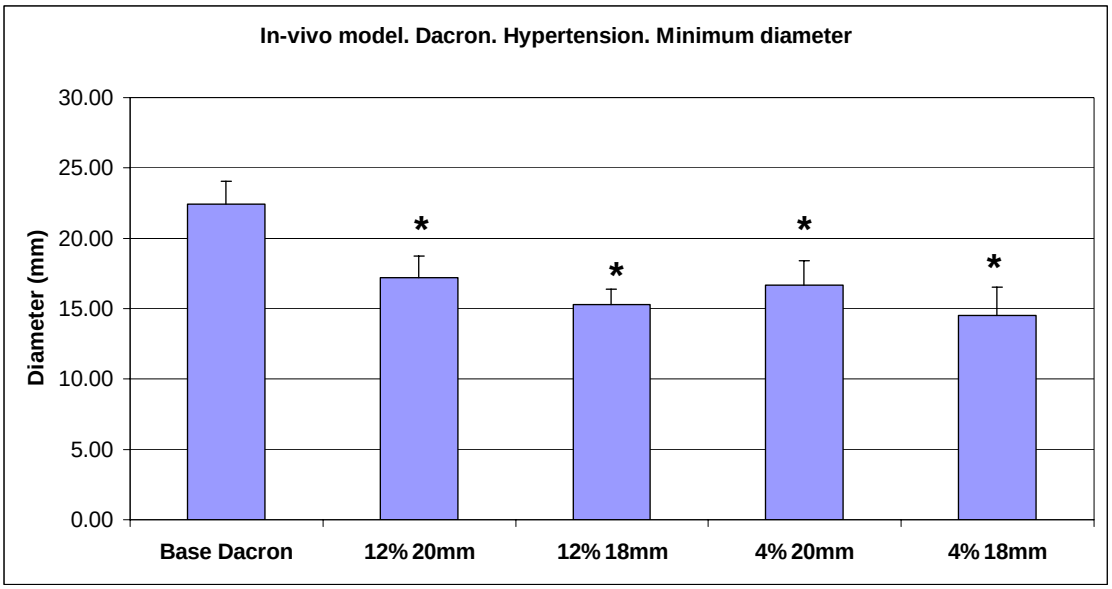


Figure 40 Alterations in minimum graft diameter following application of elastic wraps in hypertension. * p < 0.001 c/w baseline.

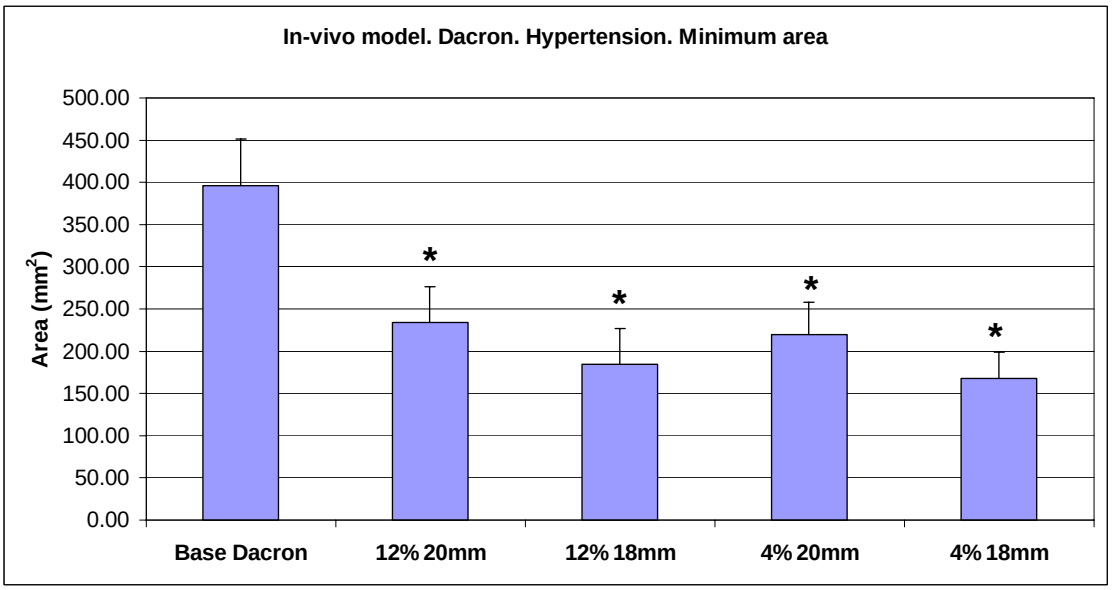


Figure 41 Alterations in minimum graft area following application of elastic wraps in hypertension.

* p < 0.001 c/w baseline.

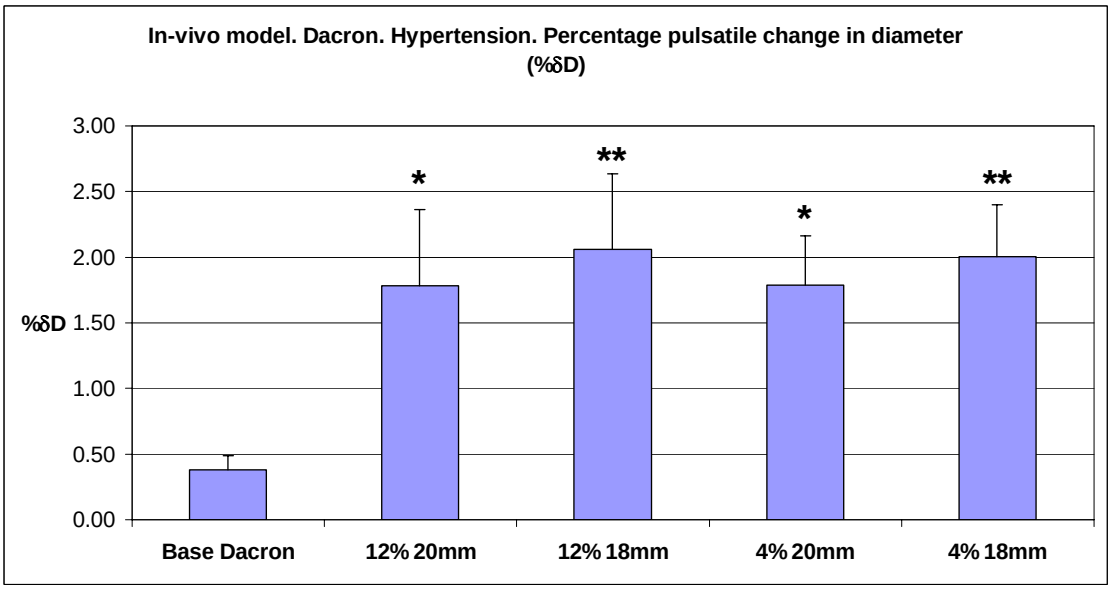


Figure 42 Alterations in percentage pulsatile change in graft diameter following application of elastic wraps in hypertension. * $p < 0.005$, ** $p < 0.001$ c/w baseline.

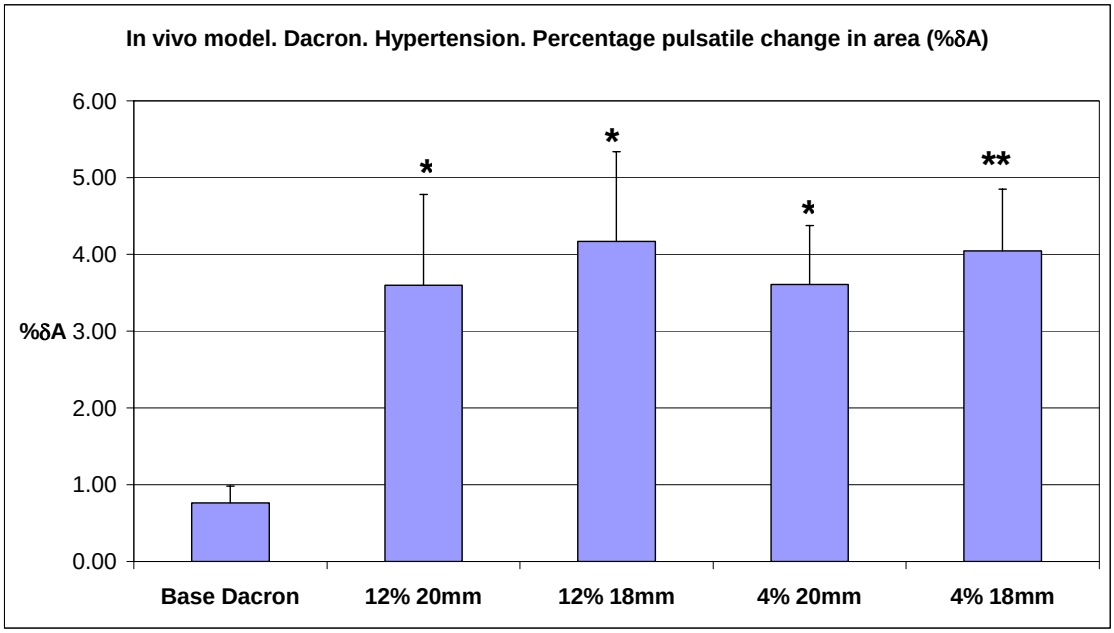


Figure 43 Alterations in percentage pulsatile change in graft area following application of elastic wraps in hypertension. * $p < 0.005$, ** $p < 0.001$ c/w baseline.

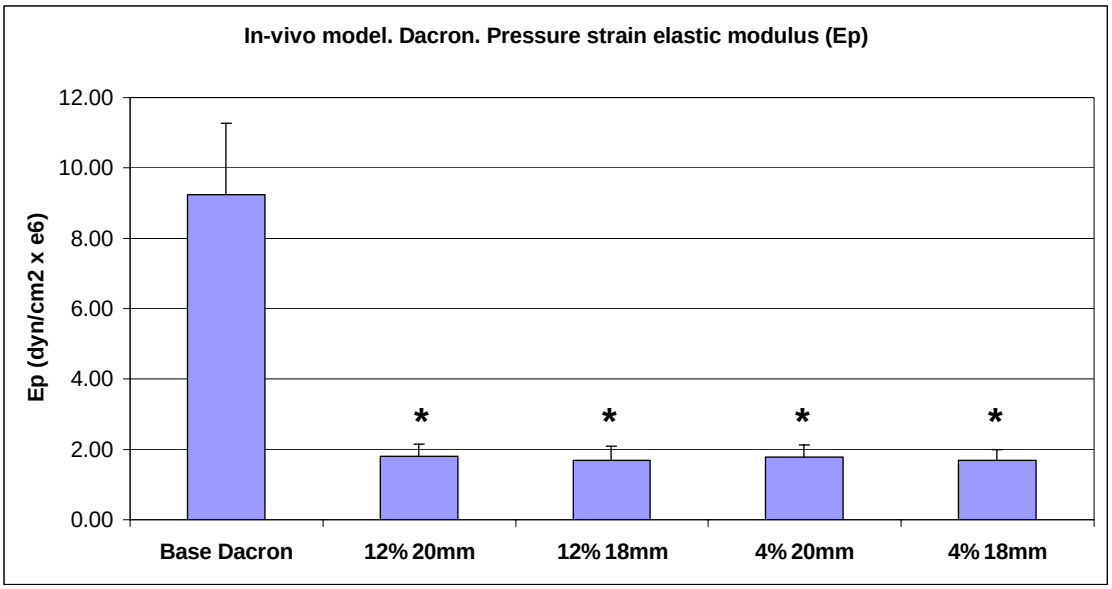


Figure 44 Alterations in pressure strain elastic modulus following application of elastic wraps in hypertension. * $p < 0.001$ c/w baseline.

4.4 DISCUSSION

4.4.1 Animal model

In this study, a large animal model of localised aortic dilatation and stiffness was developed to determine the effect of application of an external elastic wrap on arterial stiffness. Large animal models of aortic stiffening have been described by O'Rourke (1967b), Watanabe et al. (Watanabe, Ohtsuka et al. 1993), Kelly et al. (1992), and Urschel et al. (1968).

O'Rourke (O'Rourke 1967b) applied lucite ferrules to the thoracic aorta to stiffen the thoracic aorta and investigate alterations in ventricular-vascular interaction. Lucite ferrules were not applied to the ascending aorta as an electromagnetic flowmeter was placed around the ascending aorta to measure cardiac output. Watanabe et al. (1993) increased the stiffness of the thoracic aorta and proximal portions of the brachiocephalic trunk and left subclavian artery by applying rigid wraps of nylon tape. Wraps were not applied to the ascending aorta as an electromagnetic flowmeter was also placed around the ascending aorta in this study.

Urschel et al. (1968) used an extra-anatomic glass tube to bypass the descending thoracic aorta in dogs to simulate aortic stiffening. Kelly et al. (1992) described an extra-anatomic bypass extending from the proximal arch of aorta to the abdominal aorta using a 2-3cm long Dacron vascular graft connected to a long stiff plastic tube to simulate aortic stiffening with age. The ascending aorta and aortic root was not used, as replacement of the ascending aorta and aortic root is technically difficult in that it requires cardiopulmonary bypass and cardioplegic arrest, and may require deep hypothermic cardiac arrest. Furthermore, measurement of cardiac output was achieved by placement of an ultrasonic

flow probe on the ascending aorta. Similar models using Dacron vascular grafts as the extra-anatomic graft have been described in dogs (Morita, Kuboyama et al. 1991) and pigs (Mekkaoui, Rolland et al. 2003).

In this study the proximal descending thoracic aorta was resected and replaced with an anatomic oversized Dacron vascular graft to create ovine model of localised aortic dilatation and stiffness where alterations in stiffness of the conduit with wrap application could be assessed in-vivo under physiologic pressure and flow. Oversizing was not used by Kelly et al.(Kelly, Tunin et al. 1992), but was used in this study as it simulates the dilatation that is seen in the aorta and large elastic arteries with aging.

In this study, the region of the proximal descending thoracic aorta was used instead of the ascending aorta for the following reasons:

1. The endpoint of the study was the alteration in the stiffness of the Dacron graft produced by application of the elastic wrap, as opposed to alterations in arterial haemodynamics or ventricular-vascular interaction.
2. The region of the descending thoracic aorta is easily accessible through a left thoracotomy, and a reasonable length may be resected and replaced with an oversized Dacron graft without the use of cardiopulmonary bypass.
3. The ascending thoracic aorta is short in commonly available experimental animals (such as sheep, pigs, and dogs), and replacement of the ascending aorta is technically very challenging.

4.4.2 Measurement of aortic stiffness

Vascular stiffness was expressed as the pressure-strain elastic modulus (E_p) (Peterson, Jensen et al. 1960). Calculation of pressure-strain elastic modulus requires

measurement of pulsatile diameter and pressure, but not arterial wall thickness (Nichols and O'Rourke 2005). Pressure-strain elastic modulus can readily be calculated (in-vivo or in-vitro) and can be used to compare stiffness data from different studies.

The diameter of the Dacron graft was measured using sonomicrometers (Silver, Christiansen et al. 1989; Nichols and O'Rourke 2005), a technique that imposes minimal mechanical constraint on the vessel wall, allows measurement of pulsatile arterial diameter, and has relatively high resolution.

4.4.3 Dacron as a model of aortic stiffening

Polyethylene terephthalate (Dacron) is a stiff material that is used to construct artificial vascular grafts for replacement or bypass of diseased or damaged arteries including the thoracic aorta (Kouchoukos, Wareing et al. 1991; Westaby, Parry et al. 1993; Bezuidenhout and Zilla 2004). Dacron vascular grafts have been used as an extra-anatomic bypass to simulate age-related stiffening of the thoracic aorta in animal models (Morita, Kuboyama et al. 1991; Morita, Asou et al. 2002; Mekkaoui, Rolland et al. 2003).

The stiffness of Dacron aortic grafts exceeds the stiffness of the thoracic aorta of normal adult humans and experimental animals (O'Rourke, Staessen et al. 2002; Bezuidenhout and Zilla 2004). The measured stiffness (E_p) of the Dacron graft in-vivo in this study (9.23 +/- 2.04 dyn/cm^2 x e6) was significantly greater than that of the native sheep descending thoracic aorta measured in Chapter 3 (0.55 +/- 0.13 dyn/cm^2 x e6). Whereas the aorta has a two phase stress-strain curve resulting from recruitment of collagen fibres at lower pressures, the curve operates largely in the upper (more vertical) limb in aged humans with isolated systolic hypertension (Wolinsky and Glagov 1964; Wolinsky and Glagov 1967; Nakashima and Tanikawa 1971). Dacron has a linear stress strain curve

at physiological stress, and this approximates the upper limb of the stress-strain curve of the stiffened aged human aorta (Felden 2005).

4.4.4 Elastic wrap application

Application of the elastic wraps significantly reduced the stiffness of the Dacron graft. The reduction in stiffness produced by application of the 12% and 4% stiffness elastic wraps was not significantly different. Application of an 18mm circumference wrap reduced stiffness more than application of a 20mm wrap (of the same material) but this was not significant.

Application of an elastic wrap to a stiff conduit or vessel, that reduces the diameter of the vessel or conduit, is expected to reduce the stiffness of the vessel or conduit. The elastic wrap may unload the vessel wall or conduit so that the load of pulsatile pressure and flow is borne by the elastic wrap rather than the vessel wall or conduit.

The final stiffness produced by application of the elastic wrap onto the Dacron graft was similar to the final stiffness produced by elastic wrap application on the normal sheep descending thoracic aorta (Chapter 3). The stiffness of the elastic wrap is therefore a major determinant of the final stiffness of the wrapped vessel. The stiffness of the vessel wall and contour of the pressure and flow wave also play a role in the determining the final stiffness of the wrapped vessel or conduit.

In this study, there was no significant difference between the two wrap materials, and the optimal stiffness of the elastic wrap remains unclear. The stiffness of the 4% material approximates that of the young human aorta, and the stiffness of the 12% material simulates that of the young main pulmonary artery. Application of both these materials onto a stiffened and dilated ascending aorta (as seen in elderly humans) is expected to

reduce the stiffness of the ascending aorta. A reduction in the stiffness of the ascending aorta is expected to reduce ascending aortic systolic and pulse pressure, decrease cardiac load, and increase diastolic pressure and myocardial blood flow (Nichols, O'Rourke et al. 1985; Nichols, O'Rourke et al. 1986; O'Rourke, Avolio et al. 1986; Kelly, Tunin et al. 1992; Watanabe, Ohtsuka et al. 1993; Ohtsuka, Kakihana et al. 1994; Westerhof and O'Rourke 1995; Franklin, Gustin et al. 1997; Hundley, Kitzman et al. 2001; Morita, Asou et al. 2002; O'Rourke and Nichols 2005).

4.5 CONCLUSIONS

In conclusion, replacement of the sheep descending thoracic aorta with an oversized Dacron graft is a valid model for localised aortic dilatation and stiffness. Aged human aorta may easily be substituted for Dacron as the interposition graft. The model may be used to assess the alterations in stiffness of the vessel or conduit produced by elastic wrap application.

Application of an elastic wrap to the oversized Dacron aortic graft in-vivo significantly reduced the stiffness of the Dacron graft. The stiffness of the elastic wrap is a major determinant of the stiffness of the wrapped conduit. The elastic wrap may act by unloading the conduit, so that the load of pulsatile pressure and flow is partially borne by the wrap. Application of an elastic wrap to a stiffened and dilated ascending aorta (as seen in elderly humans) may bring the diameter back to that seen in youth, reduce ascending aortic stiffness, and improve ventricular-vascular interaction.

CHAPTER 5: THE EFFECT OF APPLICATION OF AN ELASTIC WRAP IN AN IN-VITRO MODEL OF THE AGED HUMAN ASCENDING AORTA

5.1 INTRODUCTION

Stiffening of the thoracic aorta and large elastic arteries is the fundamental cause of cardiac failure in the elderly (O'Rourke, Avolio et al. 1986; Westerhof and O'Rourke 1995; Hundley, Kitzman et al. 2001; Nichols and O'Rourke 2005). Arterial stiffening is responsible for the increase in systolic pressure and pulse pressure seen with aging, and the resultant increase in left ventricular load and decline in cardiac function (Merillon, Motte et al. 1982b; Nichols, O'Rourke et al. 1985; O'Rourke, Avolio et al. 1986; Westerhof and O'Rourke 1995; Hundley, Kitzman et al. 2001; Nichols and O'Rourke 2005). There is at present no satisfactory medical or surgical treatment that reduces large artery stiffening (Safar and London 2000; Van Bortel, Struijker-Boudier et al. 2001; Bristow, Linas et al. 2005; Nichols and O'Rourke 2005).

Stiffening of the aorta and large elastic arteries with aging is associated with dilatation and is due to repeated cyclic stress on the aortic wall through life (Nichols and O'Rourke 2005). The use of an external elastic wrap to reduce the diameter of a stiffened and dilated vessel so that the load is borne by the elastic wrap has been shown to reduce the stiffness of the vessel (Chapter 4). A reduction in the ascending aortic stiffness in elderly patients is expected to decrease systolic pressure and pulse pressure, increase diastolic pressure and myocardial blood flow, and reduce cardiac load by improving ventricular-

vascular interaction (Nichols, O'Rourke et al. 1985; Nichols, O'Rourke et al. 1986; O'Rourke, Avolio et al. 1986; Kelly, Tunin et al. 1992; Watanabe, Ohtsuka et al. 1993; Ohtsuka, Kakihana et al. 1994; Westerhof and O'Rourke 1995; Franklin, Gustin et al. 1997; Hundley, Kitzman et al. 2001; Morita, Asou et al. 2002; O'Rourke and Nichols 2005).

Although in-vivo animal experiments provide realistic and useful vascular pressure and diameter data, animal experiments often are time consuming and expensive. In vitro experiments on arteries and vascular conduits can provide useful pressure and diameter data using relatively simple test devices.

The aims of this study were to determine the effects of application of the elastic wrap on the stiffness of the aged human ascending aorta, and to determine the resultant changes in pressure using an in-vitro pressure model. A pressure model was constructed in which aged human ascending aorta was subjected to pulsatile pressure and flow. Ascending aortic stiffness and pulsatile pressure were measured before and after application of elastic wraps on the ascending aorta.

5.2 MATERIALS AND METHODS

5.2.1 In-vitro pressure model

Human ascending aorta was removed from aged human cadavers and placed onto the physiological pressure model. The average of the human subjects at the time of death was 82.9 +/- 10.1 years. The human tissues were harvested in accordance with institutional ethics guidelines. Based on prehoc power assessments, a sample of 9 ascending aorta was deemed adequate to demonstrate a difference in aortic stiffness between the wrap groups and baseline, and between wrap groups.

A programmable gear pump was used to produce pulsatile pressure (Ismatech BVP-Z, Switzerland). The pulse rate under resting conditions was 72 beats/min. A two phase pressure waveforms was generated.

The gear pump was computer controlled using mean and amplitude parameters to establish the required pulsatile pressure within the ascending aorta. Water was heated to 37^0C in a water bath and drawn by the gear pump through the ascending aorta. Water then flowed through a mechanical valve (600 WOG 150 SWP Milwaukee valve company Milwaukee, WI) that was used to set the mean pressure within the model. Water then flowed back to the water bath reservoir.

	Age	Sex	Cause of death	Contributing conditions
1	75	M	Heart Failure	Coronary artery disease
2	72	M	Non cardiovascular	
3	86	F	Non cardiovascular	
4	62	M	Non cardiovascular	
5	93	F	Non cardiovascular	
6	93	F	Non-cardiovascular	
7	85	M	Myocardial Infarction	
8	85	F	Motor vehicle accident	Atrial fibrillation
9	87	F	Myocardial infarct	
10	91	F	Renal Failure	Heart failure

Table 16 Age, sex, and cause of death of human subjects.

5.2.2 Instrumentation

A 7 French Millar Catheter (Model SPC-771; Millar Instruments, Houston, TX) was inserted through the rigid tubing proximal to the ascending aorta, advanced to lie within the ascending aorta, and marked at its entry point into the system. The Millar

catheter was used to measure the pressure waveform in this region, before and after the application of each elastic wrap to the ascending aorta. The position of the catheter was confirmed at its entry point to the system prior to data collection.

One pair of ultrasonic crystals (Model VD5-2; Triton technology, San Diego, Cal) was sutured onto the external surface of the ascending aorta to measure external diameter. The transit time signal of the ultrasonic signal was converted into distance using a sonomicrometer (Model 200-201; Triton Technology, San Diego, CA). They were used to measure the pulsatile external diameter of the ascending aorta before and after the application of each aortic wrap.

5.2.3 Elastic material

An elastic silicon polymer was used as the elastic wrap material. The mechanical properties of the material were measured using uniaxial tensile testing (see Chapter 8). The material was developed by Medtronic (Medtronic, Inc., Minneapolis, MN) to simulate the mechanical properties of the young human ascending aorta (4% stiffness material) and pulmonary artery (12% stiffness material) for the in-vitro testing of prosthetic valves.

Two materials of differing stiffness were used in this study:

1. 4% stiffness material: cylindrical lengths of this material show a 4% increase in diameter with each pulsation when exposed to simulated physiologic pressure and flow in an in-vitro set up.
2. 12% stiffness material: cylindrical lengths of this material show a 12% increase in diameter with each pulsation when exposed to simulated physiologic pressure and flow in an in-vitro set up.

The material comes in prefabricated cylindrical lengths. Two cylindrical segments of each elastic material (internal diameter 30mm, length 3cm) were divided along the longitudinal axis at one point to form a rectangular piece of material.

Each piece of material was marked with four sutures. The distance between these sutures indicated the internal circumference of the wrap material when the material was fixed at these sutures with an arterial clamp to form a cylinder. The arterial clamp used to fix the material around the aorta grasped the elastic material external to the sutures.

The distances between the sutures were derived by multiplying the desired external diameter of the aorta by pi (3.14). Mean aortic diameter was measured over a static pressure range of 0-220 mmHg for each aorta, and the reductions in diameter were 0.91, 0.82, and 0.70 of the mean aortic diameter.

5.2.4 Experimental protocol

Study design

A repeated measures study design was used to reduce the variation in results and therefore minimise the number of aortas required for the study.

Pulsatile pressures

The experiments were conducted at three pressure pulsations (85/60; 130/95; 160/90). The first two pressure pulsations simulated those seen in the non-survival animal study. The third pressure pulsation simulated the pressures seen in elderly patients with isolated systolic hypertension. The first pressure simulates a pulsatile pressure in-vivo where the load of pulsatile pressure and flow is predominantly taken up by the elastin fibres in the aortic wall rather than by collagen fibres. The second and third pulsatile pressures

used in this study simulate diastolic hypertension and isolated systolic hypertension, respectively.

Baseline

Baseline readings of ascending aortic diameter and pressure were taken prior to application of each elastic wrap. The position of the tip of the pressure catheter was at the same level as the ultrasonic crystals. This was confirmed prior to haemodynamic measurement.

Aortic pressure

Both the 4% stiffness material and 12% stiffness material were used in the study. The elastic wraps were applied externally to the aorta over the ultrasonic crystals to reduce the diameter of the ascending aorta to 91%, 82%, and 70%, of the mean aortic diameter (measured over a static pressure range of 0-220mmHg). The wrap was fixed with an arterial clamp at the points indicated by the sutures, and the readings taken when haemodynamic steady state was achieved. Two separate readings were taken for each diameter reduction (91%, 82%, and 70%) for both 12% and 4% stiffness materials. Application of wraps was randomised and the investigator was blinded to the nature of the material (i.e. 4% versus 12% stiffness material) to reduce bias.

5.2.5 Data analysis

A System 6 mainframe (Model 200-200; Triton Technology, San Diego, CA) was fitted with a sonomicrometer module (Model 200-201; Triton Technology, San Diego, CA) and a dual pressure model (Model 200-204; Triton Technology, San Diego, CA) for the measurement of aortic diameter and pressure. Waveforms were digitized, displayed in real

time and stored using Lab View software (version 6.1, National Instrument, USA) and a data card (PCI-6024E, National Instrument, USA). A separate Lab View program was used to set and control the gear pump for the desired operating pressure.

The pressure and diameter waveforms were sampled at a rate of 60 samples per simulated cardiac cycle and stored to hard disk using the Lab View monitoring and control system.

During the haemodynamic steady state condition a series of at least 5 beats were digitized, and processed for the calculation of:

1. Maximum, minimum and pulse pressure values
2. Maximum and minimum aortic diameter
3. Pressure-strain elastic modulus

The pressure strain-elastic modulus (Ep) is a measurement of the elastic properties (stiffness) of the aortic wall and is calculated using the following formula (Peterson, Jensen et al. 1960):

$$Ep = (dP/dD) \times D$$

Where, D_m = minimum aortic diameter

dD = pulsatile change in the aortic diameter (maximum aortic diameter minus the minimum aortic diameter).

dP = pulse pressure (maximum pressure minus minimum pressure)

Haemodynamic data and aortic diameter, area, and stiffness data are presented as mean +/- standard deviation. Data were compared graphically using Microsoft Excel (Office 2000; Microsoft Corporation), and analysed using a one-way analysis of variance (ANOVA) followed by a Tukey Honest significant difference post-hoc test using SPPS for

Windows (SPSS Inc, Chicago, Illinois). Statistical significance was set at a level of $p < 0.05$.

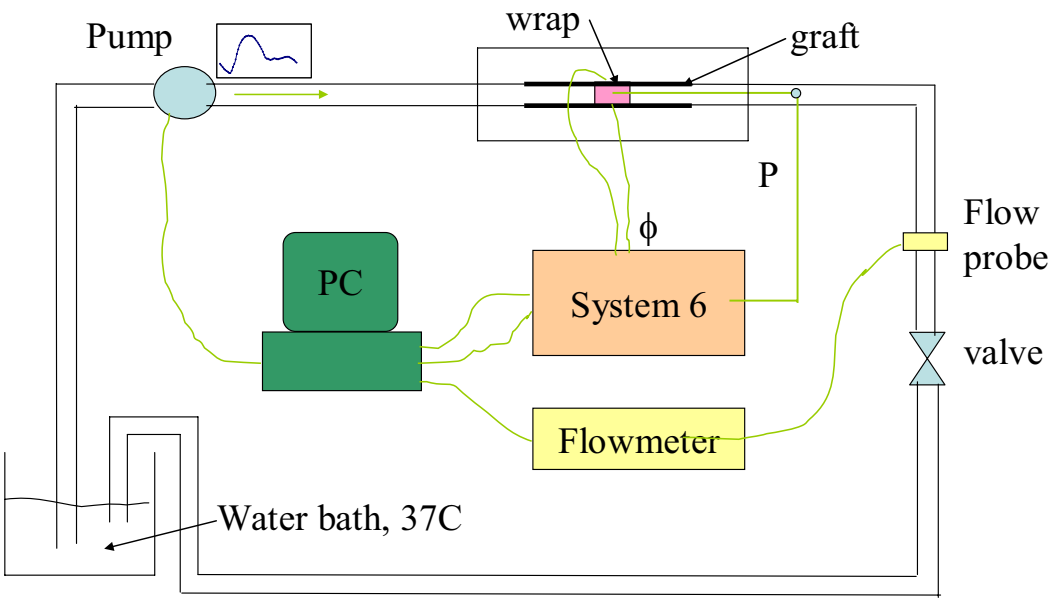


Figure 45 Schematic illustrating the in-vitro pressure model.

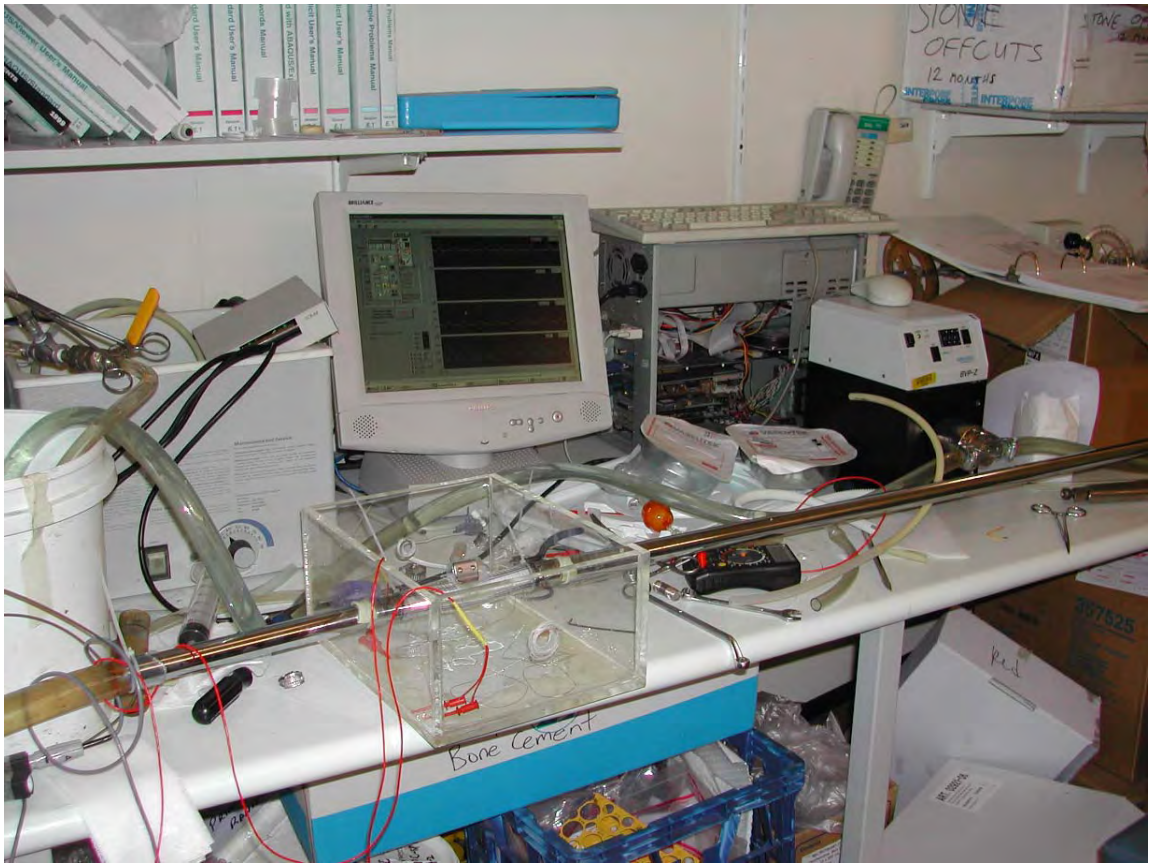


Figure 46 Photograph of the in-vitro pressure model

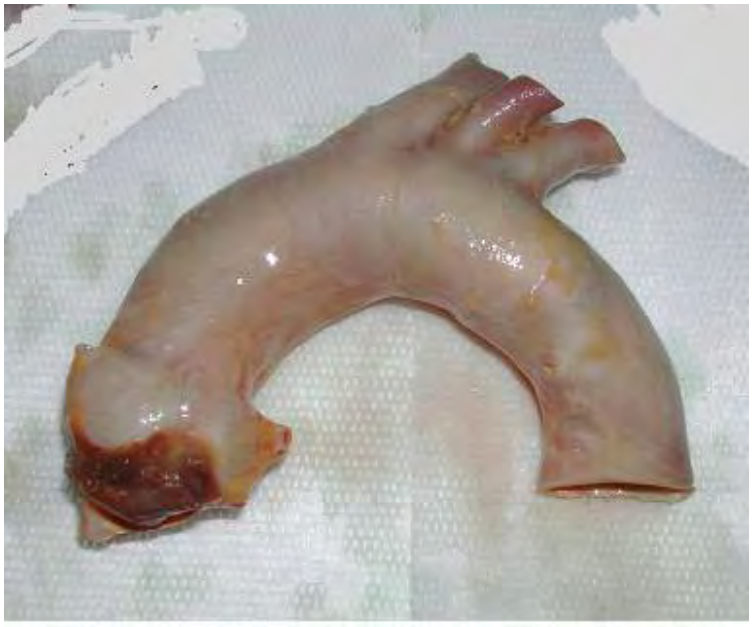


Figure 47 Excised human thoracic aorta

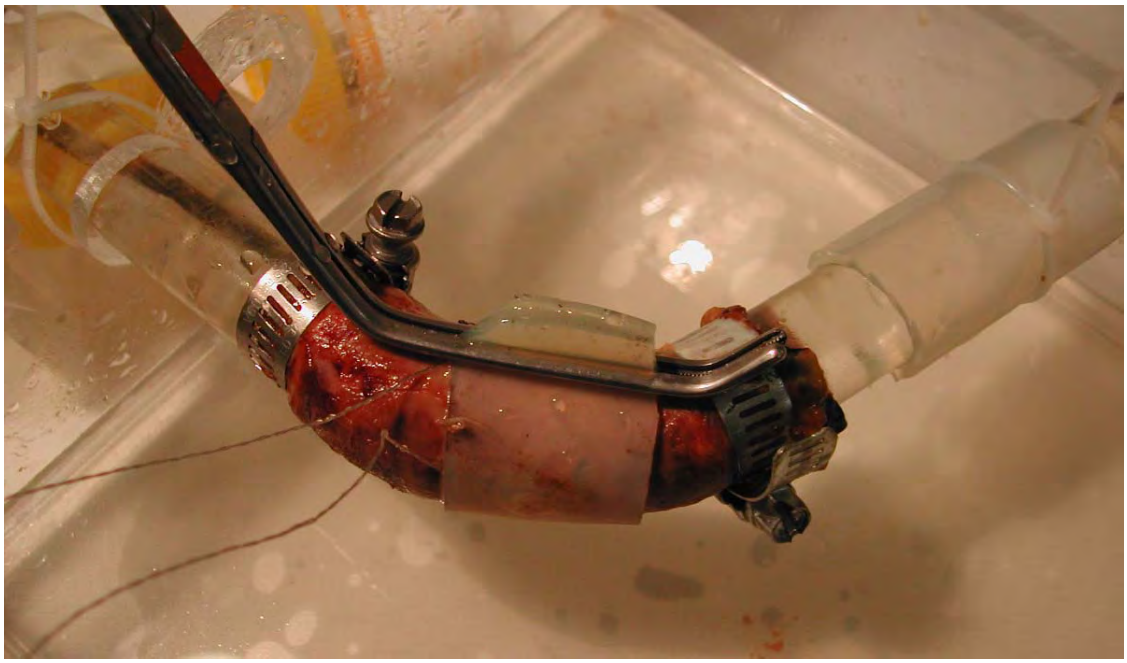


Figure 48 Elastic wrap applied to the human ascending aorta in the in-vitro pressure model.

5.3 RESULTS

5.3.1 Pulsatile pressure 1 (85/60 mmHg)

Haemodynamics

Pressure 1 85/60 (N=9)	Group 1 Aorta (Baseline)	Group 2 12% wrap 91% diam.	Group 3 12% wrap 82% diam.	Group 4 12% wrap 70% diam.	Group 5 4% wrap 91% diam.	Group 6 4% wrap 82% diam.	Group 7 4% wrap 70% diam.
Pmax (mmHg)	84.9 +/- 0.85	82.2 +/- 0.74 **	81.5 +/- 0.90 **	81.7 +/- 1.27 **	82.8 +/- 1.14 *	81.9 +/- 1.04 **	82.4 +/- 1.07 **
Pmin (mmHg)	59.5 +/- 0.85	60.9 +/- 0.95	61.7 +/- 1.05 *	62.6 +/- 1.52 **	61.2 +/- 0.90 #	61.0 +/- 1.04	61.3 +/- 1.27 #
PP (mmHg)	25.4 +/- 0.92	21.3 +/- 0.56 **	19.8 +/- 0.87 **	19.1 +/- 1.16 **	21.6 +/- 1.35 **	20.8 +/- 1.19 **	21.1 +/- 1.12 **

Pmax = maximum pressure; Pmin = minimum pressure; PP = pulse pressure. (# $p < 0.05$, * $p < 0.005$, ** $p < 0.001$ c/w baseline, data presented as mean +/- SD)

Table 17 Alterations in haemodynamic parameters following application of elastic wraps to the aorta at pressure 1.

Following application of elastic wraps there were alterations in maximum pressure, minimum pressure, and pulse pressure.

There was a significant reduction in maximum pressure in all wrap groups when compared to baseline. There were no significant differences in maximum pressure between wrap groups; however the following patterns were evident. The maximum pressure was lower in the 12% wrap groups when compared to the similar diameter reduction 4% wrap groups. For the 12% wrap groups the greatest reduction in maximum pressure occurred

with the 82% diameter reduction group. For the 4% wrap groups the greatest reduction in maximum pressure also occurred with the 82% diameter reduction group.

There was a significant increase in minimum pressure in all wrap groups when compared to baseline. There were no significant differences in minimum pressure between wrap groups; however the following patterns were evident. For the 12% wrap groups the minimum pressure increased as the diameter reduction increased. For the 4% wrap groups the minimum pressure was similar for all groups. For all groups the greatest increase in minimum pressure was in the 12% wrap 70% diameter reduction group.

There was a significant reduction in pulse pressure in all wrap groups when compared to the baseline. For the 12% wrap groups the pulse pressure fell as the diameter reduction increased. For the 4% wrap groups the pulse pressure was similar for all groups. For all groups the greatest reduction in pulse pressure was in the 12% wrap 70% diameter reduction group.

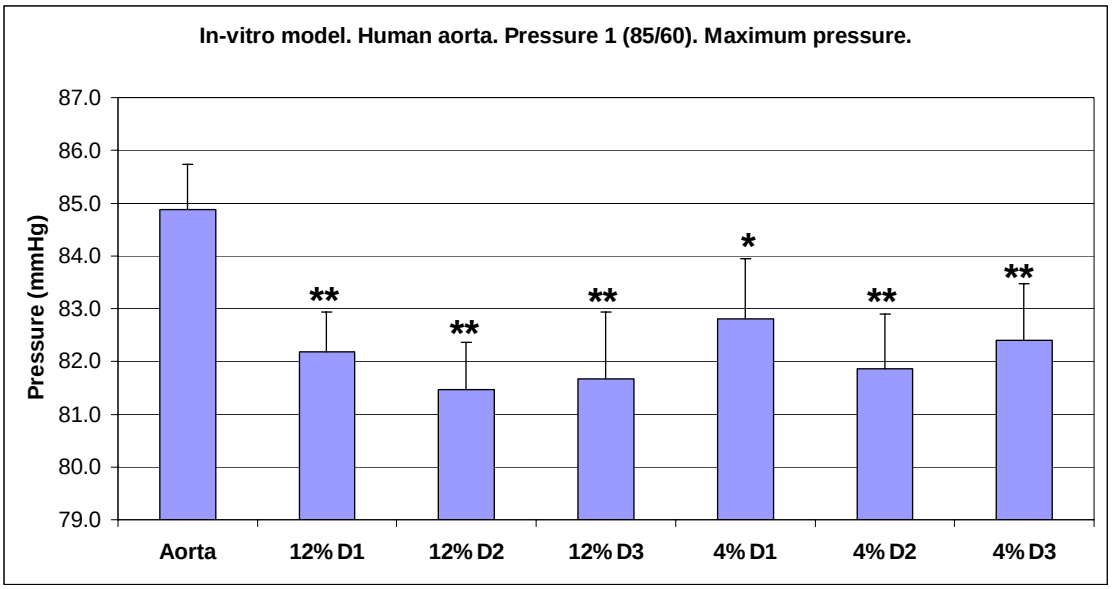


Figure 49 Alterations in maximum pressure following application of elastic wraps at pressure 1.

* $p < 0.005$, ** $p < 0.001$ c/w baseline.

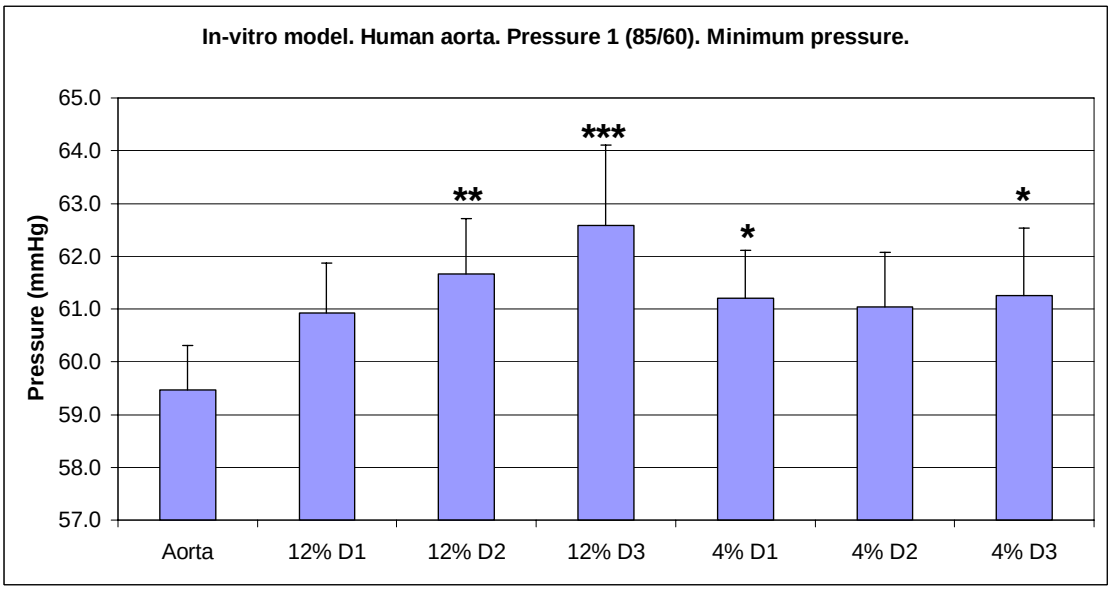


Figure 50 Alterations in minimum pressure following application of elastic wraps at pressure 1.

* $p < 0.05$, ** $p < 0.005$, *** $p < 0.001$ c/w baseline.

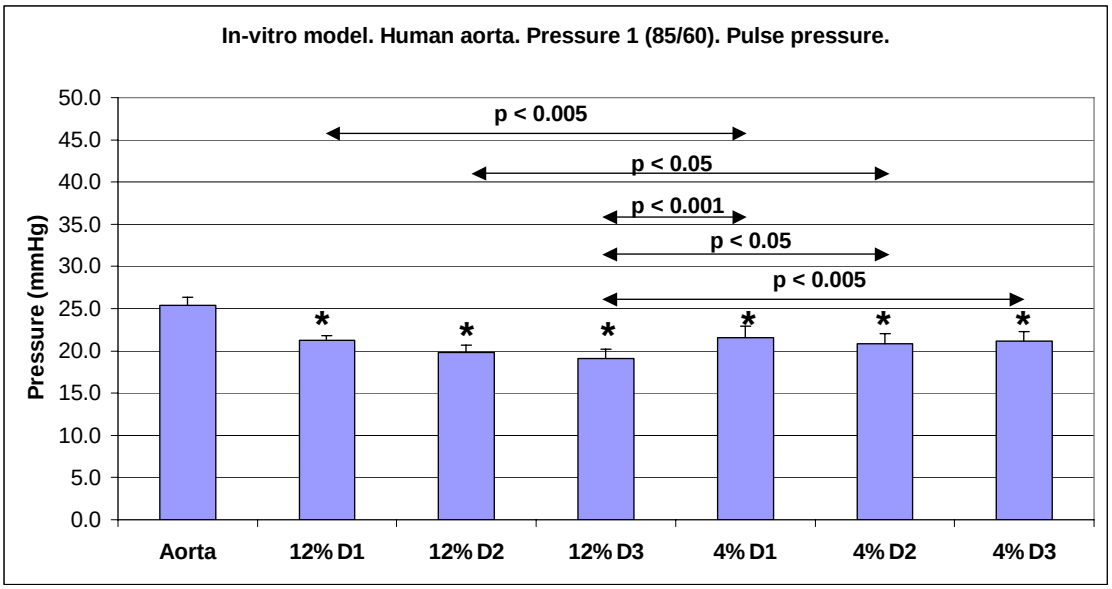


Figure 51 Alterations in pulse pressure following application of elastic wraps at pressure 1. * $p < 0.001$ c/w baseline. Arrows indicate between groups comparison.

Aortic diameter, area, and stiffness

Pressure 1 85/60 (N=9)	Group 1 Aorta (Baseline)	Group 2 12% wrap 91% diameter	Group 3 12% wrap 82% diameter	Group 4 12% wrap 70% diameter
Min D (mm)	32.00 +/- 3.05	25.94 +/- 2.26 **	25.17 +/- 2.74 **	22.20 +/- 2.97 **
Max D (mm)	32.17 +/- 3.14	26.63 +/- 2.36 *	25.98+/- 2.83 **	23.03 +/- 3.09 **
δD (mm)	0.17 +/- 0.13	0.70 +/- .15 **	0.80 +/- 0.12 **	0.83 +/- 0.14 **
%δD	0.51 +/- 0.34	2.67 +/- 0.43 **	3.19 +/- 0.36 **	3.75 +/- 0.36 **
Min A (mm^2)	810.63 +/- 154.64	531.52 +/- 92.39 **	502.79 +/- 107.22 **	392.98 +/- 105.51 **
Max A (mm^2)	819.55 +/- 160.16	560.15 +/- 99.19 **	535.37 +/- 114.22 **	423.02 +/- 113.67 **
δA (mm^2)	8.92 +/- 7.52	28.99 +/- 8.17 **	32.59 +/- 7.78 **	30.04 +/- 8.44 **
%δA	1.03 +/- 0.69	5.42 +/- 0.88 **	6.48 +/- 0.74 **	7.64 +/- 0.75 **
Ep (dyn/cm^2 x e6)	8.81 +/- 3.88	1.09 +/- 0.18 **	0.84 +/- 0.11 **	0.69 +|/- 0.10 **

Min D= minimum aortic diameter; Max D = maximum aortic diameter; δD = pulsatile change in aortic diameter; %δD = percentage pulsatile change in aortic diameter [(δD /Min D x 100)]; Min A = minimum aortic area; Max A = maximum aortic area; δA = pulsatile change in aortic area; %δA = percentage pulsatile change in aortic area [(δA /Min A x 100)]; Ep = pressure-strain elastic modulus [Ep=(PP/δD)×Min D). (* $p < 0.005$, ** $p < 0.001$ c/w baseline, data presented as mean +/- SD)

Table 18 Alterations in aortic diameter, area and stiffness following application of elastic wraps at pressure 1.

Pressure 1 85/60 (N=9)	Group 1 Aorta	Group 5 4% wrap 91% diameter	Group 6 4% wrap 82% diameter	Group 7 4% wrap 70% diameter
Min D (mm)	32.00 +/- 3.05	23.93 +/- 2.04 **	22.47 +/- 2.81 **	19.11 +/- 2.72 **
Max D (mm)	32.17 +/- 3.14	24.57 +/- 2.14 **	23.14 +/- 2.89 **	19.71 +/- 2.85 **
δD (mm)	0.17 +/- 0.13	0.64 +/- 0.13 **	0.67 +/- 0.09 **	0.60 +/- 0.13 **
%δD	0.51 +/- 0.34	2.67 +/- 0.37 **	2.99 +/- 0.22 **	3.11 +/- 0.35 **
Min A (mm^2)	810.63 +/- 154.64	452.47 +/- 77.05 **	402.17 +/- 98.72 **	292.01 +/- 85.61 **
Max A (mm^2)	819.55 +/- 160.16	477.20 +/- 83.11 **	426.52 +/- 104.67 **	310.69 +/- 92.48 **
δA (mm^2)	8.92 +/- 7.52	24.73 +/- 6.74 *	24.35 +/- 6.20 **	18.68 +/- 7.05
%δA	1.03 +/- 0.69	5.41 +/- 0.75 **	6.08 +/- 0.46 **	6.32 +/- 0.72 **
Ep (dyn/cm^2 x e6)	8.81 +/- 3.88	1.10 +/- 0.15 **	0.93 +/- 0.07 **	0.93 +/- 0.12 **

Min D= minimum aortic diameter; Max D = maximum aortic diameter; δD = pulsatile change in aortic diameter; %δD = percentage pulsatile change in aortic diameter [(δD /Min D x 100)]; Min A = minimum aortic area; Max A = maximum aortic area; δA = pulsatile change in aortic area; %δA = percentage pulsatile change in aortic area [(δA /Min A x 100)]; Ep = pressure-strain elastic modulus [Ep=(PP/δD)×Min D). (* $p < 0.005$, ** $p < 0.001$ c/w baseline, data presented as mean +/- SD)

Table 19 Alterations in aortic diameter, area and stiffness following application of elastic wraps at pressure 1.

Following application of the elastic wraps, there was a significant reduction in the minimum aortic diameter and area of all groups when compared to baseline. Application of a 4% wrap produced a smaller minimum aortic diameter and area when compared to a similarly sized 12% wrap.

There was a significant increase in the percentage pulsatile change in aortic diameter and area in all wrap groups when compared to the control group. For the 12% wrap groups and the 4% wrap groups, the percentage pulsatile change in aortic diameter and area increased as the diameter reduction increased. The percentage pulsatile change in aortic diameter and area of the 12% wrap groups was greater than the equivalent diameter reduction 4% wrap groups. For all wrap groups the greatest increase in percentage pulsatile aortic diameter and area was in the 12% wrap 70% diameter reduction group.

There was a significant reduction in aortic stiffness (E_p) in all wrap groups when compared to baseline. There were no significant differences in aortic stiffness between wrap groups; however the following patterns were evident. For the 12% wrap groups the aortic stiffness decreased as the diameter reduction increased. For the 4% wrap group the aortic stiffness decreased from group 5 (91% diameter reduction) to group 6 (82% diameter reduction), then remained unchanged in group 7 (70% diameter reduction). The aortic stiffness was lower in the 12% wrap groups when compared to similar diameter reduction 4% wrap groups.

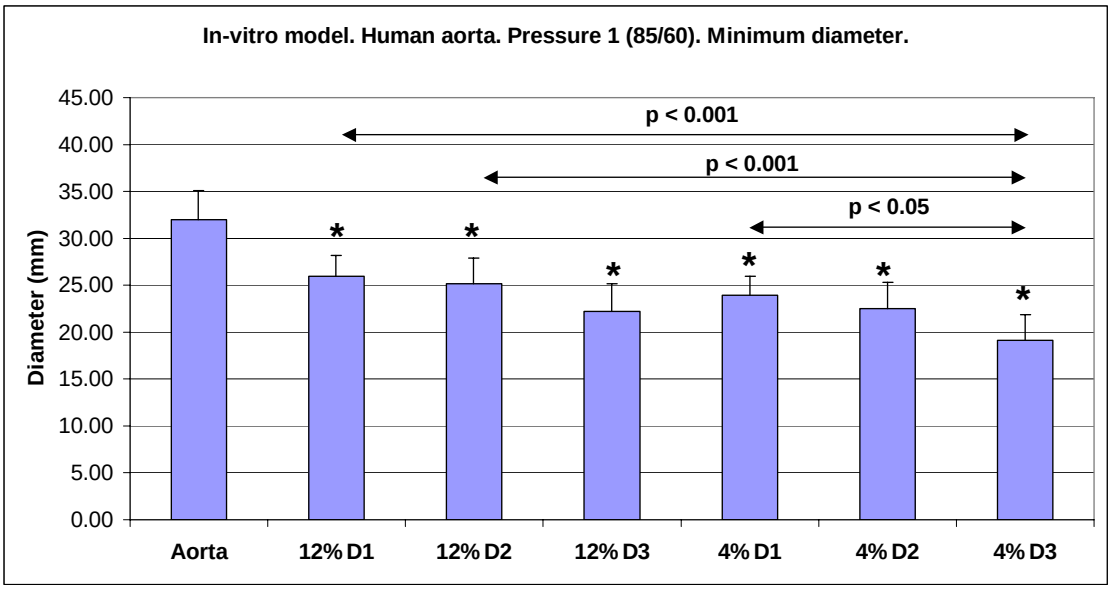


Figure 52 Alterations in minimum aortic diameter following application of elastic wraps at pressure 1.

* p < 0.001 c/w baseline. Arrows indicate between groups comparison.

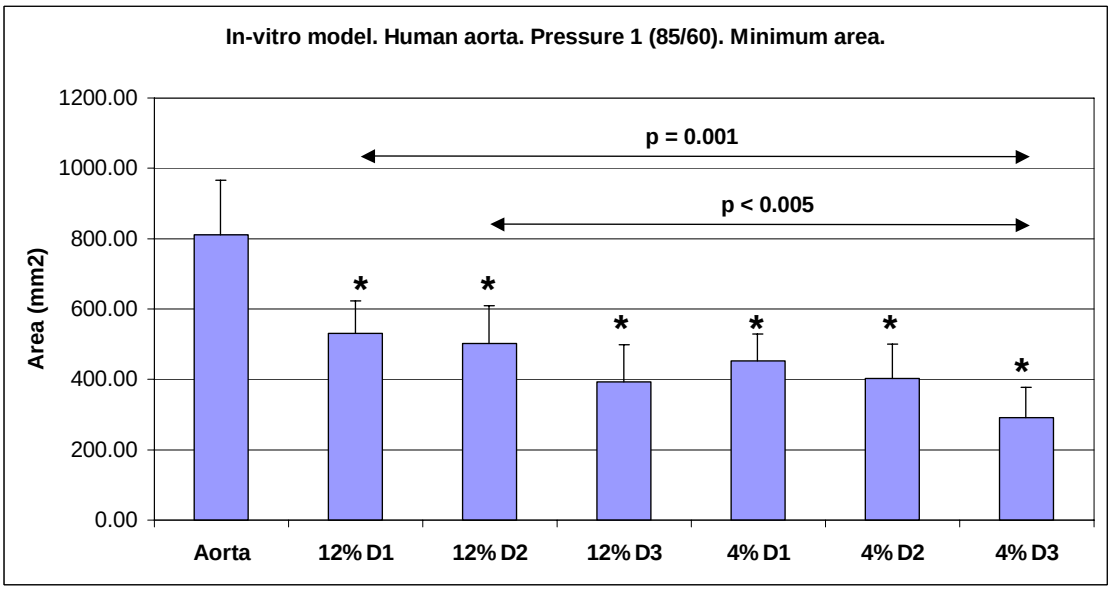


Figure 53 Alterations in minimum aortic diameter following application of elastic wraps at pressure 1.

* p < 0.001 c/w baseline. Arrows indicate between groups comparison.

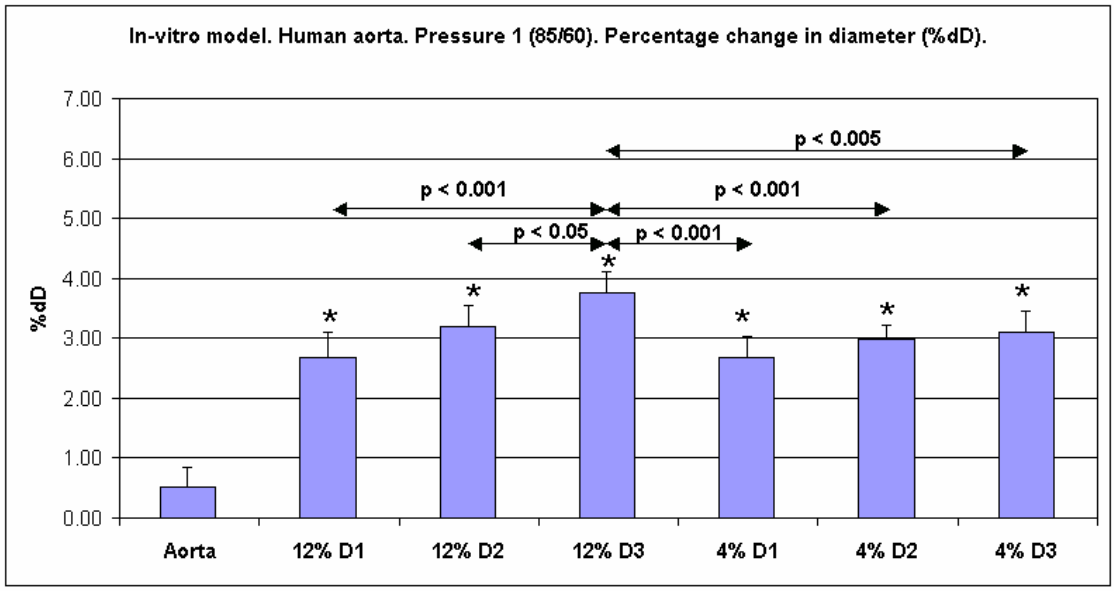


Figure 54 Alterations in percentage pulsatile change in aortic diameter following application of elastic wraps at pressure 1. * $p < 0.001$ c/w baseline. Arrows indicate between groups comparison.

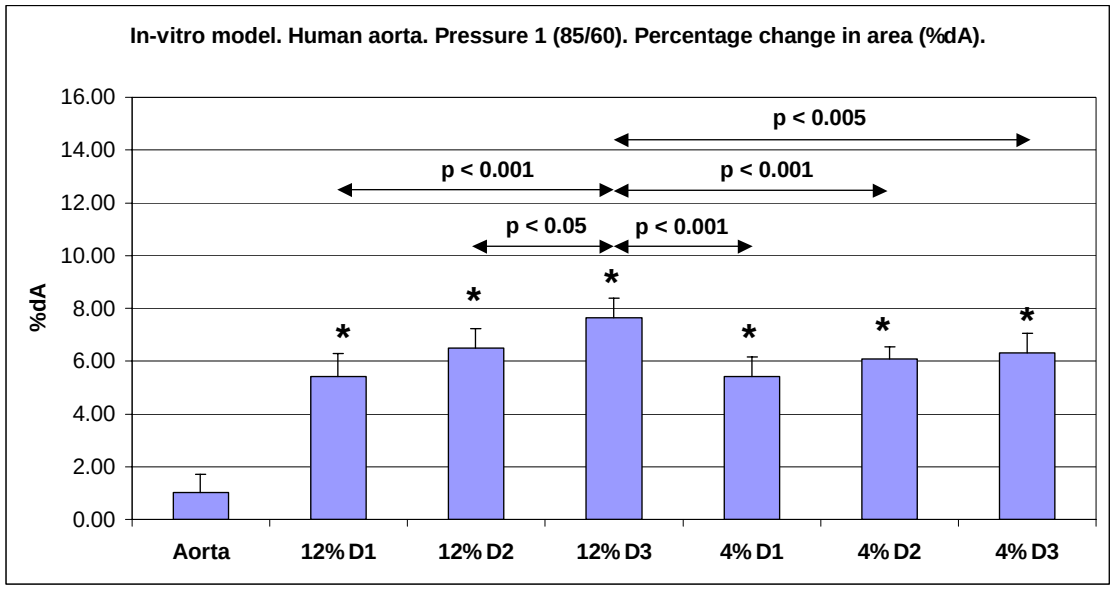


Figure 55 Alterations in percentage pulsatile change in aortic area following application of elastic wraps at pressure 1. * $p < 0.001$ c/w baseline. Arrows indicate between groups comparison.

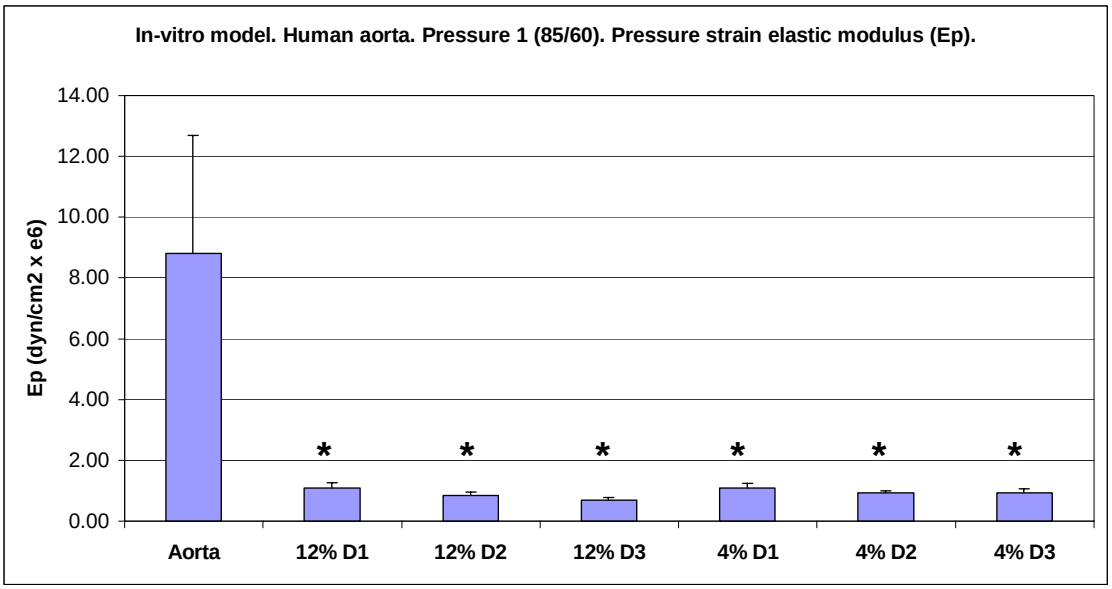


Figure 56 Alterations in pressure strain elastic modulus following application of elastic wraps at pressure 1.

* $p < 0.001$ c/w baseline.

5.3.2 Pulsatile pressure 2 (135/95 mmHg)

Haemodynamics

Pressure 2 135/95 (N=9)	Group 1 Aorta (Baseline)	Group 2 12% wrap 91% diam.	Group 3 12% wrap 82% diam.	Group 4 12% wrap 70% diam.	Group 5 4% wrap 91% diam.	Group 6 4% wrap 82% diam.	Group 7 4% wrap 70% diam.
Pmax (mmHg)	130.5 +/- 1.88	128.9 +/- 2.13	128.4 +/- 2.13	126.2 +/- 2.30 **	127.3 +/- 1.36 #	126.3 +/- 1.85 **	125.9 +/- 2.22 **
Pmin (mmHg)	94.9 +/- 1.85	96.1 +/- 2.37	98.1 +/- 2.32 #	99.5 +/- 2.43 **	96.7 +/- 1.87	98.4 +/- 1.99 #	98.8 +/- 2.35 **
PP (mmHg)	35.6 +/- 1.42	32.8 +/- 2.57	30.3 +/- 2.35 **	26.7 +/- 2.79 **	30.7 +/- 2.24 *	27.9 +/- 2.47 **	27.1 +/- 2.62 **

Pmax = maximum pressure; Pmin = minimum pressure; PP = pulse pressure. # $p < 0.05$, ## $p < 0.01$, * $p < 0.005$, ** $p < 0.001$ c/w baseline, data presented as mean +/- SD.

Table 20 Alterations in haemodynamic parameters following application of elastic wraps to the aorta at pressure 2.

Following application of the elastic wraps there were alterations in maximum pressure, minimum pressure, and pulse pressure.

There was a significant reduction in maximum pressure in wrap groups 4-7 when compared to baseline. There were no significant differences in maximum pressure between wrap groups; however the following patterns were evident. The maximum pressure was lower in the 4% wrap groups when compared to similar diameter reduction 12% wrap groups. For the 12% wrap groups and the 4% wrap groups the maximum pressure decreased as the diameter reduction increased. For all groups the greatest decrease in maximum pressure was in the 4% wrap 70% diameter reduction group.

There was a significant increase in minimum pressure in wrap groups 3, 4, 6, and 7 when compared to baseline. The minimum pressure was higher in the 4% wrap groups when compared to similar diameter reduction 12% wrap groups. For the 12% wrap groups and the 4% wrap groups the minimum pressure increased as the diameter reduction increased. For all groups the greatest increase in minimum pressure was in the 4% wrap 70% diameter reduction group.

There was a significant reduction in pulse pressure in wrap groups 3-7 when compared to baseline. For the 12% wrap groups and the 4% wrap groups the pulse pressure fell as the diameter reduction increased. For all groups the greatest reduction in pulse pressure was in the 12% wrap 70% diameter reduction group.

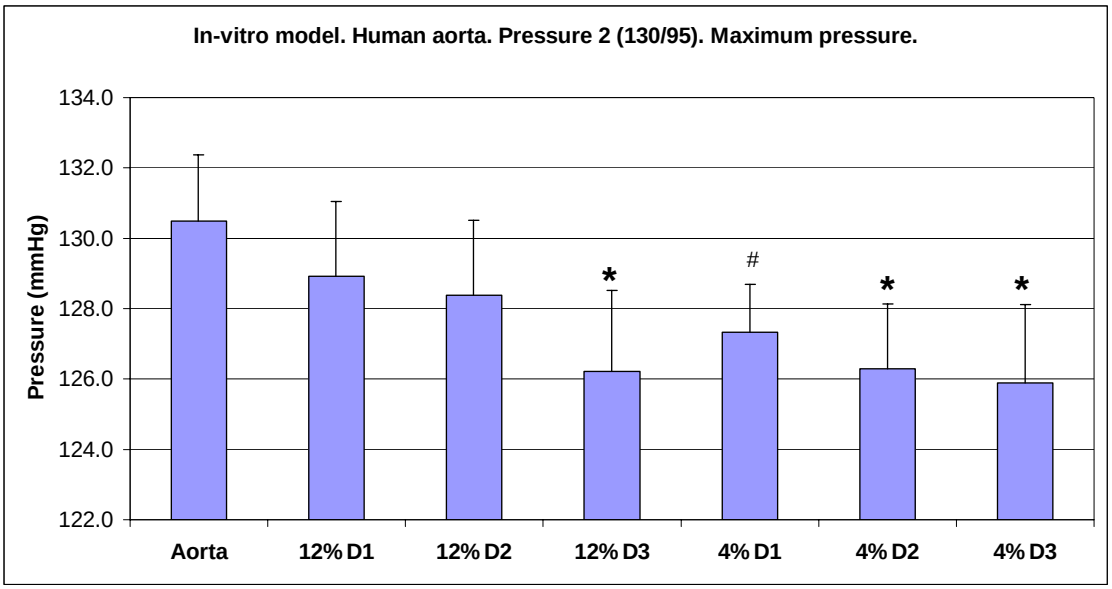


Figure 57 Alterations in maximum pressure following application of elastic wraps at pressure 2.

# $p < 0.05$, ** $p < 0.001$ c/w baseline.

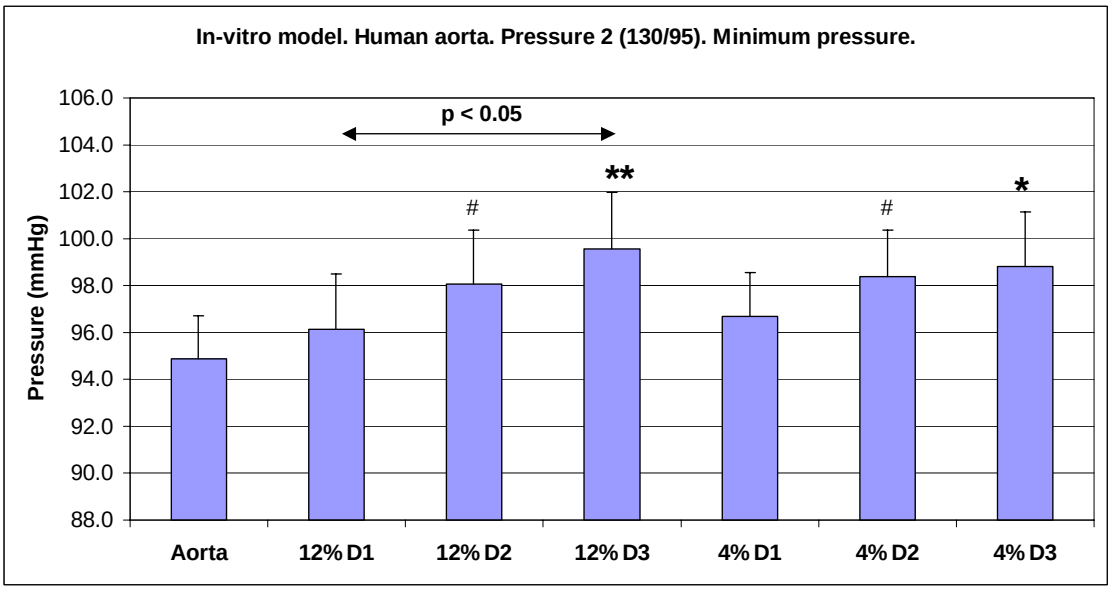


Figure 58 Alterations in minimum pressure following application of elastic wraps at pressure 2.

# $p < 0.05$, * $p < 0.01$, ** $P < 0.001$ c/w baseline.

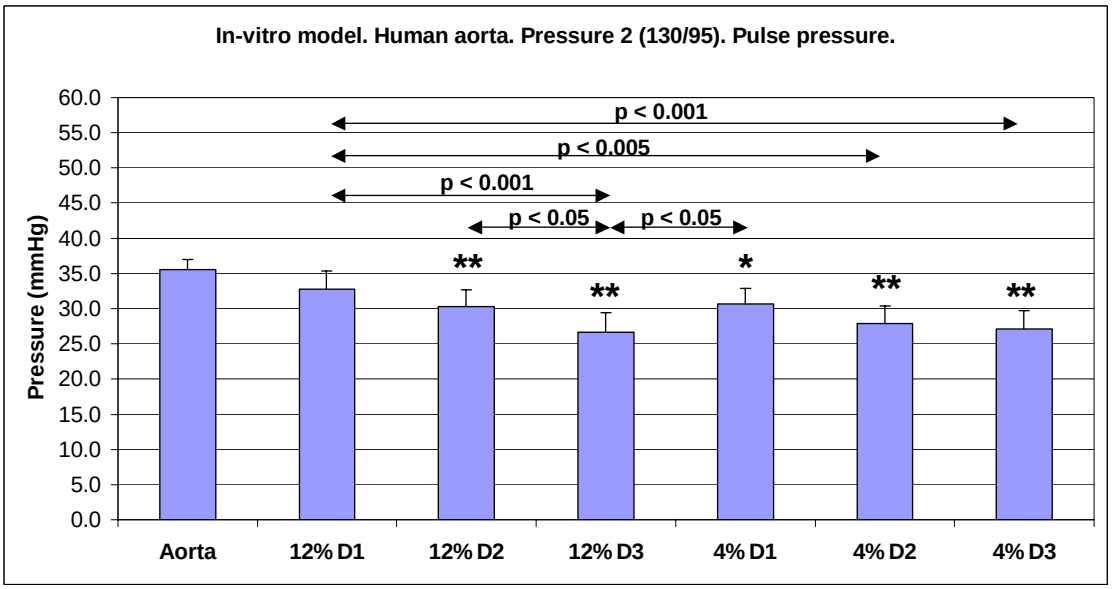


Figure 59 Alterations in pulse pressure following application of elastic wraps at pressure 2.

* p < 0.005, ** P < 0.001 c/w baseline.

Aortic diameter, area, and stiffness

Pressure 2 130/95 (N=9)	Group 1 Aorta (Baseline)	Group 2 12% wrap 91% diameter	Group 3 12% wrap 82% diameter	Group 4 12% wrap 70% diameter
Min D (mm)	32.31 +/- 3.09	27.78 +/- 2.40	27.71 +/- 3.00 #	25.51 +/- 3.14 **
Max D (mm)	32.43 +/- 3.11	28.33 +/- 2.48	28.46 +/- 3.03	26.51 +/- 3.17 *
δD (mm)	0.12 +/- 0.04	0.55 +/-0.10 **	0.75 +/- 0.10 **	1.00 +/- 0.10 **
%δD	0.36 +/- 0.11	1.99 +/- 0.25 **	2.74 +/- 0.40 **	3.97 +/- 0.51 **
Min A (mm^2)	826.27 +/- 158.17	609.50 +/- 105.99 #	609.07 +/- 130.44 #	517.74 +/- 127.59 **
Max A (mm^2)	832.38 +/- 159.89	634.17 +/- 111.68	642.41 +/- 135.40	558.84 +/- 133.56 **
δA (mm^2)	6.11 +/- 2.60	24.67 +/- 6.33 **	33.34 +/- 6.49 **	41.10 +/- 7.14 **
%δA	0.73 +/- 0.22	4.02 +/- 0.52 **	5.55 +/- 0.83 **	8.10 +/- 1.06 **
Ep (dyn/cm^2 x e6)	14.16 +/- 3.79	2.26 +/- 0.37 **	1.51 +/- 0.27 **	0.91 +/- 0.16 **

Min D= minimum aortic diameter; Max D = maximum aortic diameter; δD = pulsatile change in aortic diameter; %δD = percentage pulsatile change in aortic diameter [(δD /Min D x 100)]; Min A = minimum aortic area; Max A = maximum aortic area; δA = pulsatile change in aortic area; %δA = percentage pulsatile change in aortic area [(δA /Min A x 100)]; Ep = pressure-strain elastic modulus [Ep=(PP/δD)×Min D). (# $p < 0.05$, ## $p < 0.01$, * $p < 0.005$, ** $p < 0.001$ c/w baseline, data presented as mean +/- SD)

Table 21 Alterations in aortic diameter, area and stiffness following application of elastic wraps at pressure 2.

Pressure 2 130/95 (N=9)	Group 1 Aorta (Baseline)	Group 5 4% wrap 91% diameter	Group 6 4% wrap 82% diameter	Group 7 4% wrap 70% diameter
Min D (mm)	32.31 +/- 3.09	25.72 +/- 2.76 **	24.90 +/- 3.18 **	21.90 +/- 3.30 **
Max D (mm)	32.43 +/- 3.11	26.43 +/- 2.81 *	25.74 +/- 3.24 **	22.73 +/- 3.39 **
δD (mm)	0.12 +/- 0.04	0.71 +/- 0.09 **	0.83 +/- 0.09 **	0.83 +/- 0.10 **
%δD	0.36 +/- 0.11	2.76 +/- 0.34 **	3.37 +/- 0.32 **	3.79 +/- 0.26 **
Min A (mm^2)	826.27 +/- 158.17	524.73 +/- 110.62 **	493.89 +/- 124.62 **	384.16 +/- 115.15 **
Max A (mm^2)	832.38 +/- 159.89	553.87 +/- 116.15 *	527.27 +/- 131.02 **	413.54 +/- 122.73 **
δA (mm^2)	6.11 +/- 2.60	29.14 +/- 6.48 **	33.37 +/- 6.86 **	29.38 +/- 7.73 **
%δA	0.73 +/- 0.22	5.60 +/- 0.69 **	6.85 +/- 0.66 **	7.73 +/- 0.55 **
Ep (dyn/cm^2 x e6)	14.16 +/- 3.79	1.50 +/- 0.20 **	1.11 +/- 0.14 **	0.95 +/- 0.10 **

Min D= minimum aortic diameter; Max D = maximum aortic diameter; δD = pulsatile change in aortic diameter; %δD = percentage pulsatile change in aortic diameter [(δD /Min D x 100)]; Min A = minimum aortic area; Max A = maximum aortic area; δA = pulsatile change in aortic area; %δA = percentage pulsatile change in aortic area [(δA /Min A x 100)]; Ep = pressure-strain elastic modulus [Ep=(PP/δD)×Min D). (# $p < 0.05$, ## $p < 0.01$, * $p < 0.005$, ** $p < 0.001$ c/w baseline, data presented as mean +/- SD)

Table 22 Alterations in aortic diameter, area and stiffness following application of elastic wraps at pressure 2.

Following application of elastic wraps, there was a significant reduction in the minimum aortic diameter and area of all groups when compared to baseline. Application of

a 4% wrap produced a smaller minimum aortic diameter and area when compared to a similarly sized 12% wrap.

There was a significant increase in the percentage pulsatile change in aortic diameter and area in all wrap groups when compared to baseline. For the 12% wrap groups and the 4% wrap groups the percentage pulsatile change in aortic diameter and area increased as the diameter reduction increased. For all wrap groups the greatest increase in percentage pulsatile aortic diameter and area was in the 12% wrap 70% diameter reduction group.

There was a significant reduction aortic stiffness (E_p) in all wrap groups when compared to baseline. There were no significant differences in aortic stiffness between wrap groups, however the following patterns were evident. For the 12% wrap groups and the 4% wrap groups the aortic stiffness decreased as the diameter reduction increased. The 12% wrap 70% diameter reduction group had the lowest aortic stiffness.

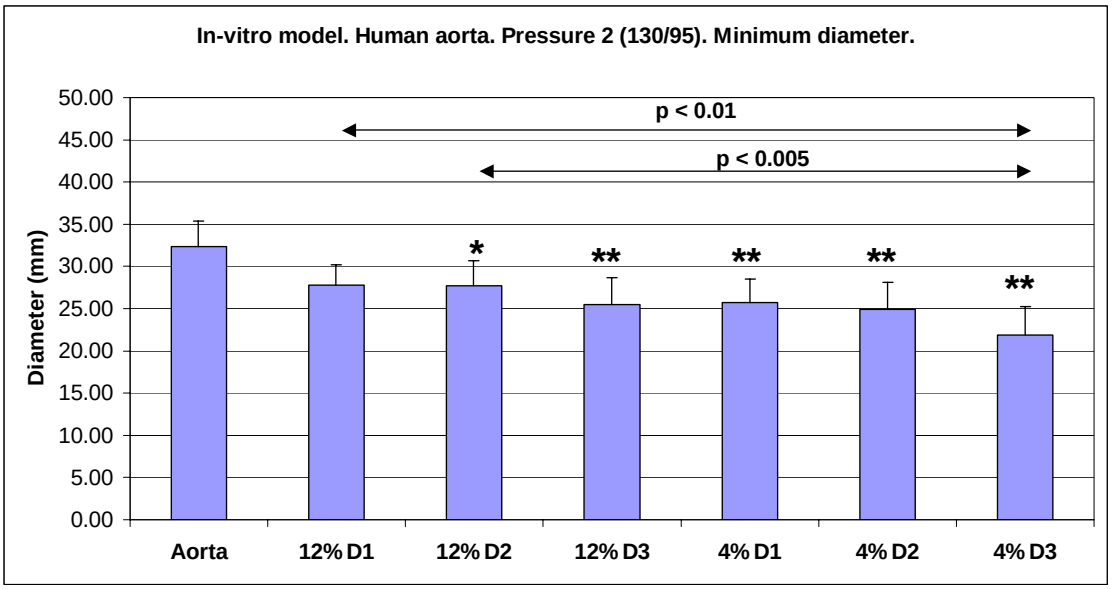


Figure 60 Alterations in minimum aortic diameter following application of elastic wraps at pressure 2. * p < 0.05, ** p < 0.001 c/w baseline. Arrows indicate between groups comparison.

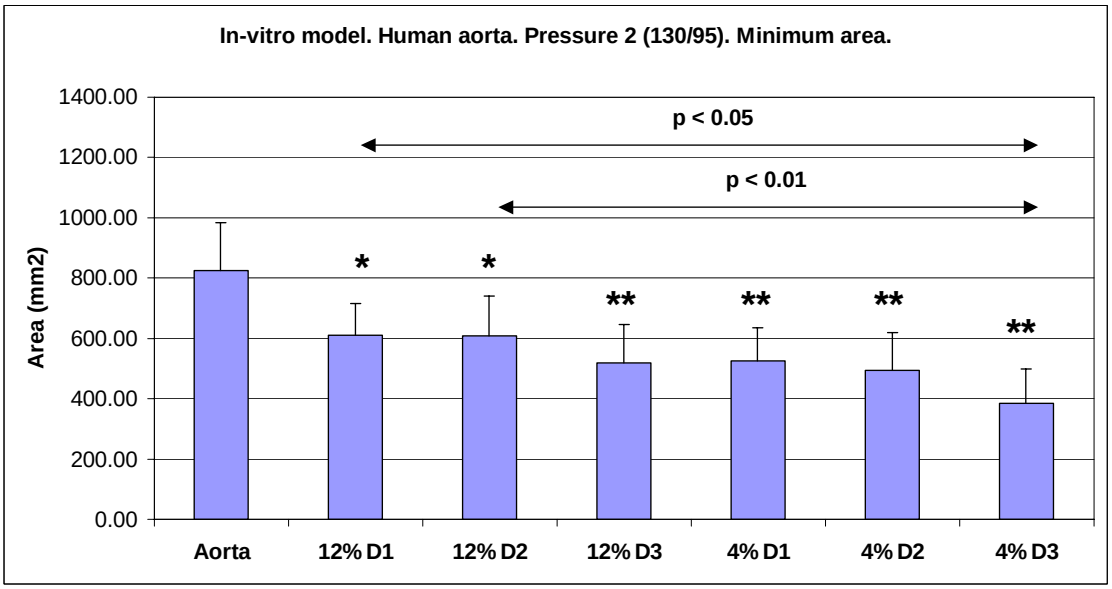


Figure 61 Alterations in minimum aortic area following application of elastic wraps at pressure 2. * p < 0.05, ** p < 0.001 c/w baseline. Arrows indicate between groups comparison.

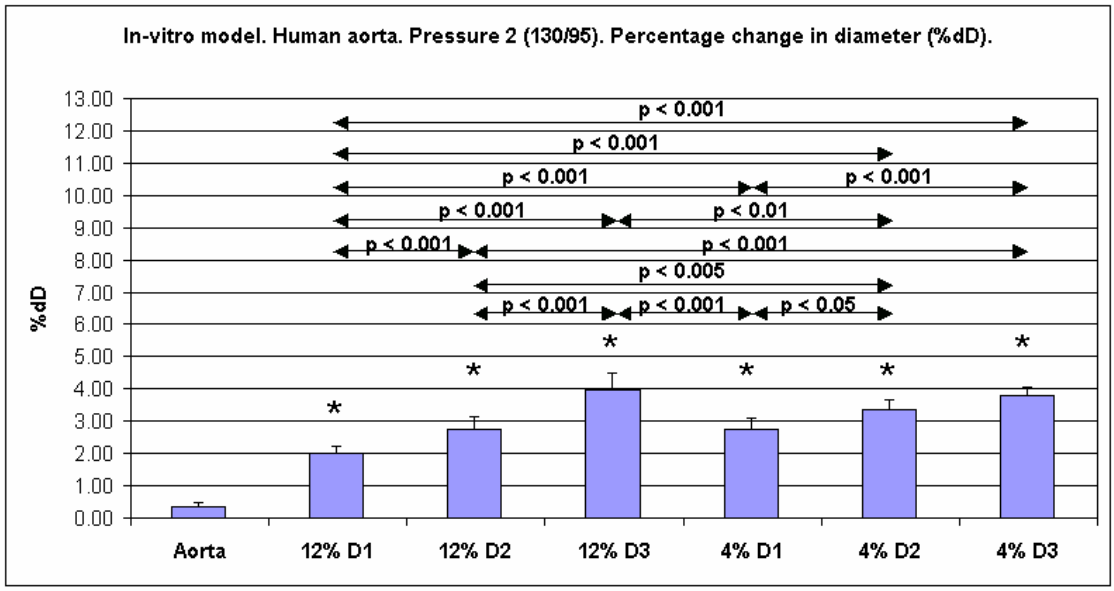


Figure 62 Alterations in percentage pulsatile change in aortic diameter following application of elastic wraps at pressure 2. * $p < 0.001$ c/w baseline. Arrows indicate between groups comparison.

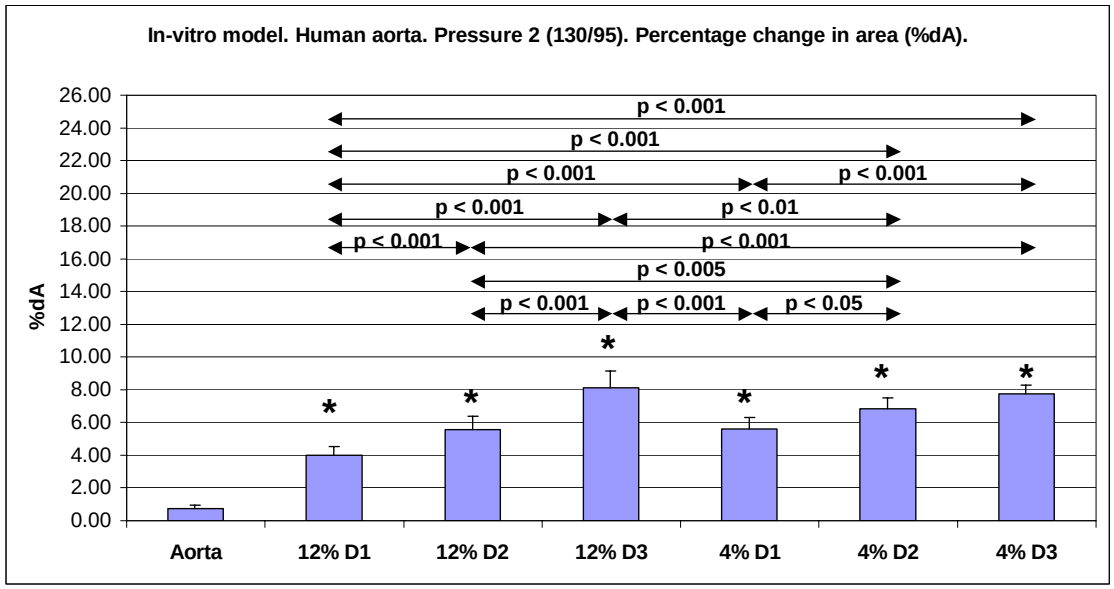


Figure 63 Alterations in percentage pulsatile change in aortic area following application of elastic wraps at pressure 2. * $p < 0.001$ c/w baseline. Arrows indicate between groups comparison.

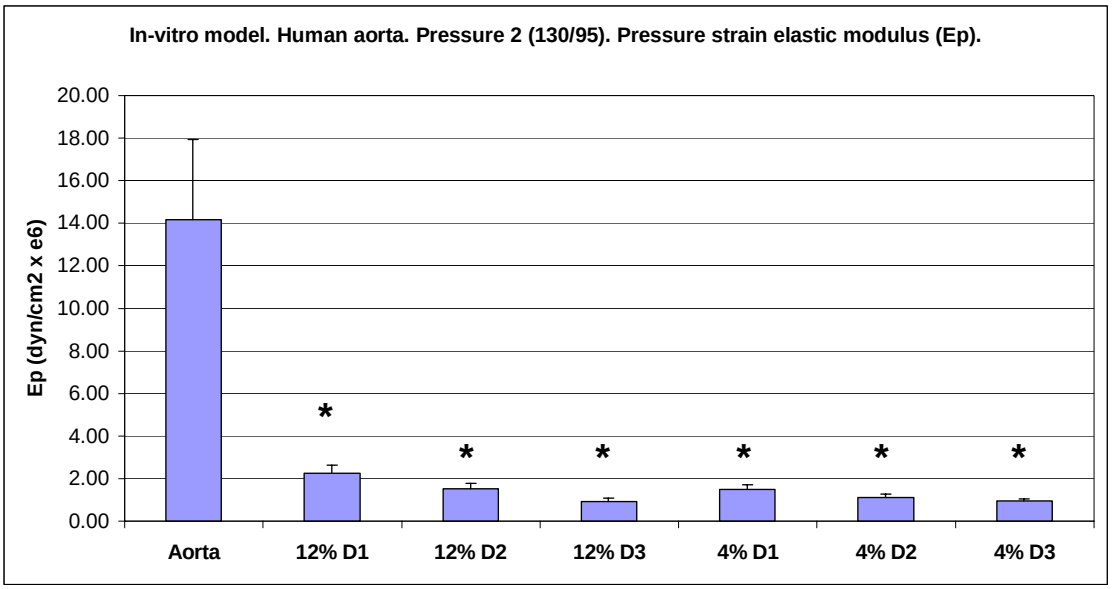


Figure 64 Alterations in pressure strain elastic modulus following application of elastic wraps at pressure 2. * $p < 0.001$ c/w baseline.

5.3.3 Pulsatile pressure 3 (160/90 mmHg)

Haemodynamics

Pressure 3 160/90 (N=9)	Group 1 Aorta (Baseline)	Group 2 12% wrap 91% diam.	Group 3 12% wrap 82% diam.	Group 4 12% wrap 70% diam.	Group 5 4% wrap 91% diam.	Group 6 4% wrap 82% diam.	Group 7 4% wrap 70% diam.
Pmax (mmHg)	159.5 +/- 3.44	157.8 +/- 3.47	156.7 +/- 3.63	154.3 +/- 3.97	155.1 +/- 2.85	154.4 +/- 3.96	153.7 +/- 4.42 #
Pmin (mmHg)	93.7 +/- 2.99	95.1 +/- 3.05	98.3 +/- 3.47	102.2 +/- 3.62 **	96.9 +/- 2.94	101.4 +/- 3.93 **	103.0 +/- 4.34 **
PP (mmHg)	65.8 +/- 2.47	62.6 +/- 3.71	58.4 +/- 3.66 **	52.1 +/- 3.82 **	58.2 +/- 3.76 *	53.1 +/- 3.95 **	50.7 +/- 4.00 **

Pmax = maximum pressure; Pmin = minimum pressure; PP = pulse pressure. # $p < 0.05$, * $p < 0.005$, ** $p < 0.001$ c/w baseline, data presented as mean +/- SD.

Table 23 Alterations in haemodynamic parameters following application of elastic wraps to the aorta at pressure 3.

Following application of elastic wraps there were alterations in maximum pressure, minimum pressure, and pulse pressure.

There was a reduction in maximum pressure in all wrap groups when compared to baseline. The reduction in maximum pressure in group 7 (4% wrap 70% diameter reduction) was significant. There were no significant differences in maximum pressure between wrap groups; however the following patterns were evident. The maximum pressure was lower in the 4% wrap groups when compared to similar diameter reduction 12% wrap groups. For the 12% wrap groups and the 4% wrap groups the maximum pressure decreased as the diameter reduction increased. For all groups the greatest decrease in maximum pressure was in the 4% wrap 70% diameter reduction group.

There was a significant increase in minimum pressure in all wrap groups when compared to baseline. The minimum pressure was higher in the 4% wrap groups when compared to similar diameter reduction 12% wrap groups. For the 12% wrap groups and the 4% wrap groups the minimum pressure increased as the diameter reduction increased. For all groups the greatest increase in minimum pressure was in the 4% wrap 70% diameter reduction group.

There was a significant reduction in pulse pressure in all wrap groups when compared to baseline. The pulse pressure was lower in the 4% wrap groups when compared to similar diameter reduction 12% wrap groups. For the 12% wrap groups and the 4% wrap groups the pulse pressure fell as the diameter reduction increased. For all groups the greatest reduction in pulse pressure was in the 4% wrap 70% diameter reduction group.

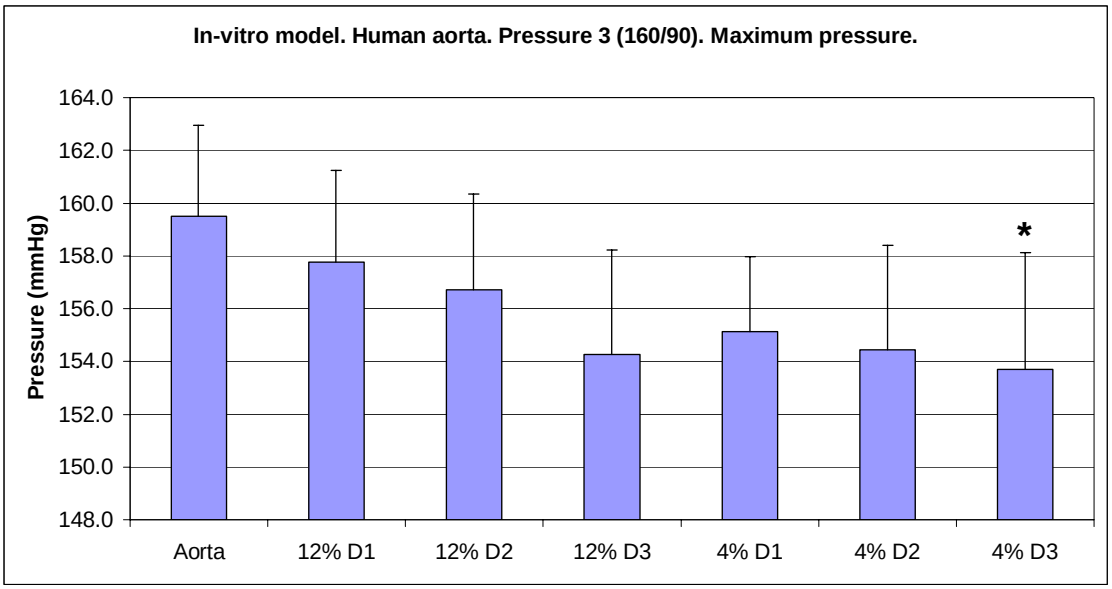


Figure 65 Alterations in maximum pressure following application of elastic wraps at pressure 3.

* $p < 0.05$ c/w baseline.

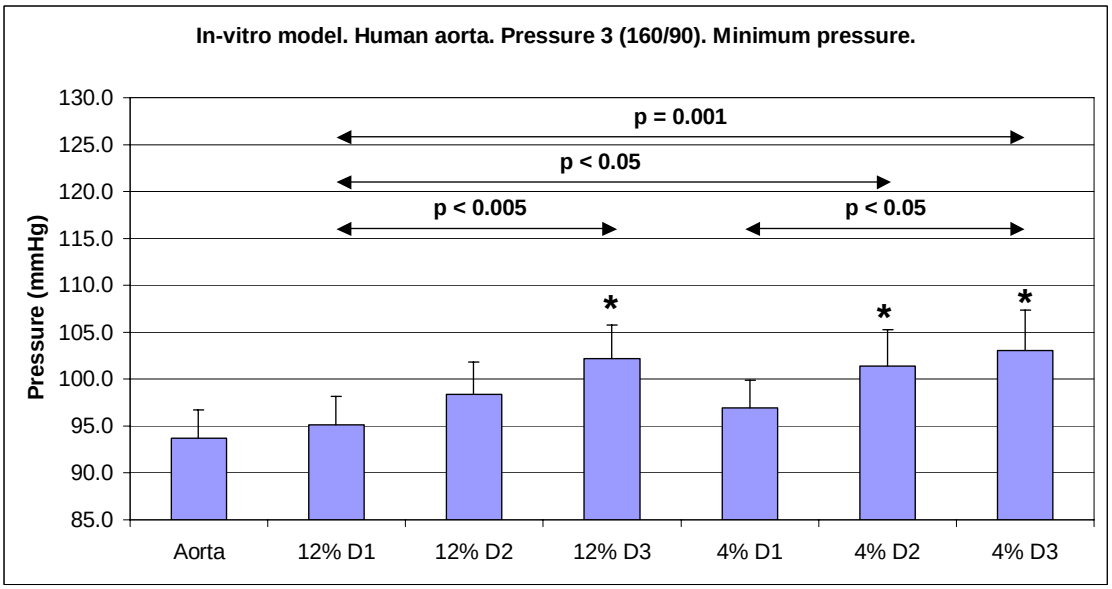


Figure 66 Alterations in minimum pressure following application of elastic wraps at pressure 3.

* $p < 0.001$ c/w baseline. Arrows indicate between groups comparison.

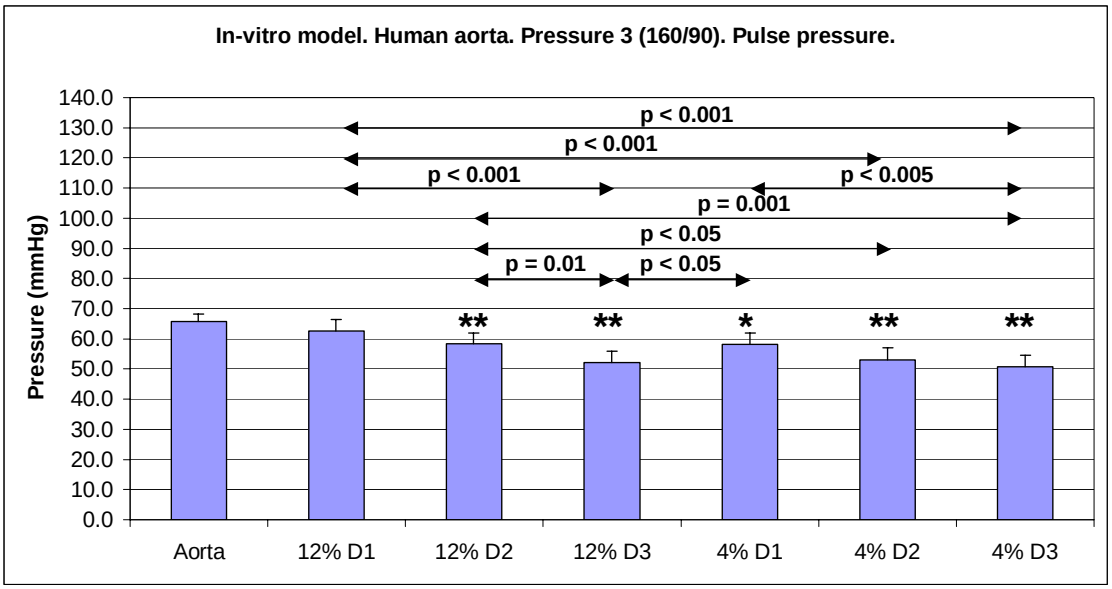


Figure 67 Alterations in pulse pressure following application of external elastic wraps at pressure 3.

* $p < 0.005$, ** $p < 0.001$ c/w baseline. Arrows indicate between groups comparison.

Aortic diameter, area, and stiffness

Pressure 3 160/90 (N=9)	Group 1 Aorta (Baseline)	Group 2 12% wrap 91% diameter	Group 3 12% wrap 82% diameter	Group 4 12% wrap 70% diameter
Min D (mm)	32.24 +/- 3.14	27.83 +/- 2.34	27.75 +/- 3.04 #	25.83 +/- 3.20 **
Max D (mm)	32.43 +/- 3.16	28.68 +/- 2.44	28.93 +/- 3.05	27.52 +/- 3.19 #
δD (mm)	0.19 +/- 0.06	0.85 +/- 0.12 **	1.18 +/- 0.11 **	1.69 +/- 0.19 **
%δD	0.60 +/- 0.17	3.06 +/- 0.28 **	4.30 +/- 0.61 **	6.63 +/- 1.14 **
Min A (mm^2)	822.60 +/- 160.75	611.76 +/- 103.62 #	611.06 +/- 132.88 #	530.87 +/- 130.86 **
Max A (mm^2)	832.47 +/- 162.76	649.89 +/- 111.34	663.75 +/- 139.18	601.54 +/- 138.17 #
δA (mm^2)	9.87 +/- 3.57	38.12 +/- 8.47 **	52.69 +/- 7.92 **	70.67 +/- 10.42 **
%δA	1.20 +/- 0.34	6.21 +/- 0.57 **	8.80 +/- 1.28 **	13.72 +/- 2.45 **
Ep (dyn/cm^2 x e6)	15.93 +/- 4.32	2.78 +/- 0.37 **	1.84 +/- .024 **	1.07 +/- 0.18 **

Min D= minimum aortic diameter; Max D = maximum aortic diameter; δD = pulsatile change in aortic diameter; %δD = percentage pulsatile change in aortic diameter [(δD /Min D x 100)]; Min A = minimum aortic area; Max A = maximum aortic area; δA = pulsatile change in aortic area; %δA = percentage pulsatile change in aortic area [(δA /Min A x 100)]; Ep = pressure-strain elastic modulus [Ep=(PP/δD)×Min D). (# $p < 0.05$, ## $p < 0.01$, * $p < 0.005$, ** $p < 0.001$ c/w baseline, data presented as mean +/- SD)

Table 24 Alterations in aortic diameter, area and stiffness following application of elastic wraps at pressure 3.

Pressure 3 160/90 (N=9)	Group 1 Aorta (Baseline)	Group 5 4% wrap 91% diameter	Group 6 4% wrap 82% diameter	Group 7 4% wrap 70% diameter
Min D (mm)	32.24 +/- 3.14	26.06 +/- 2.19 *	25.30 +/- 3.03 **	22.48 +/- 3.41 **
Max D (mm)	32.43 +/- 3.16	27.24 +/- 2.28 #	26.79 +/- 3.09 *	24.05 +/- 3.48 **
δD (mm)	0.19 +/- 0.06	1.17 +/- 0.16 **	1.48 +/- 0.15 **	1.57 +/- 0.16 **
%δD	0.60 +/- 0.17	4.51 +/- 0.55 **	5.91 +/- 0.78 **	7.09 +/- 0.99 **
Min A (mm^2)	822.60 +/- 160.75	536.61 +/- 90.43 **	509.11 +/- 121.69 **	404.80 +/- 121.73 **
Max A (mm^2)	832.47 +/- 162.76	585.95 +/- 98.19 #	569.92 +/- 130.60 *	462.55 +/- 132.50 **
δA (mm^2)	9.87 +/- 3.57	49.35 +/- 9.40 **	60.81 +/- 10.42 **	57.75 +/- 11.88 **
%δA	1.20 +/- 0.34	9.22 +/- 1.15 **	12.17 +/- 1.65 **	14.69 +/- 2.12 **
Ep (dyn/cm^2 x e6)	15.93 +/- 4.32	1.75 +/- 0.27 **	1.21 +/- 0.14 **	0.97 +/- 0.12 **

Min D= minimum aortic diameter; Max D = maximum aortic diameter; δD = pulsatile change in aortic diameter; %δD = percentage pulsatile change in aortic diameter [(δD /Min D x 100)]; Min A = minimum aortic area; Max A = maximum aortic area; δA = pulsatile change in aortic area; %δA = percentage pulsatile change in aortic area [(δA /Min A x 100)]; Ep = pressure-strain elastic modulus [Ep=(PP/δD)×Min D). (# $p < 0.05$, ## $p < 0.01$, * $p < 0.005$, ** $p < 0.001$ c/w baseline, data presented as mean +/- SD)

Table 25 Alterations in aortic diameter, area and stiffness following application of elastic wraps at pressure 3.

Following application of elastic wraps, there was a significant reduction in the minimum aortic diameter and area of all groups when compared to baseline. Application of

a 4% wrap produced a smaller minimum aortic diameter and area when compared to a similarly sized 12% wrap.

There was a significant increase in the percentage pulsatile change in aortic diameter and area in all wrap groups when compared to the control group. For the 12% wrap groups and the 4% wrap groups the percentage pulsatile change in aortic diameter and area increased as the diameter reduction increased. Application of a 4% wrap produced a larger percentage pulsatile change in aortic diameter and area when compared to a similarly sized 12% wrap. For all wrap groups the greatest increase in percentage pulsatile aortic diameter and area was in the 4% wrap 70% diameter reduction group.

There was a reduction in aortic stiffness (E_p) in all wrap groups when compared to baseline. There were no significant differences in aortic stiffness between wrap groups; however the following patterns were evident. For the 12% wrap groups and the 4% wrap groups the aortic stiffness decreased as the diameter reduction increased. Application of a 4% wrap produced a smaller aortic stiffness when compared to a similarly sized 12% wrap. The 4% wrap 70% diameter reduction group had the lowest aortic stiffness.

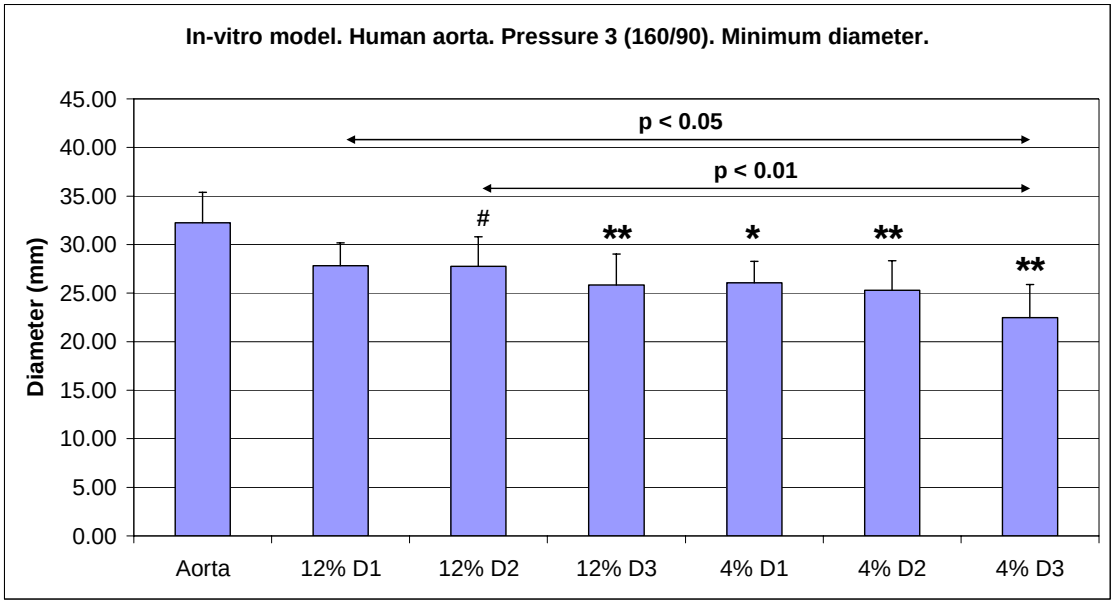


Figure 68 Alterations in minimum aortic diameter following application of elastic wraps at pressure 3. # $p < 0.05$, * $p < 0.005$, ** $p < 0.001$ c/w baseline. Arrows indicate between groups comparison.

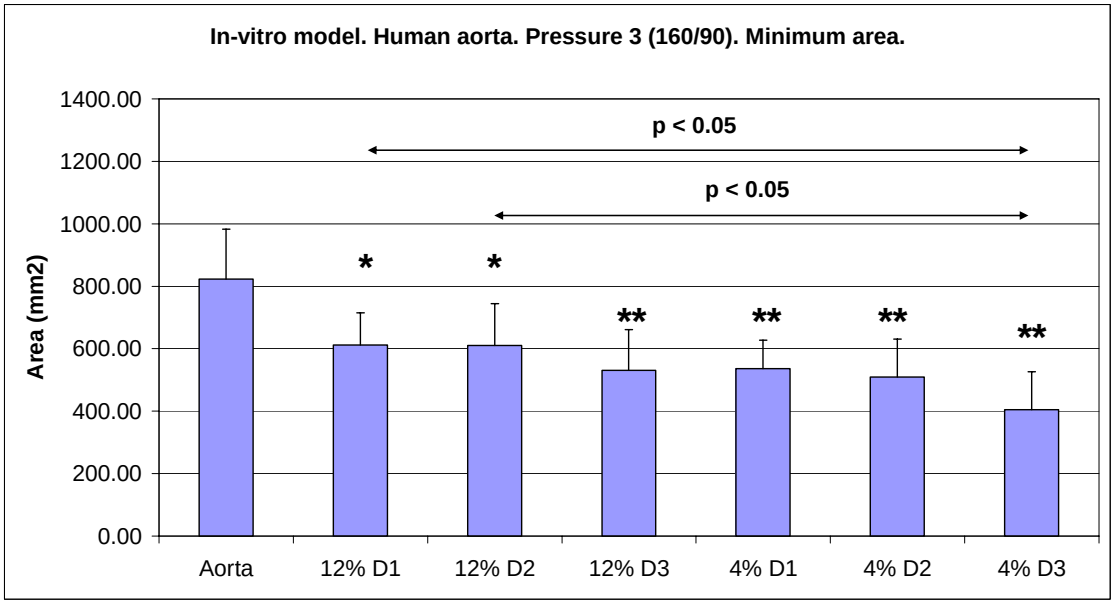


Figure 69 Alterations in minimum aortic area following application of elastic wraps at pressure 3.

* $p < 0.05$, ** $p < 0.001$ c/w baseline. Arrows indicate between groups comparison.

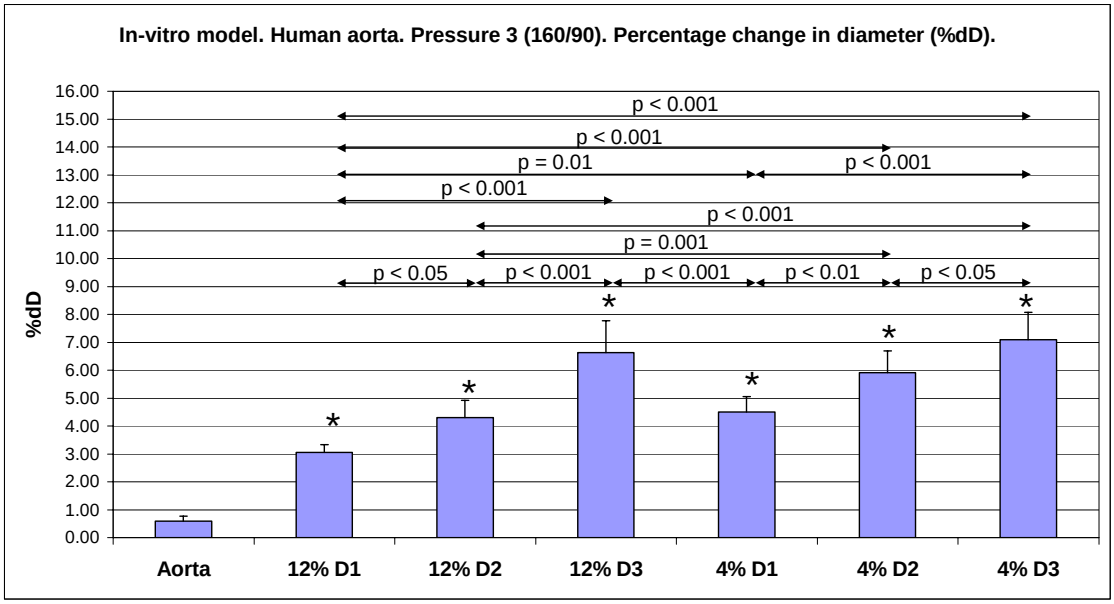


Figure 70 Alterations in percentage pulsatile change in aortic diameter following application of elastic wraps at pressure 3. * p < 0.001 c/w baseline. Arrows indicate between groups comparison.

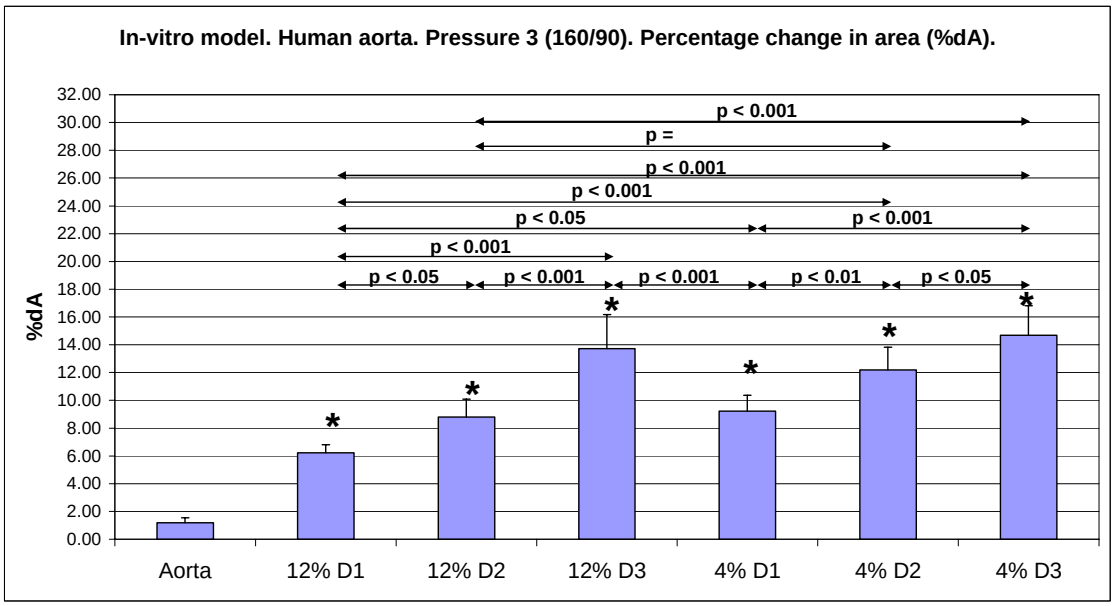


Figure 71 Alterations in percentage pulsatile change in aortic area following application of elastic wraps at pressure 2. * p < 0.001 c/w baseline. Arrows indicate between groups comparison.

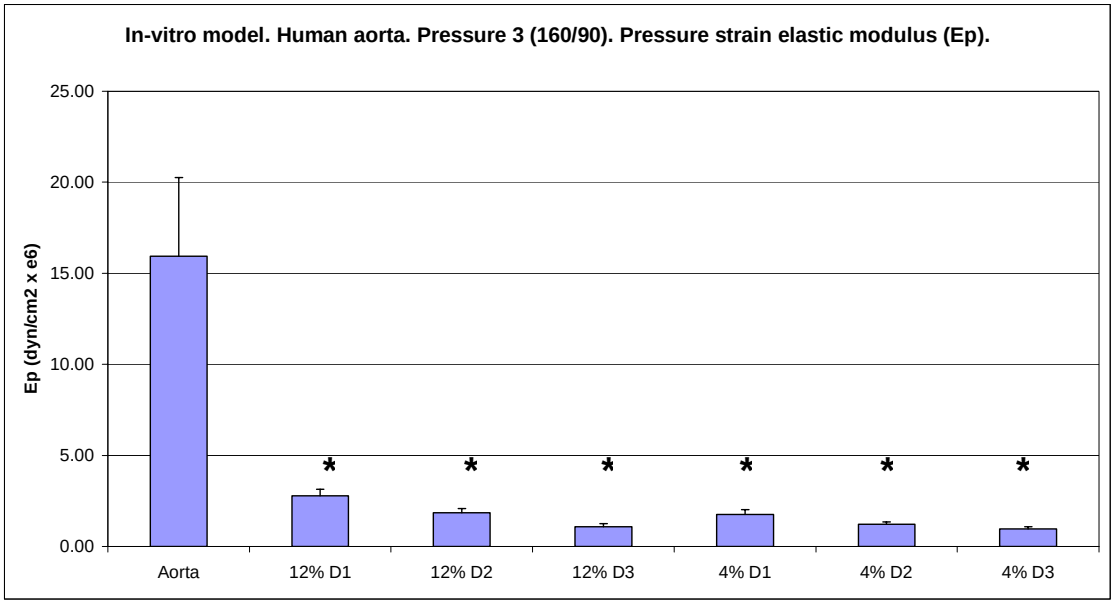


Figure 72 Alterations in pressure strain elastic modulus following application of elastic wraps at pressure 3.

* $p < 0.001$ c/w baseline.

5.3.4 Overview

Maximum pressure

Maximum pressure Ratio to aorta (N=9)	Pressure 1 85/60	Pressure 2 130/95	Pressure 3 160/90
Group 1 (Aorta – Baseline)	1.000	1.000	1.000
Group 2 (12% wrap 91% diameter)	0.968	0.988	0.989
Group 3 (12% wrap 82% diameter)	0.960	0.984	0.982
Group 4 (12% wrap 70% diameter)	0.962	0.967	0.967
Group 5 (4% wrap 91% diameter)	0.976	0.976	0.973
Group 6 (4% wrap 82% diameter)	0.964	0.968	0.968
Group 7 (4% wrap 70% diameter)	0.971	0.965	0.964

Data presented as the ratio to Group 1 (Baseline) for each pressure condition.

Table 26 Alterations in maximum pressure following application of elastic wraps.

There was a reduction in maximum pressure with application of elastic wraps. At pressure 1 application of a 12% wrap material produced a greater reduction in maximum pressure than application of a similar diameter reduction 4% wrap. At pressures 2 and 3 application of a 4% wrap produced a greater reduction in maximum pressure than application of a similar diameter reduction 12% wrap.

At pressure 1 (for both the 12% and 4% wrap materials) the greater reduction in maximum pressure occurred following application of the 82% diameter reduction wrap. At pressures 2 and 3 (for both the 12% and 4% wrap materials) the maximum pressure decreased as the diameter reduction increased.

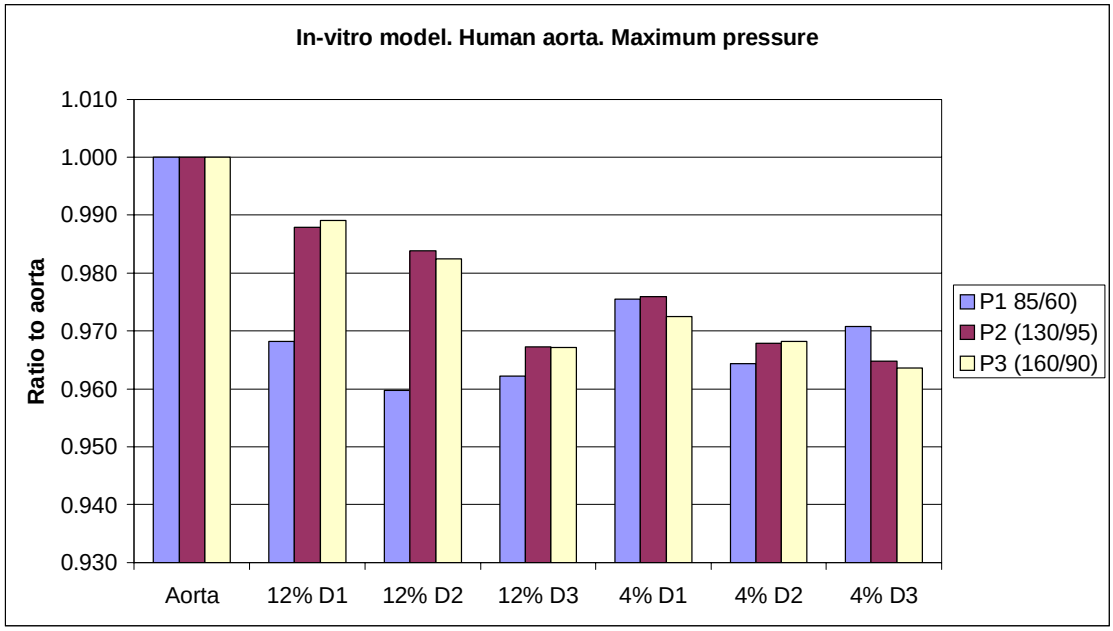


Figure 73 Alterations in maximum pressure following application of elastic wraps.

Minimum pressure

Minimum pressure Ratio to aorta (N=9)	Pressure 1 85/60	Pressure 2 130/95	Pressure 3 160/90
Group 1 (Aorta - Baseline)	1.000	1.000	1.000
Group 2 (12% wrap 91% diameter)	1.025	1.013	1.015
Group 3 (12% wrap 82% diameter)	1.037	1.033	1.049
Group 4 (12% wrap 70% diameter)	1.053	1.049	1.090
Group 5 (4% wrap 91% diameter)	1.029	1.019	1.034
Group 6 (4% wrap 82% diameter)	1.026	1.037	1.082
Group 7 (4% wrap 70% diameter)	1.030	1.041	1.100

Data presented as the ratio to Group 1 (Baseline) for each pressure condition.

Table 27 Alterations in minimum pressure following application of elastic wraps.

There was an increase in minimum pressure with application of elastic wraps. At pressures 1 and 2 the application of a 70% diameter reduction 12% wrap produced the greatest increase in minimum pressure. At pressure 3 application of a 4% wrap produced a greater increase in minimum pressure than application of a similar diameter reduction 12% wrap. At pressure 3 application of a 70% diameter reduction 4% wrap produced the greatest increase in minimum pressure.

At pressure 1 (for the 12% material) and at pressures 2 and 3 for both materials, the minimum pressure increased as the diameter reduction increased. At pressure 1 (for the 4% material) the greatest increase in minimum pressure occurred following application of the 82% diameter reduction wrap.

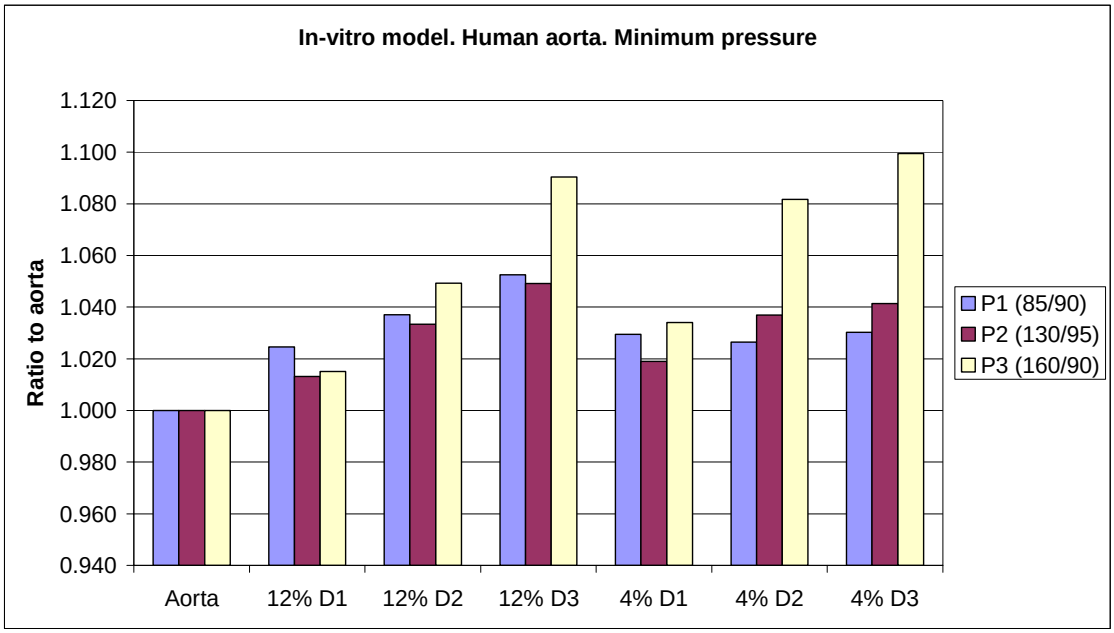


Figure 74 Alterations in minimum pressure following application of elastic wraps.

Pulse pressure

Pulse pressure Ratio to aorta (N=9)	Pressure 1 85/60	Pressure 2 130/95	Pressure 3 160/90
Group 1 (Aorta - Baseline)	1.000	1.000	1.000
Group 2 (12% wrap 91% diameter)	0.837	0.921	0.952
Group 3 (12% wrap 82% diameter)	0.779	0.852	0.887
Group 4 (12% wrap 70% diameter)	0.751	0.749	0.792
Group 5 (4% wrap 91% diameter)	0.849	0.861	0.885
Group 6 (4% wrap 82% diameter)	0.819	0.784	0.807
Group 7 (4% wrap 70% diameter)	0.832	0.761	0.770

Data presented as the ratio to Group 1 (Baseline) for each pressure condition.

Table 28 Alterations in pulse pressure following application of elastic wraps.

There was a reduction in pulse pressure with application of elastic wraps. At pressures 1 and 2 the application of a 70% diameter reduction 12% wrap produced the greatest increase in pulse pressure. At pressure 3 application of a 4% wrap produced a greater reduction in pulse pressure than application of a similar diameter reduction 12% wrap. At pressure 3 application of a 70% diameter reduction 4% wrap produced the greatest reduction in pulse pressure.

At pressure 1 (for the 12% material) and at pressures 2 and 3 for both materials, the pulse pressure fell as the diameter reduction increased. At pressure 1 (for the 4% material) the greatest reduction in pulse pressure occurred following application of the 82% diameter reduction wrap.

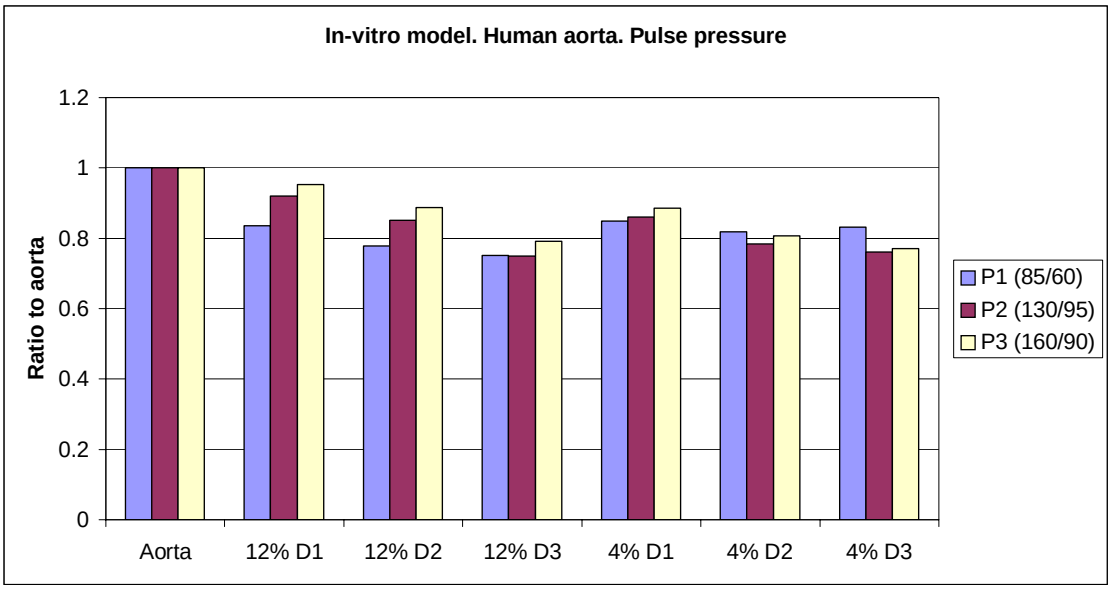


Figure 75 Alterations in pulse pressure following application of elastic wraps.

Percentage pulsatile change in diameter and area

Percentage change in diameter (%δD) Ratio to aorta (N=9)	Pressure 1 85/60	Pressure 2 130/95	Pressure 3 160/90
Group 1 (Aorta - Baseline)	1.00	1.00	1.00
Group 2 (12% wrap 91% diameter)	5.22	5.46	5.13
Group 3 (12% wrap 82% diameter)	6.23	7.53	7.21
Group 4 (12% wrap 70% diameter)	7.32	10.91	11.12
Group 5 (4% wrap 91% diameter)	5.22	7.60	7.55
Group 6 (4% wrap 82% diameter)	5.85	9.25	9.90
Group 7 (4% wrap 70% diameter)	6.08	10.43	11.88

Data presented as the ratio to Group 1 (Baseline) for each pressure condition.

Table 29 Alterations in percentage pulsatile change in aortic diameter following application of elastic wraps.

Percentage change in area (%δA) Ratio to aorta (N=9)	Pressure 1 85/60	Pressure 2 130/95	Pressure 3 160/90
Group 1 (Aorta - Baseline)	1.00	1.00	1.00
Group 2 (12% wrap 91% diameter)	5.27	5.51	5.19
Group 3 (12% wrap 82% diameter)	6.31	7.62	7.35
Group 4 (12% wrap 70% diameter)	7.43	11.11	11.46
Group 5 (4% wrap 91% diameter)	5.27	7.69	7.70
Group 6 (4% wrap 82% diameter)	5.91	9.39	10.16
Group 7 (4% wrap 70% diameter)	6.15	10.61	12.27

Data presented as the ratio to Group 1 (Baseline) for each pressure condition.

Table 30 Alterations in percentage pulsatile change in aortic area following application of elastic wraps.

There was an increase in percentage pulsatile diameter and area with application of elastic wraps. At pressure 1 application of a 12% wrap produced a greater percentage pulsatile diameter and area than application of a similar diameter reduction 4% wrap. At pressure 2 application of a 70% diameter reduction 12% wrap produced the greatest increase in percentage pulsatile diameter and area. At pressure 3 application of a 4% wrap produced a greater percentage pulsatile diameter and area than application of a similar diameter reduction 12% wrap.

At all pressures (for both the 12% and 4% material) the percentage pulsatile change in diameter and area increased as the diameter reduction increased.

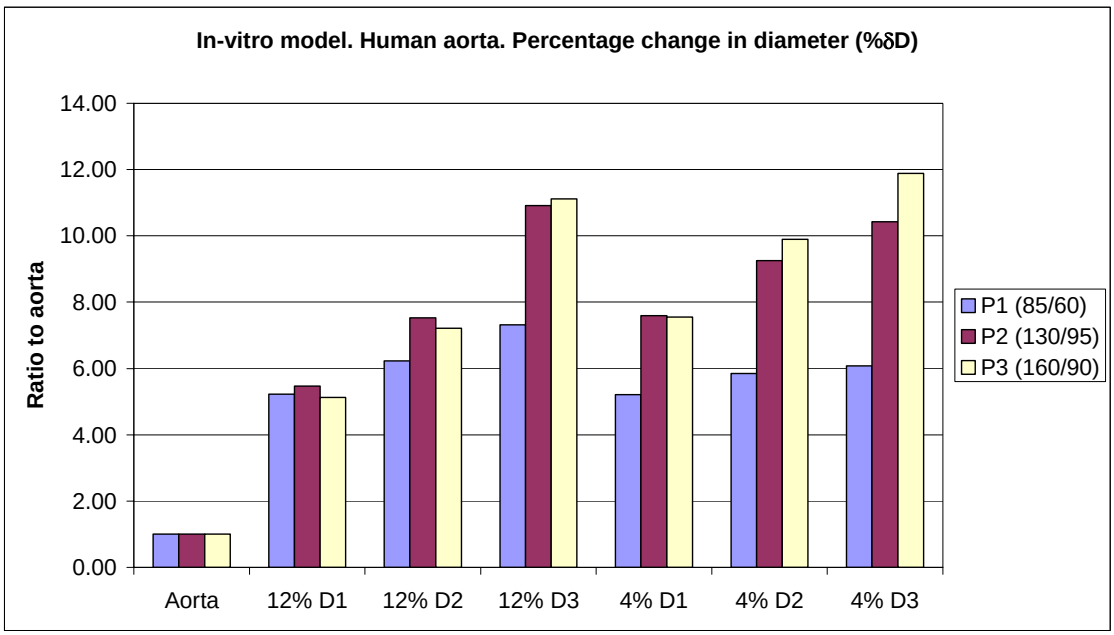


Figure 76 Alterations in percentage pulsatile change in aortic diameter following application of elastic wraps.

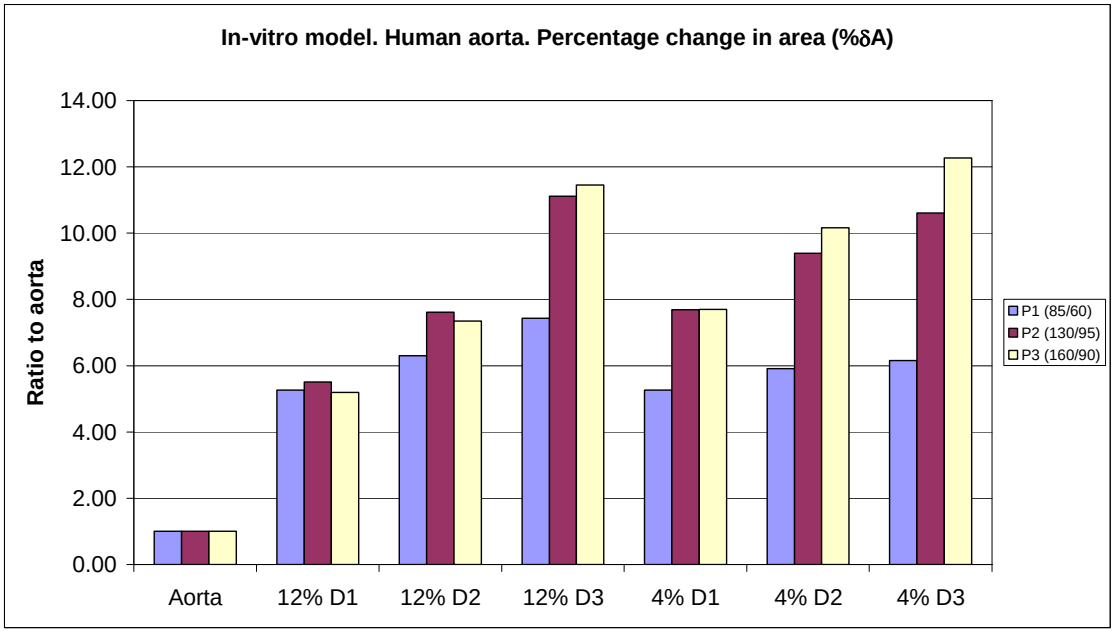


Figure 77 Alterations in percentage pulsatile change in aortic area following application of elastic wraps.

Pressure strain elastic modulus (E_p)

Pressure stain elastic modulus (E_p) Ratio to aorta (N=9)	Pressure 1 85/60	Pressure 2 130/95	Pressure 3 160/90
Group 1 (Aorta - Baseline)	1.000	1.000	1.000
Group 2 (12% wrap 91% diameter)	0.123	0.160	0.174
Group 3 (12% wrap 82% diameter)	0.095	0.107	0.116
Group 4 (12% wrap 70% diameter)	0.078	0.064	0.067
Group 5 (4% wrap 91% diameter)	0.124	0.106	0.110
Group 6 (4% wrap 82% diameter)	0.106	0.079	0.076
Group 7 (4% wrap 70% diameter)	0.106	0.067	0.061

Data presented as the ratio to Group 1 (Baseline) for each pressure condition.

Table 31 Alterations in pressure strain elastic modulus following application of elastic wraps.

There was a reduction in aortic stiffness (E_p) with application of elastic wraps. At pressure 1 application of a 12% wrap produced a smaller aortic stiffness than application of a similar diameter reduction 4% wrap. At pressure 2 application of a 70% diameter reduction 12% wrap produced the greatest reduction in aortic stiffness. At pressure 3 application of a 4% wrap produced a smaller aortic stiffness than application of a similar diameter reduction 12% wrap.

At all pressures (for both the 12% and 4% material) the aortic stiffness fell as the diameter reduction increased.

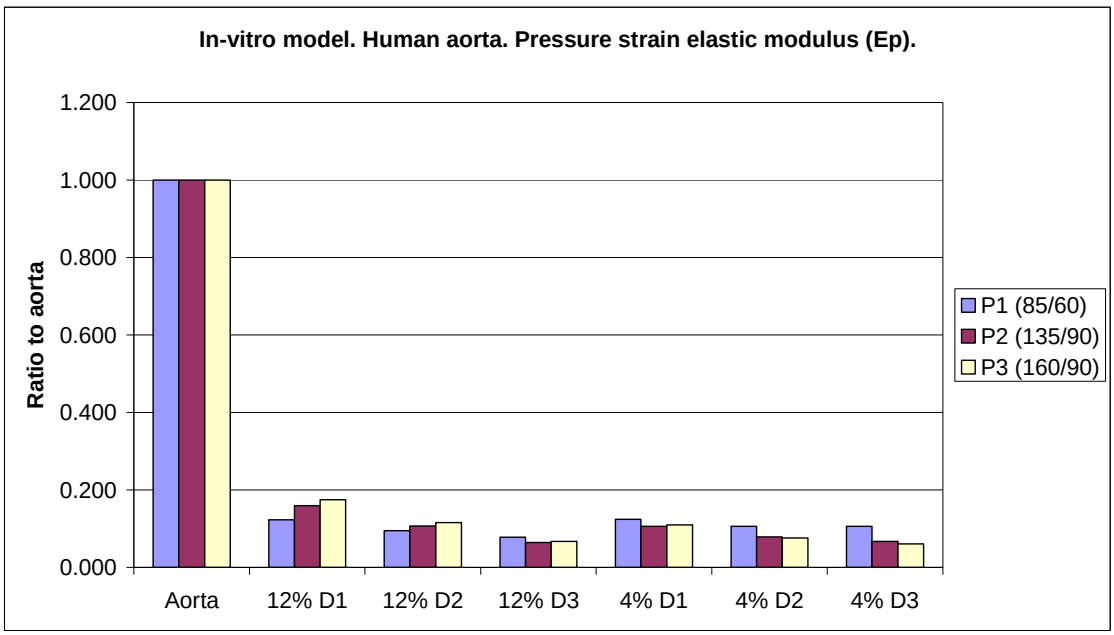


Figure 78 Alterations in pressure strain elastic modulus following application of elastic wraps.

5.4 DISCUSSION

5.4.1 In-vitro models of the aorta

In-vitro pressure and flow models of the human and animal aorta have been widely reported in the literature (Ku, Glagov et al. 1989; Peacock 1990; Moore, Ku et al. 1992; Schurink, M. Aarts et al. 1998; Joubert-Hubner, Gerdes et al. 1999; Wanitkun, Gharib et al. 1999; Gerdes, Joubert-Hubner et al. 2000; Simon-Kupilik, Schima et al. 2002; Walsh, Chin-Quee et al. 2003; DiGiorgi, Smith et al. 2004; Xiaokui, Ashraf et al. 2005). This study describes an in-vitro model of the aged human aorta subjected to pulsatile pressure and flow. The model was used to determine the alterations in stiffness of the ascending aorta as well as in pulse pressure with application of the elastic wrap to the ascending aorta. The ascending aorta and proximal arch of the ascending aorta was dissected from elderly human cadavers and connected to a circuit. A programmable gear pump was used to produce pulsatile pressure and flow.

The experimental protocol consisted of multiple wrap applications (two materials at varying diameter reduction) at three different pulsatile pressures (85/60, 130/95/160/90). The first pressure (85/60) simulates a pulsatile pressure in-vivo where the load of pulsatile pressure and flow is predominantly taken up by the elastin fibres in the aortic wall rather than by collagen fibres (Wolinsky and Glagov 1964; Wolinsky and Glagov 1967). The second and third pulsatile pressures used in this study (130/95 and 160/90) simulate diastolic hypertension and isolated systolic hypertension, respectively (Chobanian, Bakris et al. 2003).

Physiologic pulsatile pressure and flow is difficult to simulate in-vitro, however simpler pressure and flow waveforms can be used to measure the stiffness of intact arteries and vascular grafts. In-vitro testing of intact arteries and vascular grafts maintains normal vessel geometry and permits correlation of mechanical phenomena with pulsatile pressure and flow. In-vitro models provide useful data about the mechanical properties of arteries and vascular grafts and may reduce the requirement for animal experimentation, which is time-consuming, costly, and impacts on animal welfare. In-vitro testing may precede in-vivo experiments allowing fine-tuning of experimental protocols or procedures and may be used to provide data required for regulatory bodies prior to human experimentation.

5.4.2 Elastic wrap application

Application of both wrap materials at all diameter reductions tested decreased maximum pressure and pulse pressure, increased minimum pressure, and reduced aortic stiffness (E_p). Application of elastic wraps to the aorta that reduces the diameter of the aortic wall may act to unload the aortic wall and take up the load of pulsatile pressure and flow (see Chapter 3 and Chapter 4). The stiffness of the wrapped aorta is determined by the stiffness of the wrap material, the diameter of the elastic wrap, and by the stiffness of the aorta.

Stiffness of the elastic wrap

At low mean and pulsatile pressures, the 12% wrap was more effective at reducing aortic stiffness, whereas at a higher pulsatile pressure (simulating isolated systolic hypertension) the 4% wrap was more effective in reducing aortic stiffness.

Application of the 4% wrap reduced aortic stiffness more than application of the 12% wrap in the 160/90 groups. The elastic properties of the 4% wrap material simulate the elastic properties of young human aorta in vivo, and application of this wrap material may act to restore aortic stiffness to that seen in the young aorta. The 12% wrap material that simulates the stiffness of the pulmonary artery may not be sufficiently stiff enough to overcome the stiffness of the aged human ascending aorta and therefore did not reduce aortic stiffness as much as the 4% wrap did.

Application of the 12% elastic wrap reduced aortic stiffness more than application of the 4% wrap in the 85/60 groups. The 12% material applied at 70% diameter reduction produced the greatest reduction in aortic stiffness in the 135/90 groups, although the 4% material applied at 70% diameter reduction was almost as effective in reducing aortic stiffness.

Diameter reduction

The reduction in aortic stiffness increased as the reduction in diameter produced by wrap application increased. Greater reductions in diameter in-vivo beyond those tested in the study may have adverse effects related to creation of an artificial aortic coarctation (increased ascending aortic systolic pressure and cardiac load) (O'Rourke and Cartmill 1971; Declusin, Boerboom et al. 1987).

5.4.3 Alterations in pulse pressure

The reduction in ascending aortic stiffness with wrap application was associated with a decrease in maximum and pulse pressure, and increase in minimum pressure. The ascending aorta is the trunk of the arterial tree and the site of interaction between the left

ventricle and systemic arterial system (Berne and Levy 1977; Boudoulas and Wooley 1996). The thoracic aorta and large elastic arteries have an elastic function, in that they convert the pulsatile output of the left ventricle into the smoother pattern of pressure and flow seen in the peripheral circulation. The elasticity of the wall of the large elastic arteries is central to this function.

Stiffening of the thoracic aorta in humans as well as experimental animals increases systolic pressure, pulse pressure and cardiac load, and decreases coronary perfusion (Murgo, Westerhof et al. 1980; Merillon, Motte et al. 1982b; Kelly, Tunin et al. 1992; Watanabe, Ohtsuka et al. 1993; Ohtsuka, Kakihana et al. 1994; O'Rourke and Nichols 2005). Increased stiffening of the ascending aorta alone is sufficient to produce this (Bauernschmitt, Schulz et al. 1999). In this study, a reduction in ascending aortic stiffness produced a reduction in maximum and systolic pressure, and increased minimum pressure. The alterations in pressure were related to the alterations in aortic stiffness. The greater the reduction in ascending aortic stiffness, the greater the reduction in maximum and pulse pressure, and the greater the increase in minimum pressure.

Application of the 4% wrap to reduce aortic diameter by 30% (70% diameter reduction group) when exposed to a pulsatile pressure of 160/90mmHg produced the greatest reduction in pulsatile pressure and aortic stiffness. Therefore, application of an elastic wrap that simulates the mechanical properties of the young human ascending aorta, to reduce aortic diameter towards that seen in youth, showed the greatest alteration in aortic stiffness and pulsatile pressure. In this group, aortic stiffness (Ep) fell by 94%, maximum pressure fell by 4%, pulse pressure fell by 23%, and minimum pressure rose by 10%. Alterations in pulsatile pressure of this magnitude in elderly subjects are expected to have clinical benefit (Nichols and O'Rourke 2005).

5.4.4 Clinical benefits

Aortic stiffening and dilatation with aging produces isolated systolic hypertension and increased pulse pressure and is the fundamental cause of heart failure in the elderly (O'Rourke, Avolio et al. 1986; Westerhof and O'Rourke 1995; Hundley, Kitzman et al. 2001; Nichols and O'Rourke 2005). This study suggests that application of an elastic wrap to the ascending aorta in elderly patients is sufficient to produce beneficial alterations in pulsatile pressure. This is beneficial as more extensive surgery of the thoracic aorta (i.e. wrapping the arch of aorta and descending thoracic aorta) is technically very challenging, with an expected increase in morbidity and mortality (Baue, Geha et al. 1996; Cohn and Edmunds 2003; Kouchoukos, Blackstone et al. 2003).

At present, the cornerstone agents for the pharmacological therapy of heart failure are the ACE inhibitors. These act by reducing cardiac load and have been reported to reduce ascending aortic systolic and pulse pressure (London, Asmar et al. 2004; Hirata, Vlachopoulos et al. 2005). ACE inhibitors (and other vasodilators) act by producing arterial vasodilatation, a delay in the reflection of the pressure wave, and a reduction in systolic augmentation of ascending aortic pressure by the reflected pressure wave (Yaginuma, Avolio et al. 1986; Kelly, Gibbs et al. 1990; Chen, Ting et al. 1995; Ting, Chen et al. 1995; Jiang, O'Rourke et al. 2002; London, Asmar et al. 2004; Hirata, Vlachopoulos et al. 2005; Nichols and O'Rourke 2005). They do not treat the underlying cause of isolated systolic hypertension and heart failure in the elderly- aortic stiffening and dilatation (Safar and London 2000; Van Bortel, Struijker-Boudier et al. 2001; Bristow, Linas et al. 2005; Nichols and O'Rourke 2005).

This study suggests that the aortic wrap procedure may produce greater beneficial alteration of the ascending aortic pressure wave than pharmacologic agents, by directly altering the stiffness of the ascending aorta. Alterations of this magnitude are expected to improve ventricular-vascular interaction, reduce cardiac load, and increase coronary perfusion, and may improve clinical outcome in patients with isolated systolic hypertension, heart failure, and myocardial ischaemia (O'Rourke, Avolio et al. 1986; Westerhof and O'Rourke 1995; Nichols and O'Rourke 2005).

5.5 CONCLUSIONS

In conclusion, application of an elastic wrap to an in-vitro model of the aged human ascending aorta reduced the stiffness of the aorta, reduced maximum pressure and pulse pressure, and increased minimum pressure. The alterations in pressure were related to the decrease in aortic stiffness produced by wrap application. When isolated systolic hypertension was simulated, the greatest reduction in stiffness and alteration in pressure was produced by the 4% wrap when applied to restore ascending aortic diameter to values seen in young subjects. Application of the elastic wrap to the ascending aorta alone may be sufficient to beneficially alter pulsatile pressure and ventricular-vascular interaction in elderly human subjects.

CHAPTER 6: THE EFFECT OF THE AORTIC WRAP PROCEDURE ON PULSE PRESSURE USING A MULTIBRANCHED MODEL OF THE HUMAN ARTERIAL MODEL

6.1 INTRODUCTION

The physical properties of the arterial system determine the propagation of pressure and flow waves and affect left ventricular load (Milnor 1989; O'Rourke, Kelly et al. 1992; Li 2000; Li 2004; Nichols and O'Rourke 2005; Westerhof, Stergiopoulos et al. 2005). Mathematical models of the arterial system may be used to investigate the effects of alterations of the physical and mechanical properties of the arterial system on blood pressure propagation and left ventricular load (Westerhof, Bosman et al. 1969; Avolio 1980; O'Rourke and Avolio 1980; Stergiopulos, Young et al. 1992; Karamanoglu, Gallagher et al. 1994; Karamanoglu, Gallagher et al. 1995; Wang and Parker 2004).

The human arterial system may be modelled using electrical engineering principles and represented as an electric network (Avolio 1980; Milnor 1989; Westerhof, Stergiopoulos et al. 2005). In these models (distributed or transmission line models), the human arterial system is divided into an anatomically accurate branching network of arterial segments whose properties can be altered to simulate different physiological and pathological conditions.

Aging is associated with stiffening and dilatation of the large elastic arteries and a consequent increase in systolic pressure, pulse pressure, and left ventricular load (Nichols, O'Rourke et al. 1985; O'Rourke, Avolio et al. 1986; Nichols, Nicolini et al. 1992; Franklin, Gustin et al. 1997; Lakatta and Boluyt 2000; Lakatta and Levy 2003a; Lakatta and Levy 2003b; Nichols and O'Rourke 2005). The application of an elastic wrap that reduces the diameter of the dilated ascending aorta and restores elasticity is expected to reduce systolic pressure and pulse pressure, increase diastolic pressure and coronary blood flow, and improve ventricular-vascular interaction to reduce cardiac load (Nichols, O'Rourke et al. 1985; Nichols, O'Rourke et al. 1986; O'Rourke, Avolio et al. 1986; Kelly, Tunin et al. 1992; Watanabe, Ohtsuka et al. 1993; Ohtsuka, Kakihana et al. 1994; Westerhof and O'Rourke 1995; Franklin, Gustin et al. 1997; Hundley, Kitzman et al. 2001; Morita, Asou et al. 2002; O'Rourke and Nichols 2005).

In this study, a multi-branched human arterial model was used to determine the change in ascending aortic pulse pressure (PP) with altered ascending aortic stiffness and dilatation. The wall stiffness (E) of the ascending aorta was varied and the reduction in pulse pressure (PP) was calculated for a similar stroke volume.

6.2 METHODS

6.2.1 Mathematical model

A multi-branched model of the human arterial system based on that described by Avolio (1980) was used in this study. The model is a based on electrical transmission line theory and is a realistic anatomic representation of the human arterial system consisting of 142 arterial segments. Each arterial segment is represented by a uniform circular elastic

tube, and the haemodynamic properties are described in terms of the tube physical properties:

(i) length

(ii) radius

(iii) wall thickness

(iv) Young's modulus (E)

(v) Poisson ratio

(vi) wall viscoelasticity

(vii) blood density

(viii) blood viscosity

The model has been programmed in Matlab language. Pressure can be determined throughout the arterial tree using a flow input at the ascending aorta; and the effect of changing the properties of specific segments on pulse pressure can be determined for a given stroke volume.

6.2.2 Altered ascending aortic stiffness and diameter

To simulate the increase in ascending aortic stiffness and radius with aging and the effects of application of an elastic wrap, the wall stiffness (E) and the radius of the ascending aorta were altered. The wall stiffness (E) of the ascending aorta was increased by 100%, and the radius of the ascending aorta was increased by 30%. Wall stiffness of the ascending aorta was altered in increments of 5% and the radius was altered in increments of 5%. The ascending aortic pulse pressure was determined at each given stiffness and radius.

Ascending aortic pulse pressures were normalised to the maximum predicted pulse pressure generated, and tabulated and compared graphically using Microsoft Excel (Office

2000; Microsoft Corporation). Predicted pulse pressure data represented the alterations in ascending aortic pulse pressure with reductions in ascending aortic wall stiffness and radius, to simulate application of an elastic wrap to the ascending aorta. Pulse pressure data generated from the in-vitro human model (at a pulsatile pressure of 160/90) were compared to predicted pulse pressures generated by the mathematical model.

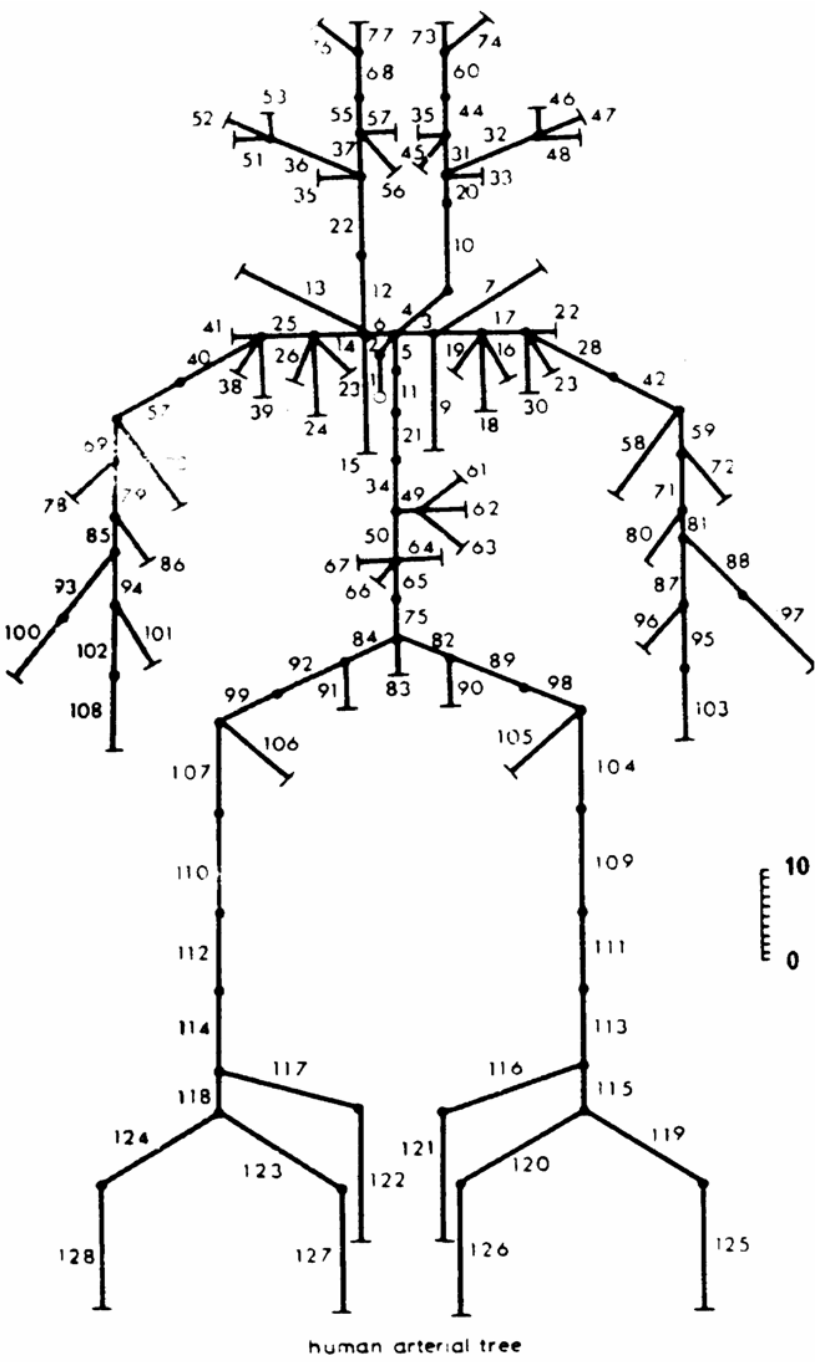


Figure 79 Multi-branched model of the human arterial system (Avolio 1980).

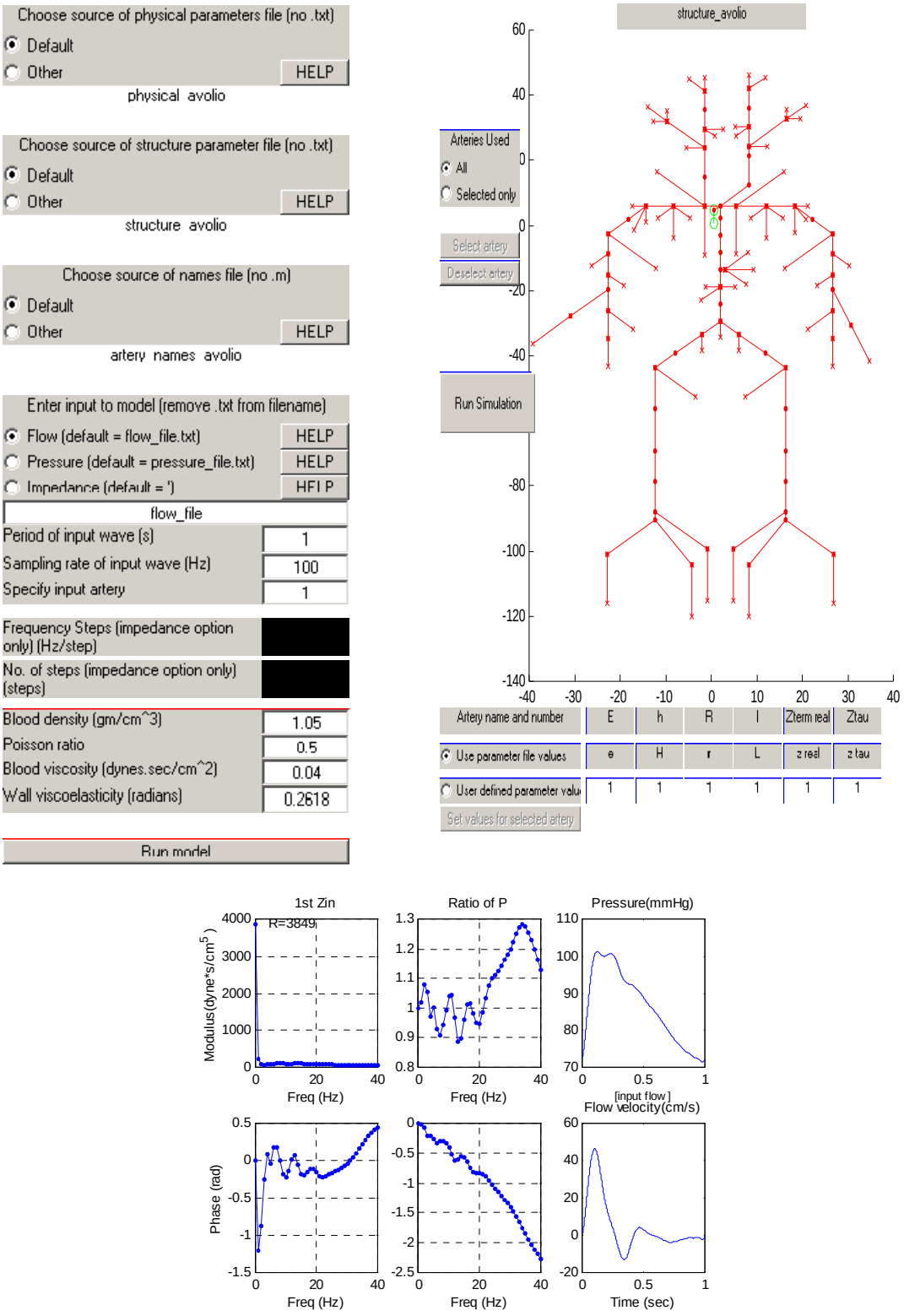


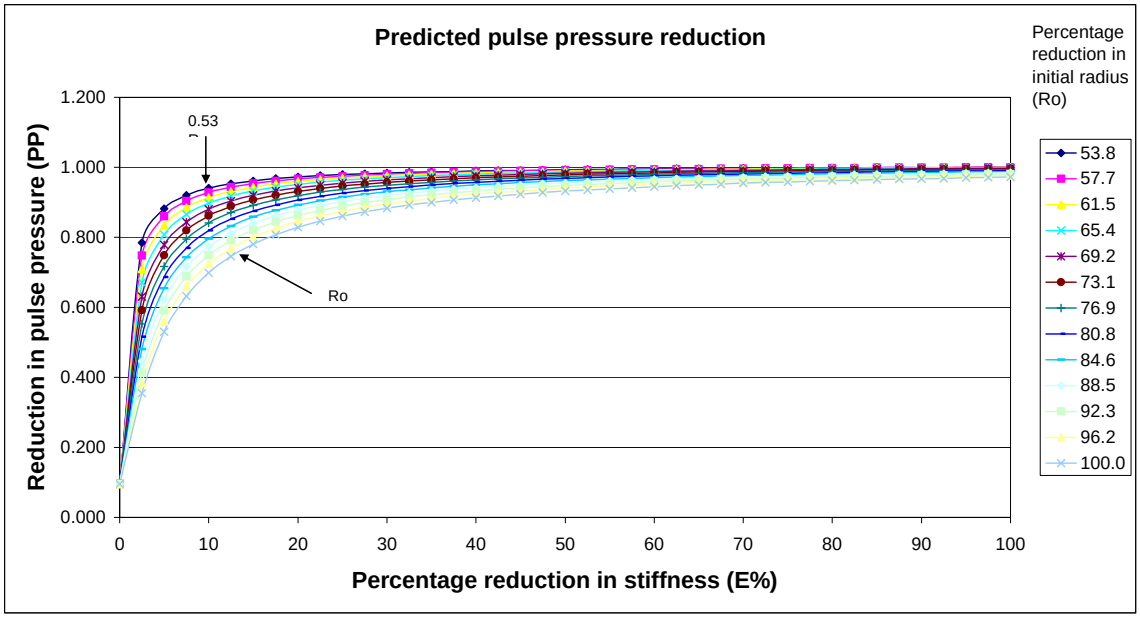
Figure 80 Matlab model output

6.3 RESULTS

E%	Ro 53.8%	Ro 57.7%	Ro 61.5%	Ro 65.4%	Ro 69.2%	Ro 73.1%	Ro 76.9%	Ro 80.8%	Ro 84.6%	Ro 88.5%	Ro 92.3%	Ro 96.2%	Ro 100%
0%	0.095	0.095	0.095	0.095	0.095	0.095	0.095	0.095	0.095	0.095	0.095	0.095	0.095
2.5%	0.785	0.748	0.710	0.670	0.631	0.591	0.553	0.516	0.480	0.446	0.414	0.383	0.355
5%	0.882	0.859	0.834	0.807	0.778	0.748	0.717	0.686	0.654	0.622	0.591	0.560	0.530
7.5%	0.920	0.904	0.886	0.865	0.843	0.820	0.795	0.769	0.743	0.715	0.688	0.660	0.632
10%	0.940	0.928	0.914	0.898	0.880	0.861	0.841	0.819	0.796	0.773	0.749	0.724	0.699
12.5%	0.953	0.943	0.932	0.918	0.904	0.888	0.870	0.852	0.832	0.812	0.790	0.768	0.746
15%	0.961	0.953	0.944	0.933	0.920	0.906	0.891	0.875	0.858	0.840	0.821	0.801	0.781
17.5%	0.968	0.961	0.953	0.943	0.932	0.920	0.907	0.893	0.877	0.861	0.844	0.826	0.807
20%	0.972	0.967	0.960	0.951	0.942	0.931	0.919	0.906	0.893	0.878	0.862	0.846	0.829
22.5%	0.976	0.971	0.965	0.958	0.949	0.939	0.929	0.917	0.905	0.891	0.877	0.862	0.846
25%	0.979	0.975	0.969	0.963	0.955	0.946	0.937	0.926	0.915	0.902	0.889	0.875	0.861
27.5%	0.982	0.978	0.973	0.967	0.960	0.952	0.943	0.933	0.923	0.911	0.899	0.886	0.873
30%	0.984	0.980	0.976	0.970	0.964	0.957	0.949	0.940	0.930	0.919	0.908	0.896	0.883
35%	0.987	0.984	0.981	0.976	0.971	0.964	0.957	0.950	0.941	0.932	0.922	0.911	0.900
40%	0.989	0.987	0.984	0.980	0.976	0.970	0.964	0.957	0.950	0.941	0.933	0.923	0.913
45%	0.991	0.990	0.987	0.984	0.980	0.975	0.969	0.963	0.956	0.949	0.941	0.933	0.923
50%	0.993	0.991	0.989	0.986	0.983	0.978	0.974	0.968	0.962	0.955	0.948	0.940	0.932
55%	0.994	0.993	0.991	0.989	0.985	0.982	0.977	0.972	0.967	0.960	0.954	0.947	0.939
60%	0.995	0.994	0.993	0.990	0.988	0.984	0.980	0.975	0.970	0.965	0.959	0.952	0.945
65%	0.996	0.995	0.994	0.992	0.989	0.986	0.983	0.978	0.974	0.968	0.963	0.957	0.950
70%	0.997	0.996	0.995	0.993	0.991	0.988	0.985	0.981	0.976	0.972	0.966	0.961	0.954
75%	0.997	0.997	0.996	0.995	0.992	0.990	0.987	0.983	0.979	0.974	0.969	0.964	0.958
80%	0.998	0.998	0.997	0.996	0.994	0.991	0.988	0.985	0.981	0.977	0.972	0.967	0.962
85%	0.999	0.998	0.998	0.996	0.995	0.992	0.990	0.987	0.983	0.979	0.975	0.970	0.965
90%	0.999	0.999	0.998	0.997	0.996	0.994	0.991	0.988	0.985	0.981	0.977	0.972	0.967
95%	0.999	1.000	0.999	0.998	0.996	0.995	0.992	0.989	0.986	0.983	0.979	0.974	0.970
100%	1.000	1.000	1.000	0.999	0.997	0.995	0.993	0.991	0.988	0.984	0.981	0.976	0.972

E% = percentage reduction in ascending aortic wall stiffness (E) following elastic wrap placement; Ro = initial ascending aortic radius (percentage indicates percentage reduction in Ro following elastic wrap application); data represent ascending aortic pulse pressure reduction normalised to maximal pulse pressure generated.

Table 32 Predicted reductions in ascending aortic pulse pressure (PP) following application of an elastic wrap on a dilated and stiffened ascending aorta. Highlighted cells show reductions of ascending aortic pulse pressure from 0.50 to 0.80 of maximum pulse pressure generated.



E% = percentage reduction in ascending aortic wall stiffness (E) following elastic wrap placement; Ro = initial ascending aortic radius (percentage indicates percentage reduction in Ro following elastic wrap application); PP = ascending aortic pulse pressure reduction normalized to maximal pulse pressure generated.

Figure 81 Predicted reduction in ascending aortic pulse pressure (PP) following application of an elastic wrap on a dilated and stiffened ascending aorta.

For each radius reduction curve there was an asymptotic relation between pulse pressure (PP) and stiffness (E) of the ascending aorta. The greatest reduction in pulse pressure was produced when ascending aortic stiffness was reduced without reducing ascending aortic diameter. As the diameter of the ascending aorta was decreased at a constant ascending aortic stiffness, the reduction in pulse pressure diminished.

Human in-vitro model group (160/90)	Measured reduction in AoD (in-vitro model)	Measured reduction in Ep (in-vitro model)	Measured reduction in PP (in-vitro model)	Predicted reduction in PP (multi-branched model)
Aorta - Baseline	1.000	1.000	1.000	1.00
12% wrap 91% diameter	0.863	0.174	0.952	0.87
12% wrap 82% diameter	0.861	0.116	0.887	0.82
12% wrap 70% diameter	0.801	0.067	0.792	0.78
Group 5 4% wrap 91% diameter	0.809	0.110	0.885	0.84
Group 6 4% wrap 82% diameter	0.785	0.076	0.807	0.78
Group 7 4% wrap 70% diameter	0.697	0.061	0.770	0.77

Ao Diameter = ascending aortic diameter (in-vitro model; Chapter 5); Ep = pressure strain elastic modulus (in-vitro model; Chapter 5); PP = ascending aortic pulse pressure. Data presented as the ratio to the Aorta-Baseline group.

Table 33 Comparison of the reduction in pulse pressure (PP) following elastic wrap application in the in-vitro human model and multi-branched model.

There was agreement between the relative reductions in pulse pressure measured experimentally (in the human in-vitro study at pulsatile pressure 160/90) and those calculated by the multi-branched model. The multi-branched model did however overestimate the measured reduction in pulse pressure in the 91% and 82% diameter reduction groups for both 12% and 4% materials.

The predicted pulse pressure for application of a 4% wrap was less than the predicted pulse pressure for application of a similarly sized 12% wrap in this study. In the in-vitro human study, application of a 4% wrap also produced a greater reduction in pulse pressure than application of a similar diameter reduction 12% wrap.

For the 12% wrap groups and the 4% wrap groups the predicted pulse pressure fell as the diameter reduction increased. In the human in-vitro study, the pulse pressure also fell as the diameter reduction increased.

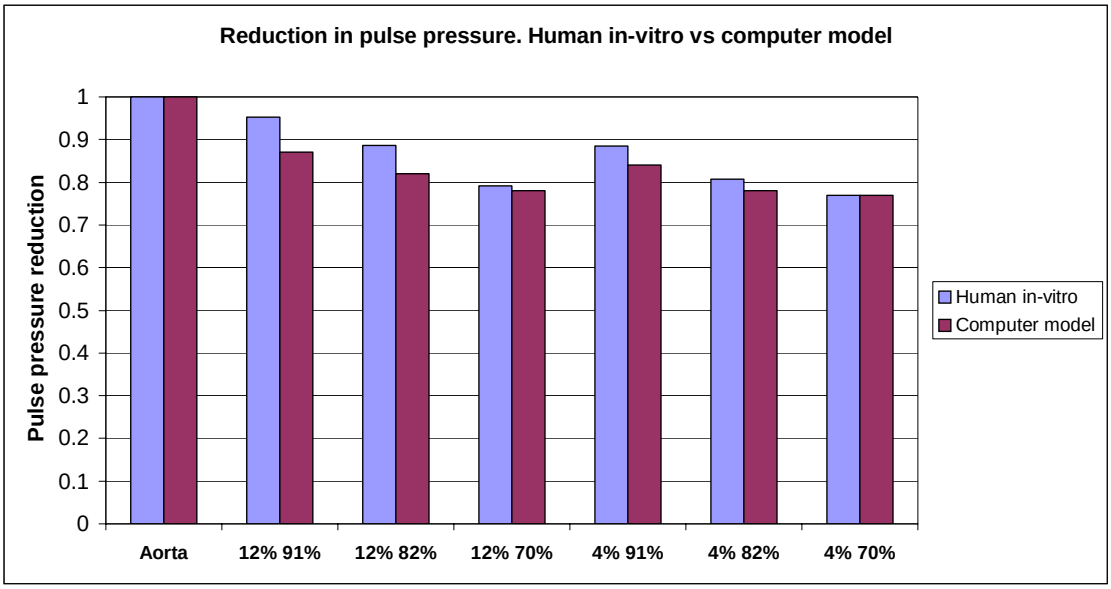


Figure 82 Comparison of the reduction in pulse pressure (PP) following elastic wrap application to the ascending aorta in the in-vitro human model (160/90) and multi-branched model.

6.4. DISCUSSION

6.4.1 Mathematical models of the arterial system

The effect of reduction of ascending aortic stiffness and diameter resulting from application of an elastic wrap was investigated using an anatomically accurate multi-branched model of the arterial system. The model is based on linear transmission theory and was originally described by Avolio (1980). Previous validation studies of the model have shown good concordance with data collected from in-vivo experiments.

A similar model was used to simulate the haemodynamic alterations produced by replacement of the thoracic aorta with a stiff vascular graft (Bauernschmitt, Schulz et al. 1999). Stiffening of the ascending aorta and aortic arch was sufficient to increase systolic and pulse pressure, and reduce diastolic pressure. Alterations in the ascending aortic impedance spectrum showed an increase in characteristic impedance and an increase in the modulus of the first harmonic. These findings indicate an increase in cardiac load and loss of efficient interaction between the arterial system and left ventricle (Nichols and O'Rourke 2005).

The aorta and large elastic arteries have an elastic function in that they absorb the pulsatile output of the left ventricle and convert it into the smoother type of flow seen in the peripheral circulation, and act to maintain blood flow during diastole (Berne and Levy 1977; Nichols and O'Rourke 1998; Li 2000; Li 2004; Isselbacher 2005). The ascending aorta is the site of interaction between the arterial system and the left ventricle, and loss of its elastic function is sufficient to reduce the elastic function of entire aorta and large elastic arteries (Bauernschmitt, Schulz et al. 1999).

6.4.2 Limitations of animal models

Animal models of aortic stiffness are inadequate to study the effect of alterations in ascending aortic stiffness and diameter on pulse pressure (see Chapter 4). In-vitro and mathematical models may be used to accurately provide the same information. There are no animal models of aortic stiffness and dilatation that adequately model ascending aortic stiffness and dilatation (O'Rourke 1967b; Morita, Kuboyama et al. 1991; Kelly, Tunin et al. 1992; Watanabe, Ohtsuka et al. 1993; Mekkaoui, Rolland et al. 2003). The animal models described by Morita et al. (Morita, Kuboyama et al. 1991) and Kelly et al. (Kelly, Tunin et al. 1992) use a prosthetic tube as an extra-anatomic bypass extending from the arch of the aorta to the distal descending thoracic aorta or proximal abdominal aorta, with the native ascending aorta left intact. These models cannot be used to determine the effect that wrapping the ascending aorta will have on ascending aortic pulse pressure as the bypass tube is anastomosed distal to the ascending aorta.

An accurate model of aortic dilatation and stiffness would require replacement of the aorta from the aortic root to the diaphragm with an anatomically accurate and oversized Dacron (or other stiff) vascular conduit. Replacement of the thoracic aorta with an oversized Dacron vascular conduit is a technically challenging procedure with a relatively high incidence of morbidity and mortality even in human subjects (Baue, Geha et al. 1996; Cohn and Edmunds 2003; Kouchoukos, Blackstone et al. 2003). Replacement of the thoracic aorta (or the ascending aorta alone) in an animal model with a Dacron graft requires the use of cardiopulmonary bypass, cardioplegic arrest, and deep hypothermic circulatory arrest. Technical problems relate to the (Baue, Geha et al. 1996; Cohn and Edmunds 2003; Kouchoukos, Blackstone et al. 2003):

1. Anastomosis between the aortic root and Dacron graft that alters ventricular-vascular interaction.
2. Alterations in myocardial function relating to cardiopulmonary bypass, cardioplegic arrest, and hypothermia.
3. Relatively high incidence of bleeding requiring transfusion of blood and coagulation products.
4. Relatively high incidence of complications such as respiratory dysfunction, cerebrovascular accident, spinal chord ischaemia, and renal failure.

All of the above may impact on measurement of haemodynamic function and ventricular-vascular interaction as well as impact on the survival of the animal.

The effect of altering ascending aortic stiffness and diameter is more easily assessed using mathematical as well as in-vitro models of the human arterial system.

6.4.3 Alterations in ascending aortic stiffness and diameter

In this study, the effect of altering ascending aortic stiffness and/or diameter on pulse pressure was assessed using the mathematical model described above. A reduction in ascending aortic stiffness without a reduction in ascending aortic diameter produced the greatest reduction in ascending aortic pulse pressure. As the ascending aortic diameter is decreased while the ascending aortic stiffness is kept constant, the pulse pressure reduction diminishes. These findings are consistent with theoretical principles (Nichols and O'Rourke 2005).

An alteration in ascending aortic stiffness without altering ascending aortic diameter is therefore expected to produce the greatest reduction in pulse pressure. The alteration of ascending aortic stiffness without an alteration in ascending aortic diameter cannot be

achieved by the aortic wrap procedure in-vivo as the aortic wrap procedure inherently involves a reduction in the diameter of the aorta. The elastic material is applied to reduce the diameter of the aorta so that the load is borne (at least partially) by the elastic wrap rather than the arterial wall i.e. the reduction of aortic diameter is integral to the functioning of the wrap.

6.4.4 Predicted alterations in pulse pressure

The alterations in ascending aortic stiffness calculated in the human in-vitro study were used to predict the alterations in pulse pressure that application of an elastic wrap to the human ascending aorta would produce in-vivo. There was good concordance between the predicted reduction in pulse pressure generated by the mathematical model and the reduction in pulse pressure measured in the in-vitro model (at a pulsatile pressure of 160/90).

Application of the 4% wrap produced a greater predicted reduction in pulse pressure in the theoretic model than application of a similarly sized 12% stiffness wrap. The predicted reduction in pulse pressure increased as the reduction in diameter produced by wrap application increased. These findings were also present in the in-vitro human study.

The greatest predicted reduction in pulse pressure was seen with the 4% wrap applied at 70% diameter reduction. The thoracic aorta dilates by 40% or more between ages 20 and 80, and the 4% wrap simulates the properties of the human ascending aorta in young subjects (Nichols, O'Rourke et al. 1985; Pearson, Guo et al. 1994; Hager, Kaemmerer et al. 2002). The pulse pressure reduction is therefore greatest when aortic ascending diameter and stiffness are reduced towards values seen in young subjects i.e. when the diameter and stiffness of the aorta are restored to values seen in the young.

6.4.5 Clinical benefit

A reduction in the stiffness of the ascending aorta alone produced a predicted reduction in pulse pressure that is expected to produce beneficial clinical outcome (Nichols and O'Rourke 2005). Application of the 4% wrap at 70% diameter reduction produced a predicted reduction in ascending aortic pulse pressure of 23%. In comparison, the ACE inhibitors have been reported to reduce ascending aortic pulse pressure by 24% (London, Asmar et al. 2004; Hirata, Vlachopoulos et al. 2005). ACE inhibitors are the most effective drugs for the treatment of heart failure and improve survival, functional class, and left ventricular geometry in patients with heart failure. ACE inhibitors (and other vasodilators) are used to treat isolated systolic hypertension and heart failure but do not treat their underlying cause- aortic stiffening and dilatation (Safar and London 2000; Van Bortel, Struijker-Boudier et al. 2001; Bristow, Linas et al. 2005; Nichols and O'Rourke 2005)

The combination of the aortic wrap procedure and pharmacologic therapy with ACE inhibitors (or other vasodilator therapy) may have additive effects. ACE inhibitors (and other vasodilators) act by producing arterial vasodilatation, a delay in the reflection of the pressure wave, and a reduction in systolic augmentation of ascending aortic pressure by the reflected pressure wave (Yaginuma, Avolio et al. 1986; Kelly, Gibbs et al. 1990; Chen, Ting et al. 1995; Ting, Chen et al. 1995; Jiang, O'Rourke et al. 2002; London, Asmar et al. 2004; Hirata, Vlachopoulos et al. 2005; Nichols and O'Rourke 2005).

6.4.6 Implications for the surgical procedure in humans

Pulse pressure is a sensitive indicator of cardiovascular risk, and a reduction in pulse pressure is expected to reduce cardiac load and improve coronary artery blood flow (Madhavan, Ooi et al. 1994; Benetos, Safar et al. 1997; Mitchell, Moye et al. 1997;

Benetos, Rudnichi et al. 1998; Chae, Pfeffer et al. 1999; Domanski, Davis et al. 1999; Franklin, Khan et al. 1999; Vaccarino, Holford et al. 2000; Safar 2000a; Safar, Blacher et al. 2000b; Franklin, Larson et al. 2001b; Safar, Blacher et al. 2002). Reduction in pulse pressure with application of the external elastic wrap to the ascending aorta alone is fortuitous. Application of elastic wraps to the arch of the aorta is technically difficult because of the great vessels that arise from its convexity and because of the vital structures that it is intimately related to e.g. the phrenic nerve (Baue, Geha et al. 1996; Cohn and Edmunds 2003; Kouchoukos, Blackstone et al. 2003). Similarly, the numerous intercostal arteries complicate application of elastic wraps to the descending thoracic aorta. Damage to the intercostal arteries may produce spinal chord ischaemia and paralysis, and my also increase aortic stiffness (Angouras, Sokolis et al. 2000; Cohn and Edmunds 2003).

6.5 CONCLUSIONS

In conclusion, a mathematical model of the human circulation was used to predict the alteration in ascending aortic pulse pressure that would result from a reduction in aortic stiffness and diameter with application of an elastic wrap to the ascending aorta. There was good concordance between the predicted reduction in pulse pressure generated by the mathematical model and the reduction in pulse pressure measured in the in-vitro model (at a pulsatile pressure of 160/90). Restoration of ascending aortic diameter and stiffness towards values seen in young subjects produced the greatest predicted reduction in pulse pressure. Application of the elastic wrap to the ascending aorta alone produced a reduction in pulse pressure that may result in clinical improvement in heart failure as well as isolated systolic hypertension.

CHAPTER 7: THE CHRONIC EFFECT OF APPLICATON OF AN ELASTIC WRAP ON THE OVINE THORACIC AORTA

7.1 INTRODUCTION

Application of an elastic wrap on the ascending aorta in elderly human patients has been proposed as a surgical treatment of isolated systolic hypertension and heart failure in elderly patients with aortic stiffening. The chronic effects of elastic wrap placement on aortic structure and function has not been investigated.

Application of a rigid wrap onto the ascending aorta is currently used in clinical practice to treat ascending aortic aneurysms (Robicsek 1982; Carrel, von Segesser et al. 1991; Bauer, Pasic et al. 2002; Arsan, Akgun et al. 2004; Robicsek, Cook et al. 2004; Olearchyk 2004a; Olearchyk 2004b). Application of rigid wraps on the thoracic aorta is also used experimentally to induce hypertension and increase cardiac load in experimental animals (O'Rourke 1967b; Xu, Glagov et al. 1991; Watanabe, Ohtsuka et al. 1993; Ohtsuka, Kakihana et al. 1994; Tropea, Huie et al. 1996; Tropea, Schwarzacher et al. 2000; Ioannou, Stergiopulos et al. 2003) . Whereas the alterations in cardiac function that result from application of rigid wraps on the ascending aorta has been studied in experimental animals, the effect on aortic structure and function has not been well described.

In this study, the chronic effects of elastic wrap application on aortic structure and function were investigated by applying an elastic wrap to the ovine proximal descending thoracic aorta for 10 weeks. The aims of this study were:

1. To assess the effect of chronic application of the elastic wrap on aortic structure (macroscopic and microscopic).

2. To measure the changes in the uniaxial tensile properties of the aorta with chronic application of the aortic wrap.
3. To determine if the wrap material and clamp mechanism fatigue or fail with chronic implantation.

7.2 MATERIALS AND METHODS

Two neutered adult male sheep were used in this study (see Appendix 1). Only two animals were used in this study for the following reasons:

1. Only the 4% stiffness material was evaluated (see below).
2. The data from these two animals was sufficient to characterise the chronic effect of the elastic wrap on aortic structure and function.
3. The surgical, anaesthetic and measurement techniques were refined in the non-survival in-vivo studies.
4. Further biocompatibility studies in experimental animals will be required with further development of the elastic wrap and clamp.

The impact on animal well-being was minimised in accordance with the principles of animal experimentation. These broad principles are the refinement of investigative techniques to reduce the impact on animals, and ultimately the replacement of animals with other methods.

Control specimens for histologic analysis were obtained by harvesting the proximal descending thoracic aorta of two neutered adult male sheep that did not undergo elastic wrap application. Control data for mechanical testing were obtained by testing aortic strips harvested from eight neutered adult male sheep that did not undergo elastic wrap application (see Chapter 8).

7.2.1 Anaesthesia and preparation for surgery

Adult sheep underwent intravenous induction of general anaesthesia (Pentobarbitone sodium; 30mg/kg), which was maintained after endotracheal intubation using inhalational agents (halothane 2-3% in 100% oxygen). Lung ventilation was achieved using a positive pressure ventilator. Physiologic parameters were monitored during the procedure (see Appendix 1).

The animal was positioned, the left chest clipped free of wool, and the skin prepared for aseptic surgery by scrubbing with povidone-iodine solution and draped with sterile surgical drapes.

7.2.2 Surgery

The procedure was performed trough a left thoracotomy incision. At the level of the fourth intercostal space, a **minimal access** skin incision was made from the ventral border of the latissimus dorsi ventrally along the cranial margin of the fourth rib for a distance of approximately 7cm. The external and internal intercostal muscles were incised at the cranial margin of the fifth rib, and the pleural space was entered by bluntly perforating the pleura with a Pean forceps. The pleura was incised along the length of the skin incision.

The ribs were retracted to expose the proximal descending thoracic aorta, pericardium, left lung root, and left azygos vein. The upper lobe of the left lung was packed with surgical gauze to facilitate exposure of these structures. The proximal part of the descending thoracic aorta (lying cranial to the left azygos vein) has no intercostal branches and was dissected free from surrounding structures to facilitate placement of ultrasonic crystals and a segmental aortic wrap.

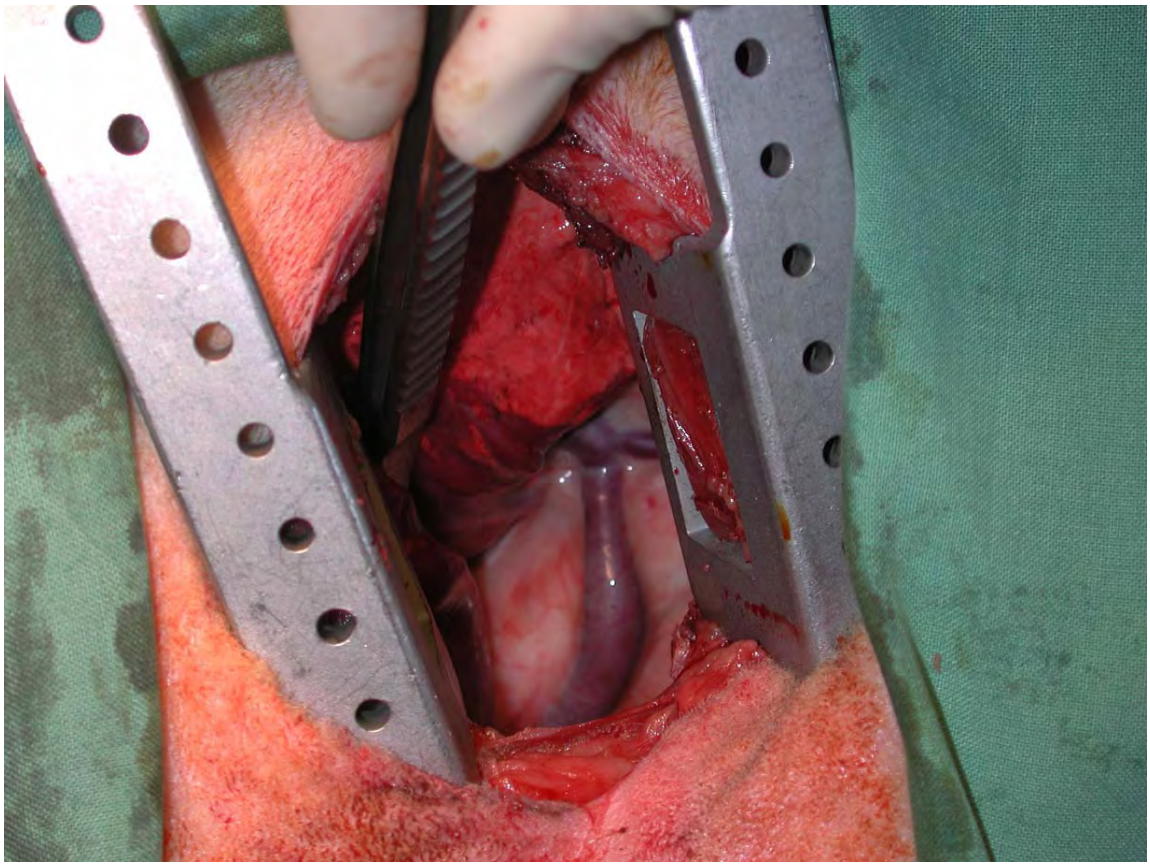


Figure 83 Minimal access left thoracotomy incision. The left azygos vein is seen overlying the proximal descending thoracic aorta.

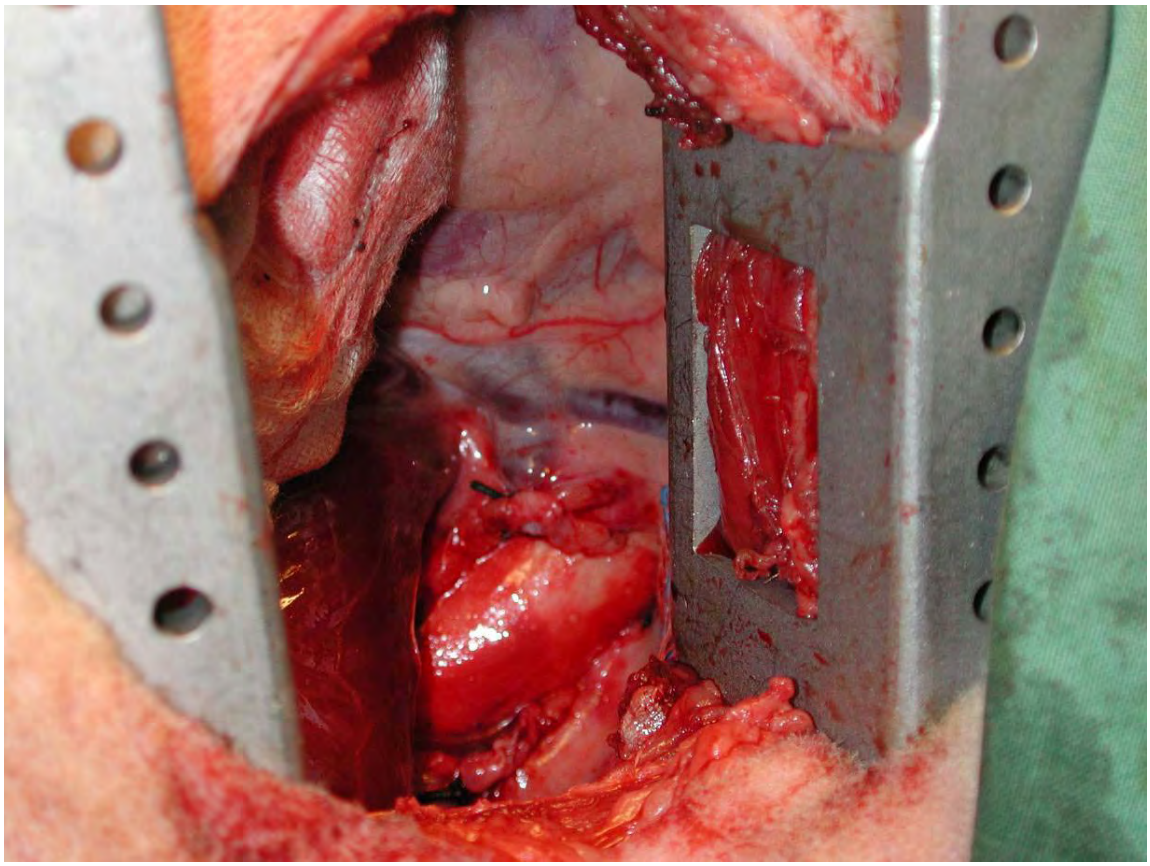


Figure 84 The left azygos vein has been ligated and divided without damaging the aortic adventitia.

7.2.3 Elastic material

An elastic silicon polymer was used as the elastic wrap material. The material was developed by Medtronic (Medtronic, Inc., Minneapolis, MN) for use as a simulator of the aorta (4% stiffness material) and pulmonary artery (12% stiffness material) in the in-vitro testing of artificial heart valves. Only the 4% stiffness material was used in this study as the 4% and 12% stiffness materials produced similar alterations in graft stiffness in the ovine model of aortic dilatation and stiffness (see Chapter 4), and the 4% stiffness material produced the most beneficial alteration in pressure in the human in-vitro model (Chapter 5).

The material comes in prefabricated cylindrical lengths (internal diameter 30mm, length 3cm) and has mechanical properties similar to healthy young human aorta (4% stiffness material). A cylindrical segment of the elastic material was divided along the longitudinal axis at one point to form a rectangular piece of material that was placed around the aorta.

7.2.4 Clamp

A clamp device was developed to secure the material once placed around the aorta. The material was initially fixed with an arterial clamp and the clamp device was then used to secure the material. The clamp device is made from stainless steel and consists of two jaws that are held and tightened by two screws.

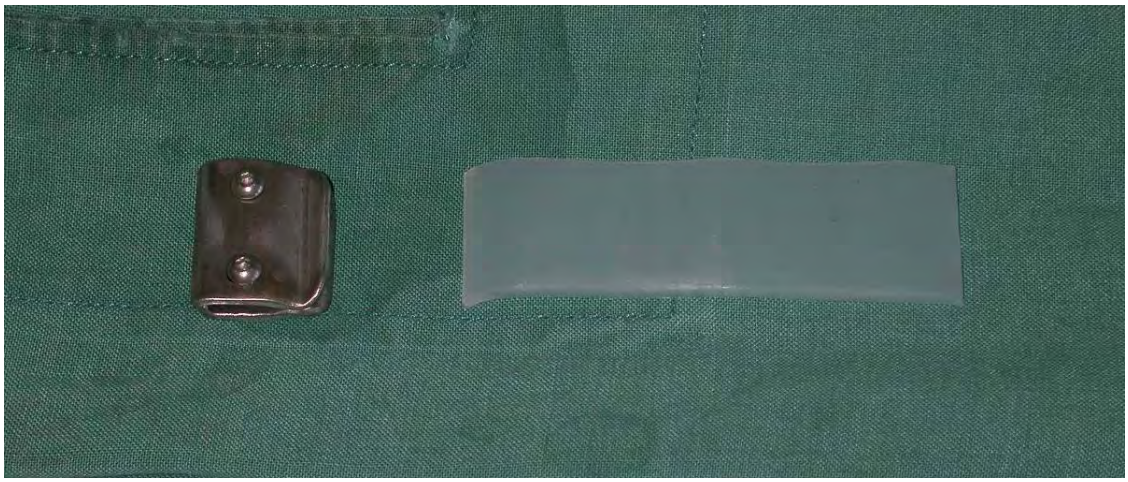


Figure 85 The clamp and elastic wrap material.

7.2.5 Experimental protocol

A segmental aortic wrap was applied to the ovine proximal descending thoracic aorta to reduce the circumference of the native aorta by 10%. A length of #1 silk was used to measure the approximate circumference of the proximal descending thoracic aorta (measurement A), which was recorded.

The measurement of aortic circumference was reduced by 10% (measurement B) and recorded to obtain the desired aortic circumference following application of the segmental aortic wrap. This measurement represented the internal circumference of the wrap material, when the material was clamped around the aorta to form a cylindrical segment. A further 16 mm (8 mm times 2) was added to measurement B, as 8 mm of material was required for fixation of each end of the material by the jaws of the clamp. The material was cut to the desired length.

An arterial clamp was used to cross-clamp the aorta in the region of the distal aortic arch (i.e. proximal to the region of application) to facilitate application of the segmental aortic wrap by unloading the descending thoracic aorta. The material was placed around the proximal descending aorta and fixed using the clamp device.

The left lung was expanded under direct vision prior to closure of the surgical wound to expand any areas of lung collapse. The fourth and fifth ribs were apposed using two interrupted figure-of-eight sutures. The intercostal muscles, subcuticular tissues and skin were closed in layers. A chest drain was not inserted.

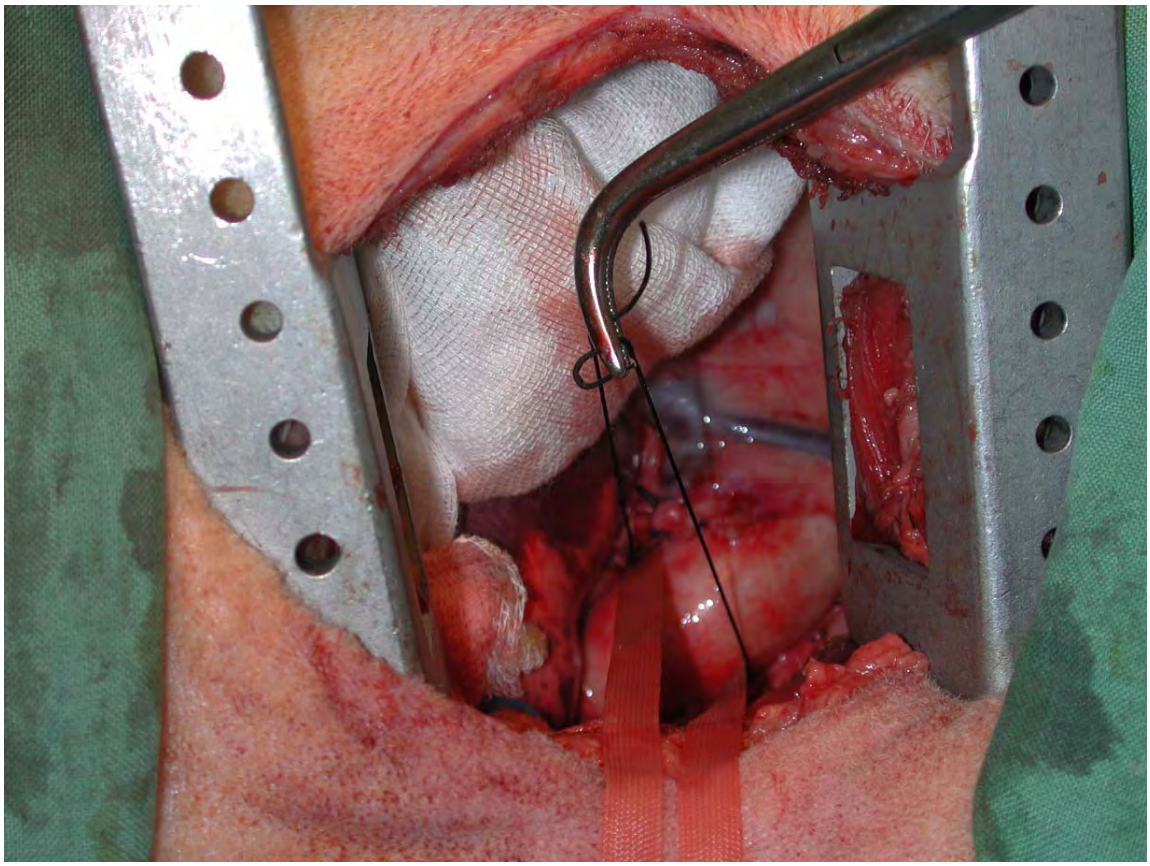


Figure 86 #1 silk ligature used to approximate the diameter of the aorta.

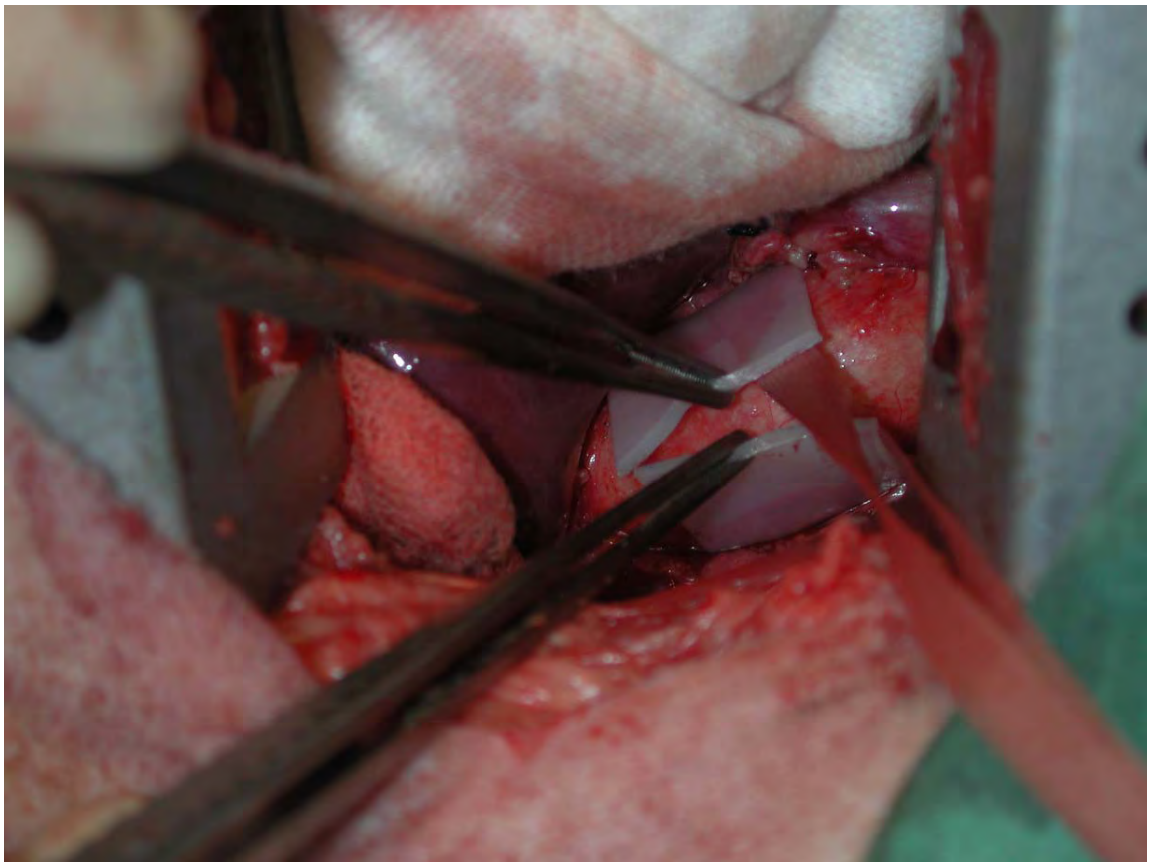


Figure 87 The elastic wrap material placed around the aorta.

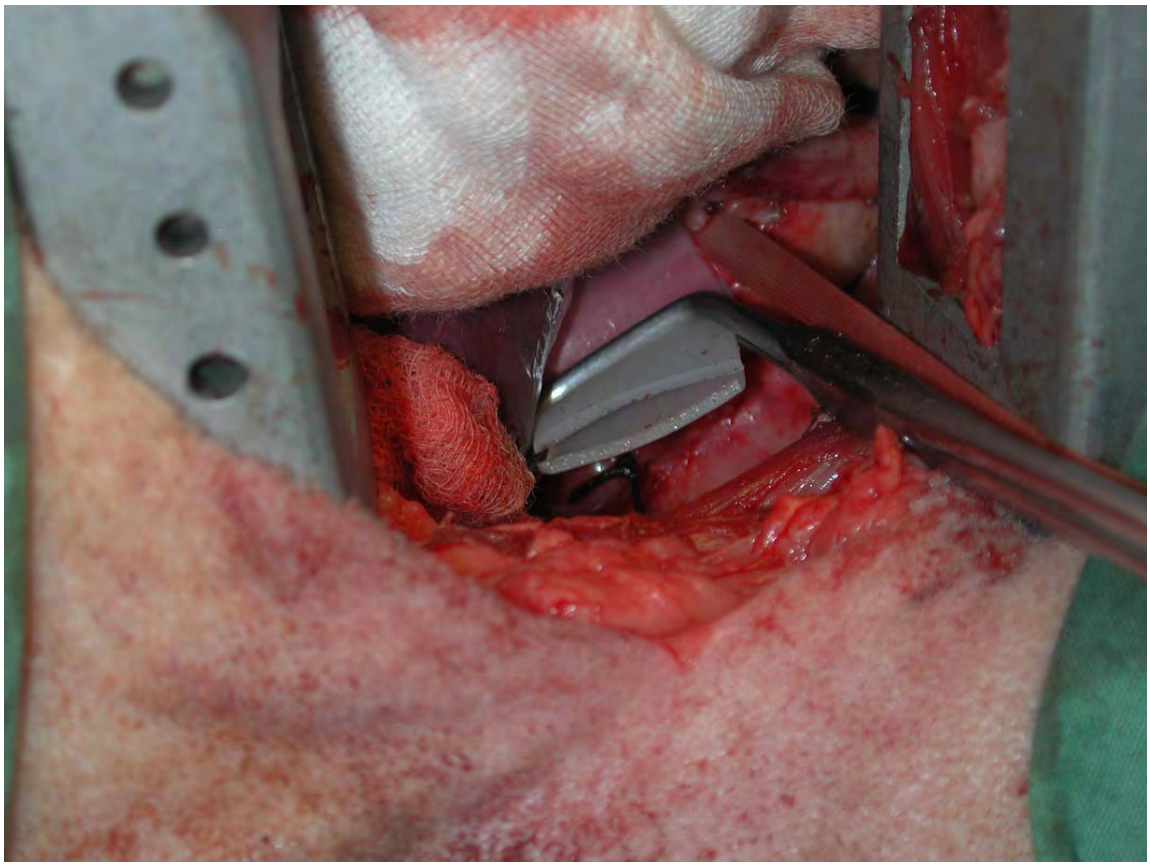


Figure 88 An arterial clamp is used to stabilise the wrap prior to placement of the clamp.

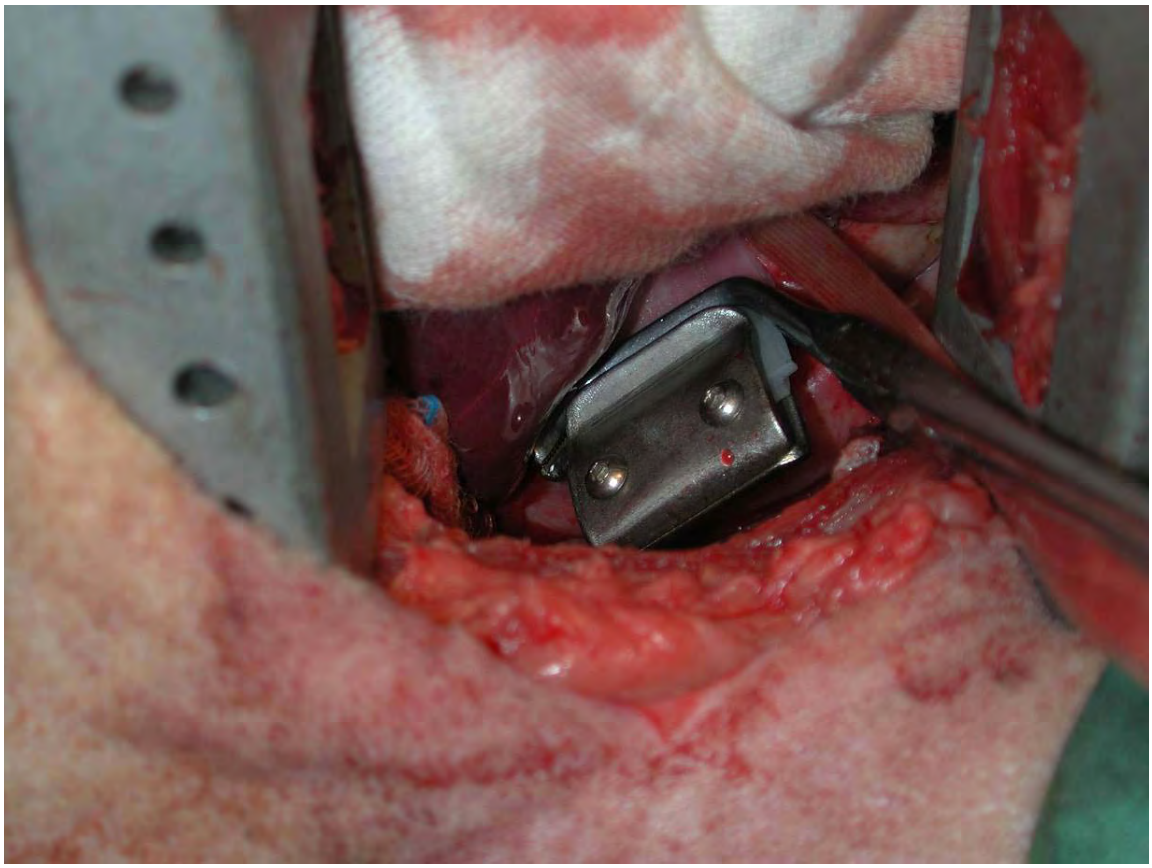


Figure 89 Placement of the clamp to secure the wrap.

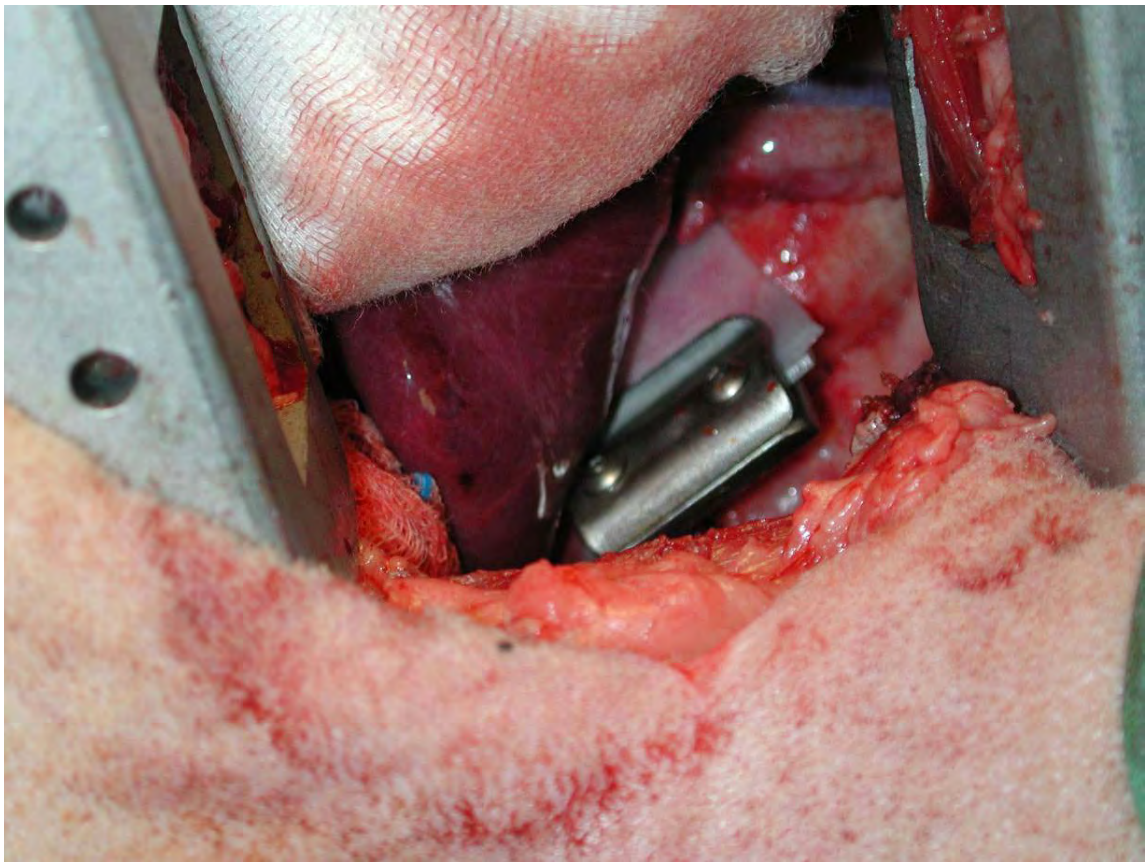


Figure 90 Clamped elastic wrap encircling the aorta.

7.2.6 Recovery and postoperative monitoring

The animals were recovered and received postoperative care for 10 weeks (see appendix 1).

7.2.7 Sacrifice

The animals were humanely euthanised at 10 weeks postoperatively by an intravenous overdose of barbiturate (Pentobarbitone 90mg/kg).

7.2.8 Macroscopic analysis

An incision through the previous surgical scar was made to access the thorax. The extent of thoracic adhesions was recorded using a digital photographic camera. The lung was dissected free from the thoracic wall, pericardium, left lung root, and great vessels. The extent of adhesions, as well as the macroscopic appearance of structures in the region of the aortic wrap was recorded. The integrity and appearance of the clamp device was also recorded.

The distal arch of aorta, proximal descending thoracic aorta with overlying wrap, as well as the remaining descending thoracic aorta, was dissected free en masse from surrounding structures for morphologic analysis (macroscopic and microscopic). The clamp was unscrewed to release the wrap material that was released from around the aorta. The aorta was resected at the dissected proximal and distal ends and placed into normal saline at room temperature.

7.2.9 Specimen preparation

Aorta

The aorta was divided longitudinally to form a rectangular piece of material. A transverse (circumferential) rectangular strip (transverse length 35mm, longitudinal length 10mm) was cut from the wrapped region of the aorta using Vernier callipers and surgical loupes. This strip was used for uniaxial tensile testing.

10mm wide circumferential strips were also cut from the following regions of the aorta for histological analysis:

1. The region of aorta above the segment of wrapped aorta.

2. The wrapped region of aorta.

Similarly, 10mm circumferential strips were cut from the proximal descending thoracic aorta of two control animals that did not undergo surgical intervention and were used for histologic analysis.

Elastic wrap material

A 35 mm by 10mm transverse (circumferential) strip was cut from the explanted aortic wrap using Vernier callipers and surgical loupes. This strip of material was used for uniaxial tensile testing.

7.2.10 Mechanical testing

Uniaxial tensile testing of the aortic strips as well as strips of the elastic wrap material were performed using a Mach-1 micromechanical testing machine (Biosyntech Canada Inc., Quebec, Canada) fitted with a 10N load-cell. The strips were mounted onto screw tightened stainless steel grips that were lined with sandpaper for added grip. The strips were loaded in air at room temperature at a stress free gauge length of 8mm.

The strips were tested in normal saline at room temperature. Prior to testing the strips were preconditioned using dynamic sinusoids in displacement control from 0um to 2000um for 30 cycles at a frequency of 0.1Hz (see Chapter 8). The strips were subjected to a uniaxial tensile test and stretched at a constant rate of 4mm/sec to a displacement of 20,000um, while the load and displacement were measured. The aortic strips were tested to failure.

7.2.11 Data analysis

During testing, load and displacement were logged on to a PC at a sampling rate of 10 Hz. A load (grams) versus displacement curve (micrometres) was obtained using Microsoft Excel (Office 2000; Microsoft Corporation). Four parameters were calculated for each specimen from its load displacement curve:

1. Stiffness (gm/um): the slopes of the load displacement curve
2. Ultimate/maximum tensile strength (peak load): the load at failure (aortic strips) or the maximum load (elastic material)
3. Failure or tensile energy (gm.um): the area between the load displacement curve and the x-axis at the peak load for the aortic strips (failure energy) or elastic material (tensile energy)
4. Ultimate/maximum tensile displacement (peak displacement)

The elastic material was not tested to failure, as this occurs at strains that are beyond the testing capability of the testing apparatus and beyond strains that would be encountered in vivo.

The stiffness of the strips (aorta and elastic material) was calculated using Matlab. The load-displacement curves of the aortic strips and elastic material are characteristically biphasic. The stiffness was determined by calculating the slope of the load-displacement curve in each phase of the curve (stiffness 1 and stiffness 2) (see Section 8.2.5 Data analysis).

Mechanical testing data are presented as mean +/- standard deviation. Data were compared graphically using Microsoft Excel (Office 2000; Microsoft Corporation), and

analysed using the two-tailed Student's t test using SPPS for Windows (SPSS Inc, Chicago, Illinois). Statistical significance was set at a level of $p < 0.05$.

Figure 91 Mach-1 micromechanical testing machine.

7.2.12 Histology

10mm wide circumferential strips were promptly fixed in 10% buffered formalin. All specimens were embedded in paraffin using standard techniques. Tissue blocks were cut into 5-micrometre sections that were treated by specific staining to obtain a monochromatic colour associated with the various structures studied in the aortic media (Hematoxylin and eosin stain, Van Gieson stain, and Verhoeff's elastica). The Van Gieson stain was used for collagen staining and Verhoeff's elastica was used for elastin fibre staining. Glass slides were coded and assessed blindly.

The sections were examined under a Zeiss light microscope (Germany). The microscopic structure of the wrapped section of the treated aortas was compared to the microscopic structure of the:

1. Control aortas
2. Proximal non-wrapped section of the wrapped aortas.

The microscopic structure of the aortas was compared specifically looking for regions of ischaemia, haemorrhage, alterations of elastin and collagen fibres, trauma of the elastic fibre lamellae, alterations in the vasa vasorum network, fibroblast proliferation in the adventitia, and leucocytic infiltrates.

7.3 RESULTS

There were no operative or postoperative complications. Specifically, there was no evidence of wound infection, wound dehiscence, haemodynamic compromise, and respiratory or gastrointestinal complications in the two animals that underwent the surgical procedure.

Both animals recovered well from the procedure and were standing and drinking within a few hours, and mobilised and eating by the first postoperative day. Postoperative analgesia was not required beyond the first postoperative day. The wound was macroscopically well healed after 4 weeks.

Aortic diameter	Measurement A (unwrapped)	Measurement B (wrapped)
Sheep 1	67cm	60cm
Sheep 2	52 cm	47 cm

Table 34 Acute reductions in aortic diameter following application of elastic wraps to the proximal ovine descending thoracic aorta.

7.3.1 Macroscopic changes

The wound was well healed at 10 weeks postoperatively. There were sparse thin adhesions between the left lung and chest wall that were easily broken down by finger dissection. There were thin adhesions between the left lung and the proximal descending thoracic aorta and overlying wrap that were easily broken down by finger dissection.

A thin fibrous tissue layer encapsulated the wrap material variably. The capsule variably enclosed the whole wrap material and clamp device. The capsule was not adherent to the underlying wrap material and clamp device and was easily reflected from it. There were no adhesions between the capsule and wrap material or clamp device.

The wrap material was not adherent to the underlying aorta, and there were no adhesions between the wrap material and underlying aorta. There were clear lines of demarcation at the margins of the wrap material on the underlying aorta. The wrapped aorta appeared compressed by the wrap material, and the wrapped aorta appeared thinner than the unwrapped aorta.

The capsule extended from the aorta at the margins of the wrap material to overly the wrap material and clamp device.

The clamp device and wrap material appeared intact and undamaged. There was no obvious loosening of the clamp device or slippage of the wrap material from the jaws of the clamp device.

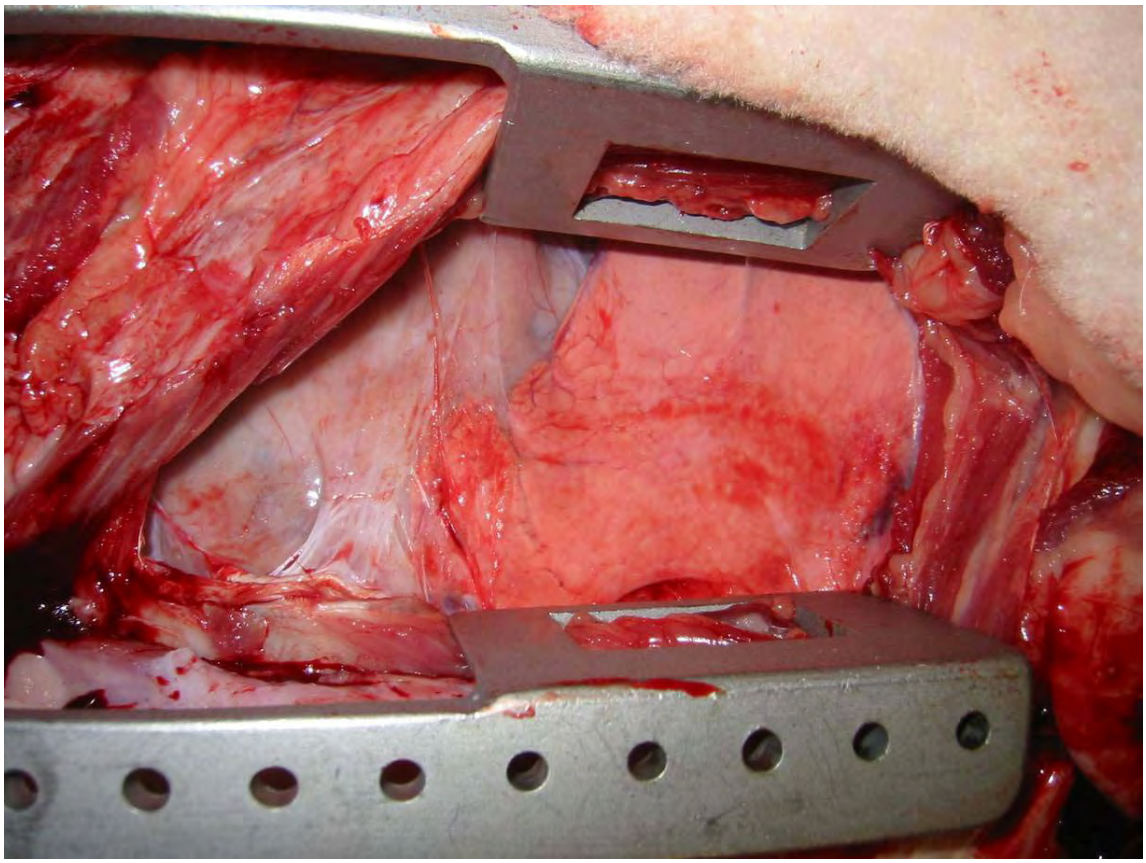


Figure 92 Animal 1: Sparse adhesions in the left hemithorax.

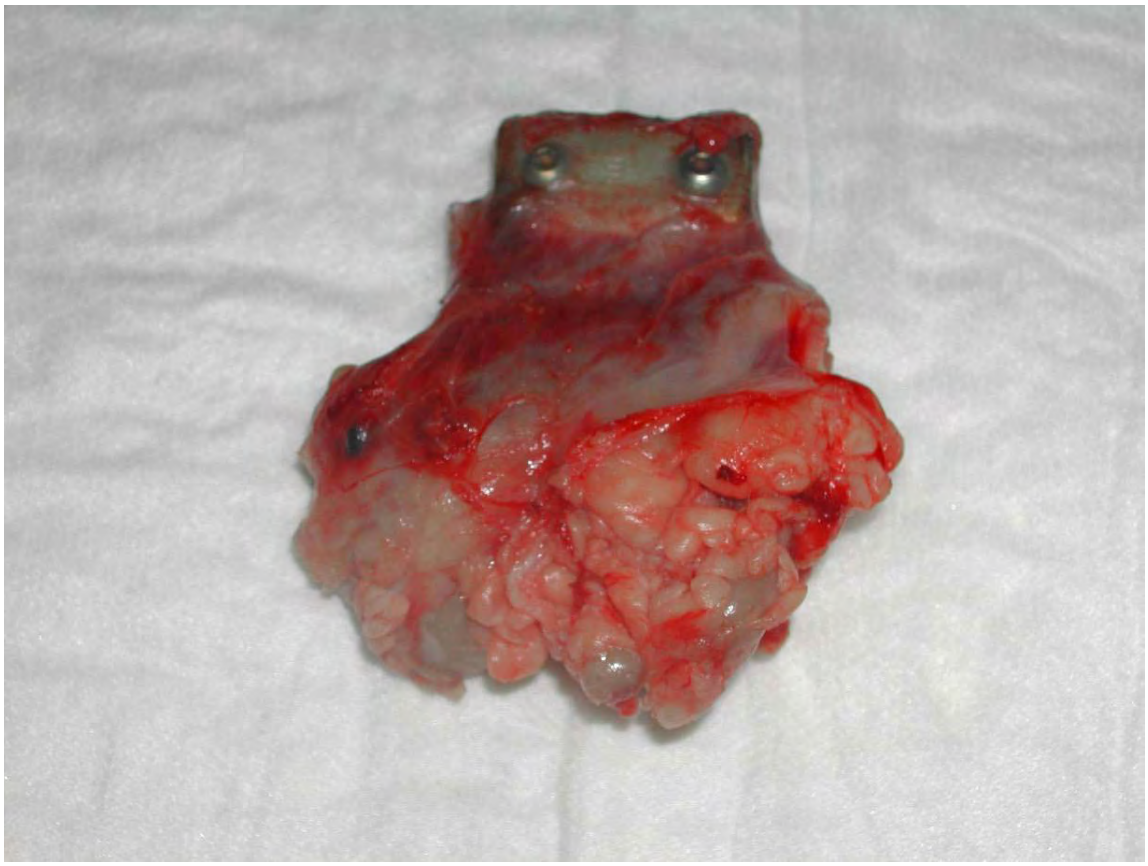


Figure 93 Animal 1: The resected aorta with encapsulated clamp and elastic material.

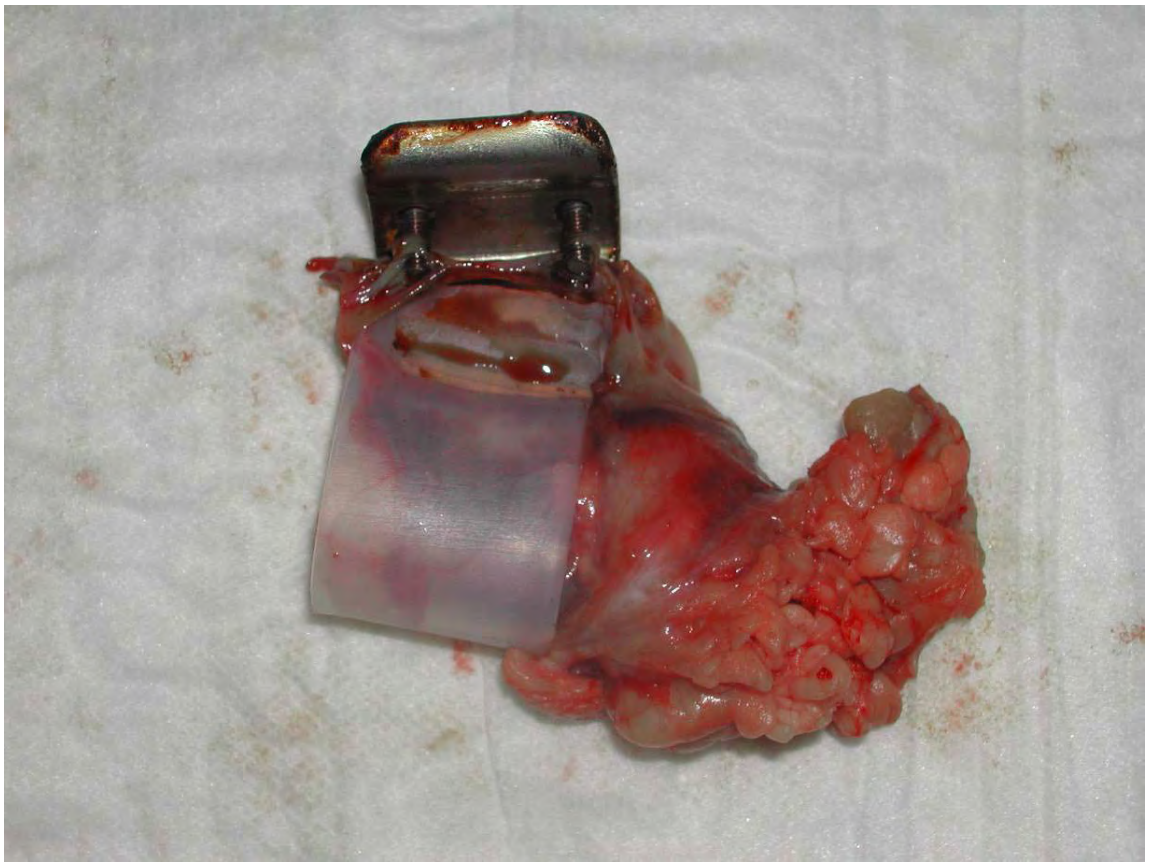


Figure 94 Animal 1: The fibrous capsule has been divided and reflected to expose the clamp (unscrewed) and the elastic wrap.

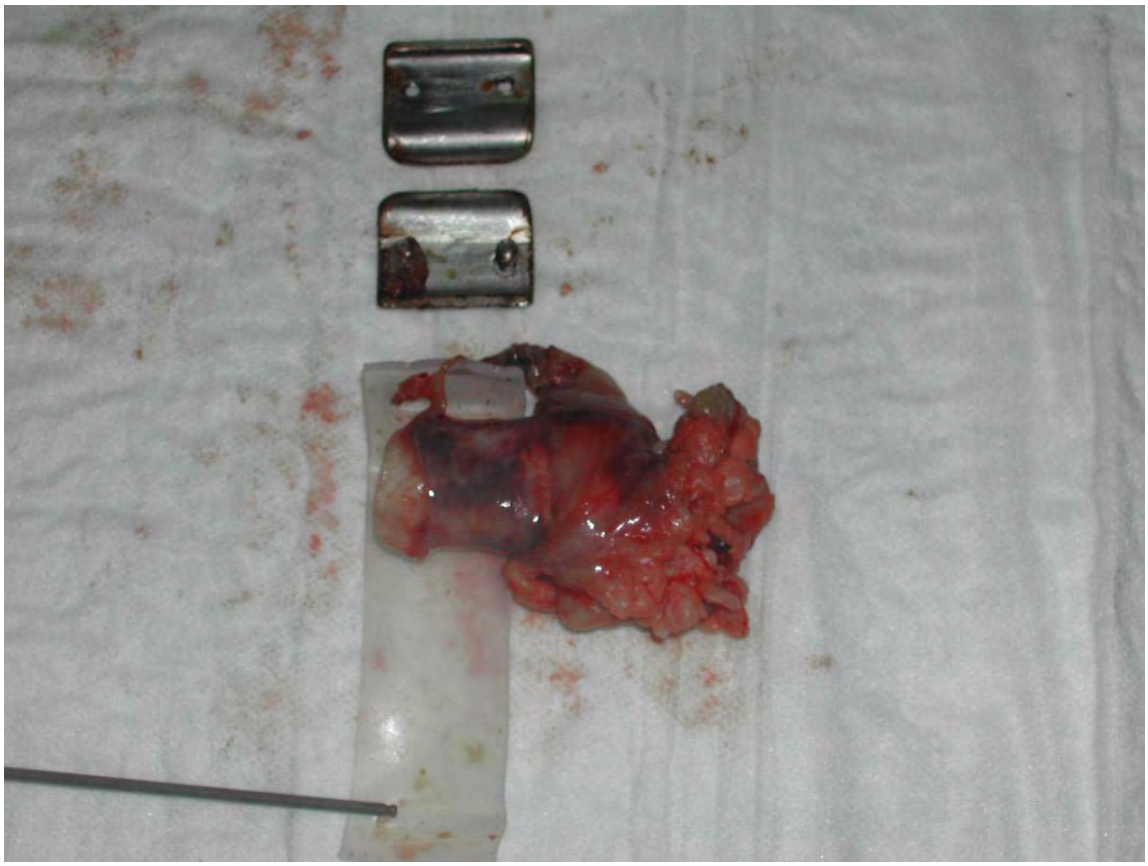


Figure 95 Animal 1: The aorta, capsule, clamp, and elastic wrap.

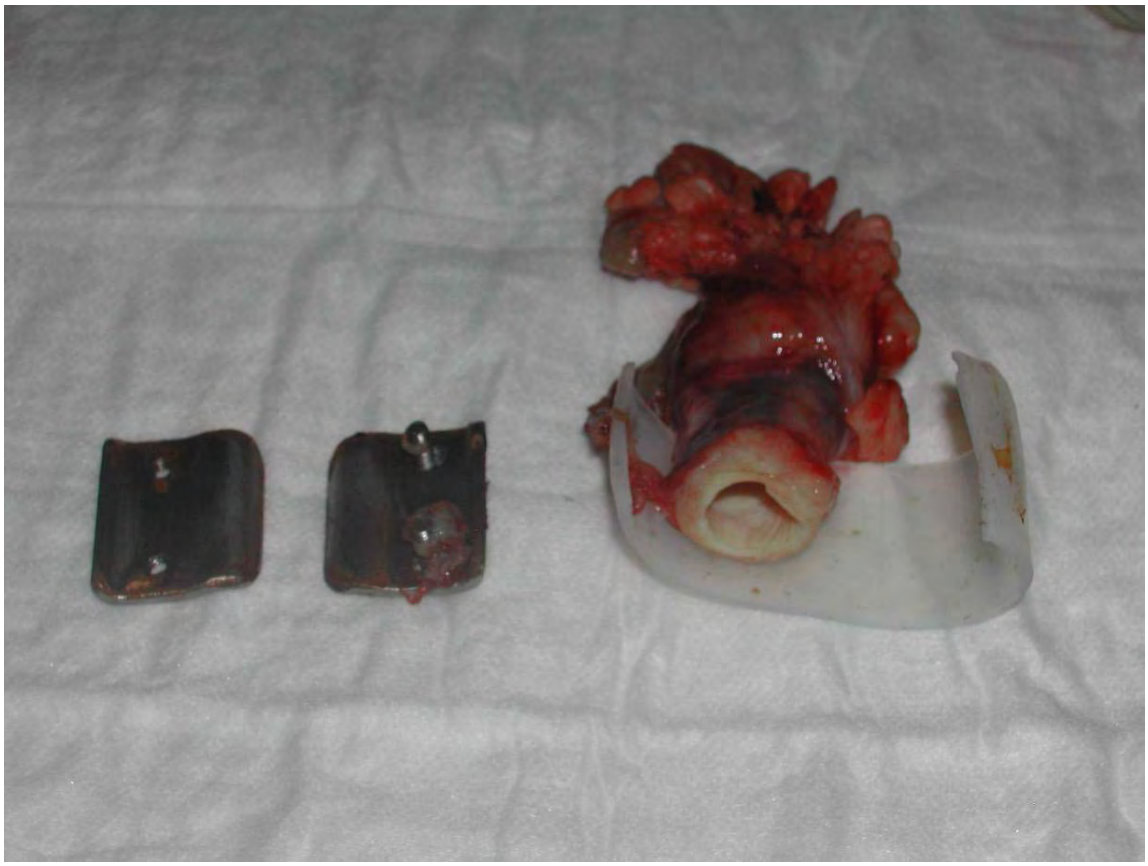


Figure 96 Animal 1: Alternate view of the aorta, capsule, clamp, and elastic wrap.

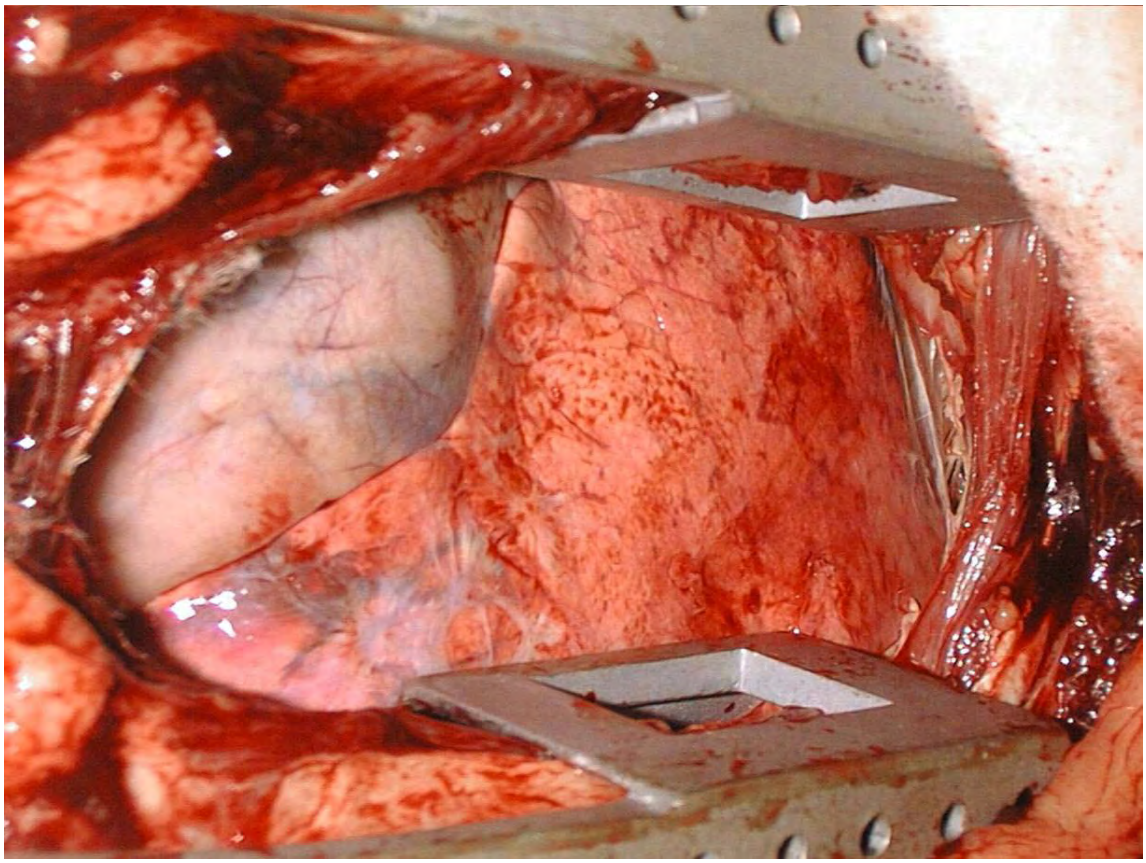


Figure 97 Animal 2: Sparse adhesions in the left hemithorax.

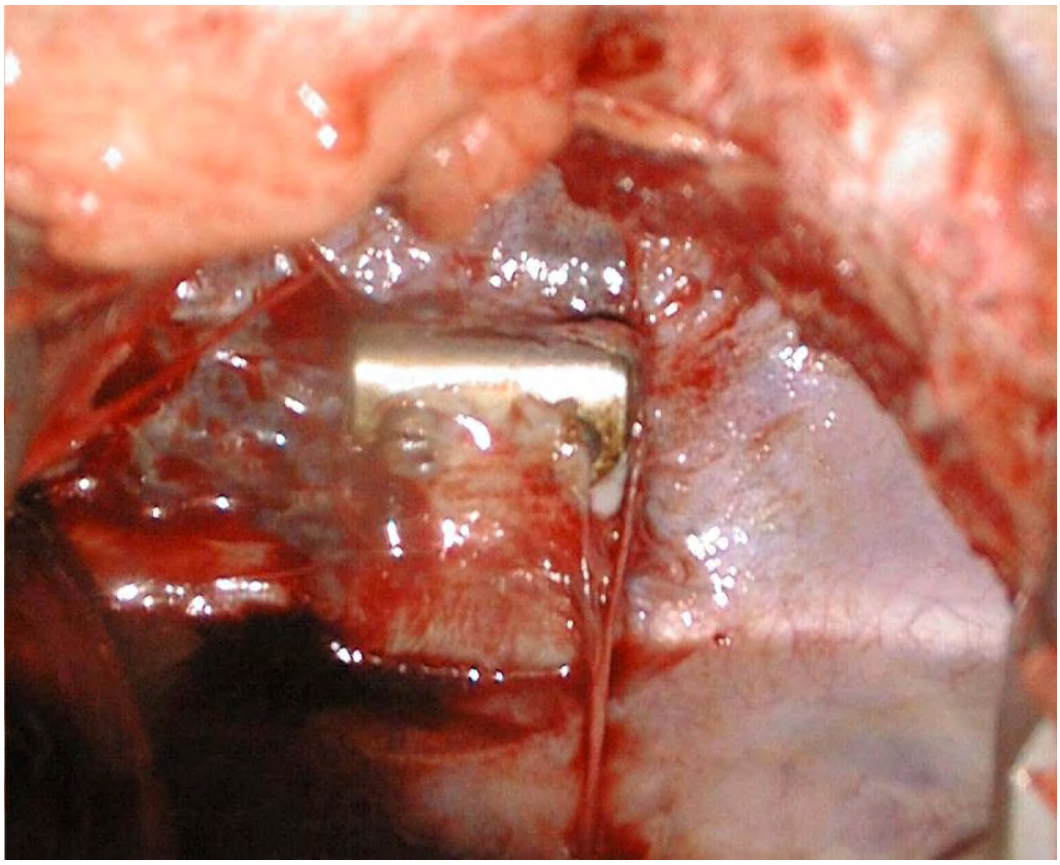


Figure 98 Animal 2: Magnified view of the encapsulated clamp and elastic wrap encircling the aorta.

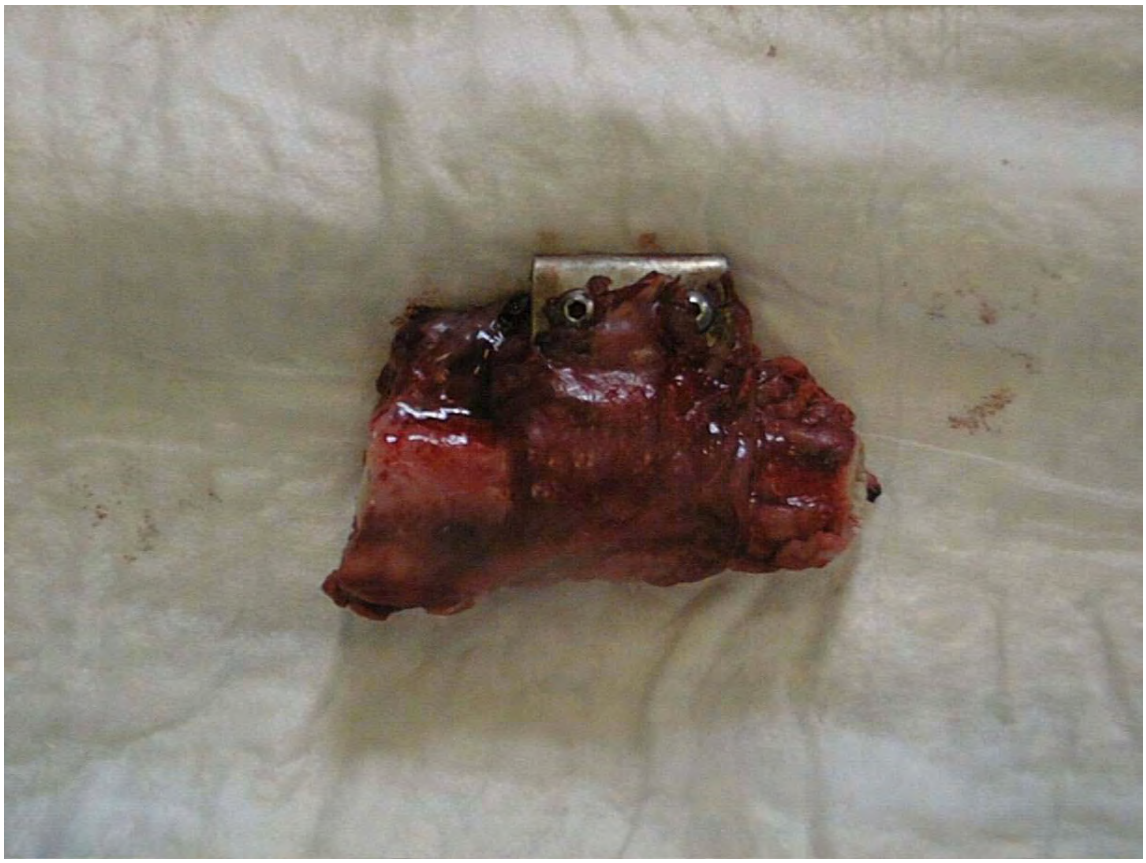


Figure 99 Animal 2: The resected aorta with encapsulated clamp and elastic material.

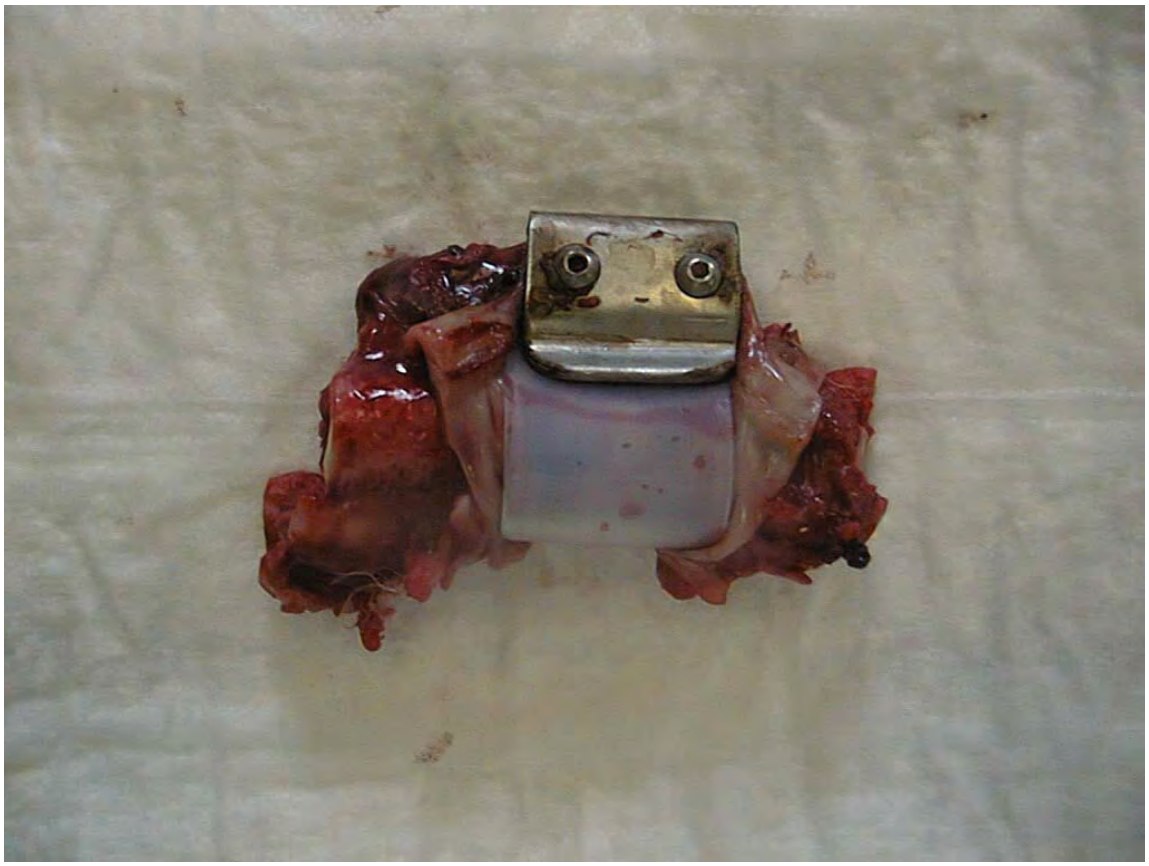


Figure 100 Animal 2: The fibrous capsule has been divided and reflected to expose the clamp and the elastic wrap.

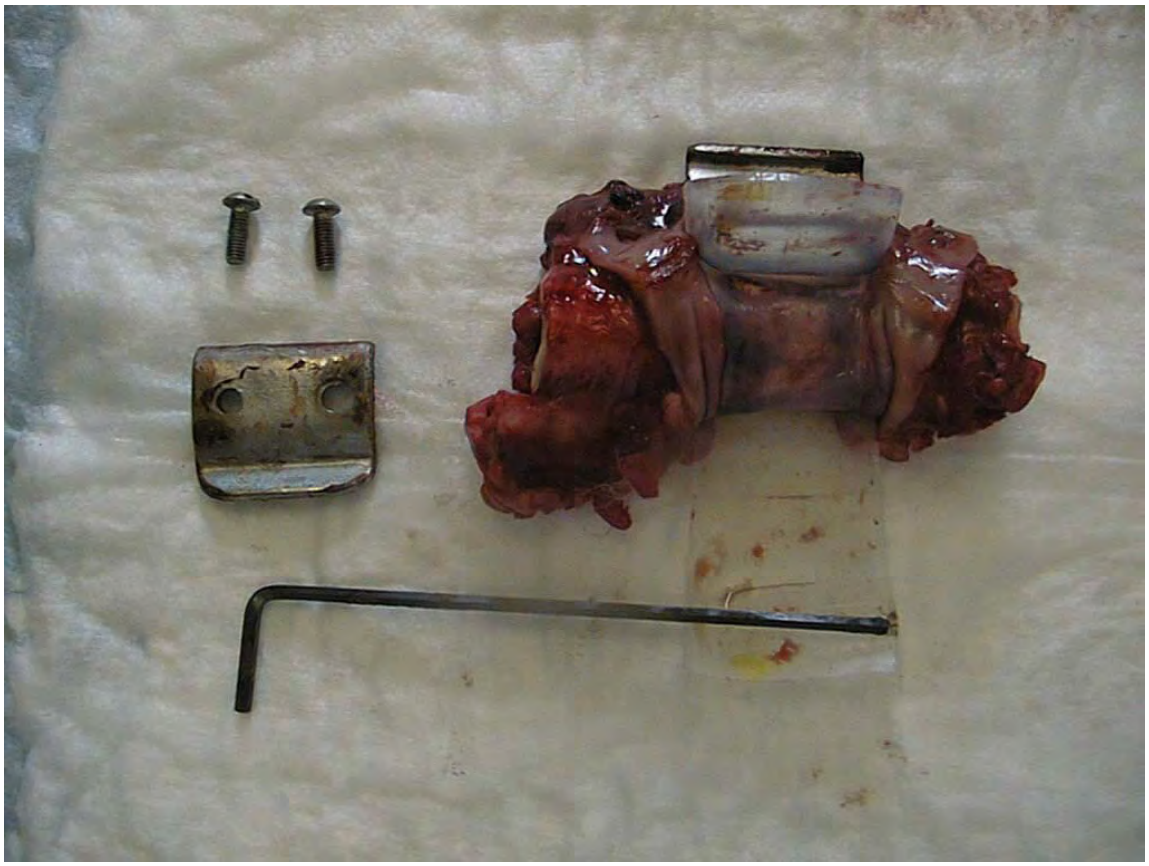


Figure 101 Animal 2: The aorta, capsule, clamp, and elastic wrap.

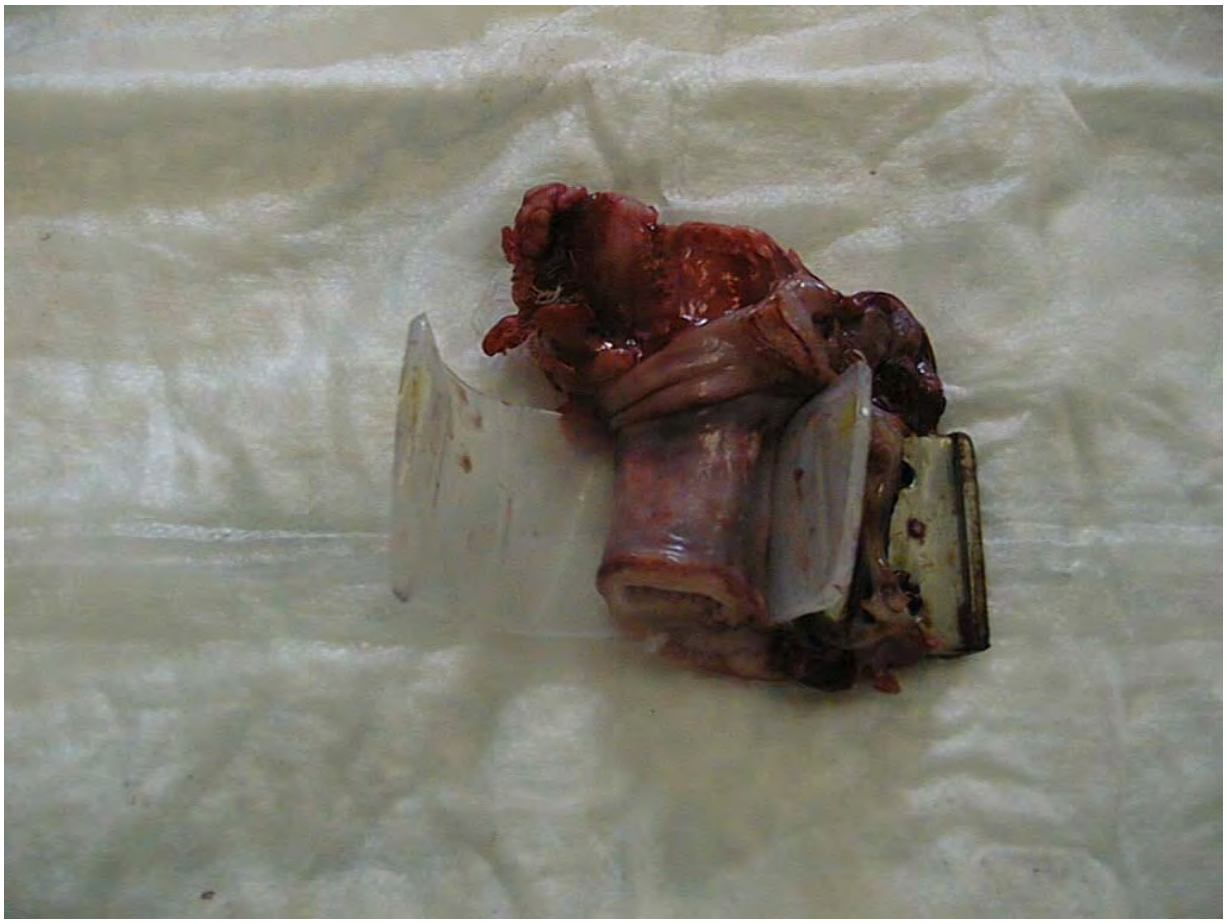


Figure 102 Animal 2: Alternate view of the aorta, capsule, clamp, and elastic wrap.

7.3.2 Mechanical testing

Aorta

Chronic application of the elastic wrap increased the stiffness of the proximal descending thoracic aorta. Stiffness 2 was 3.85 times greater in the chronically wrapped group than the control group.

The rupture load was significantly greater in the chronically wrapped group. The rupture displacement was significantly less in the chronically wrapped group.

Proximal descending thoracic aorta	Control (N = 8)	Wrapped aorta (10 weeks) (N = 2)	Significance
Stiffness 1 (gm/um)	0.0271 +/- 0.0062	0.808 +/- 0.0188	$P < 0.001$
Stiffness 2 (gm/um)	0.0723 +/- 0.008	0.2787 +/- 0.0124	$P < 0.001$
Peak load (gm)	1155.45 +/- 184.22	1734.26 +/- 97.2	N/S
Peak displacement (um)	22670.85 +/- 4335.55	10355.40 +/- 1455.23	$P < 0.005$
Failure energy (gm.um)	1.24×10^7 +/- 3.93×10^6	8.23×10^6 +/- 6.83×10^4	$P = 0.005$

Table 35 Alterations in aortic stiffness, rupture load and displacement and failure energy with application of the elastic external wrap to the ovine proximal descending thoracic aorta for 10 weeks.

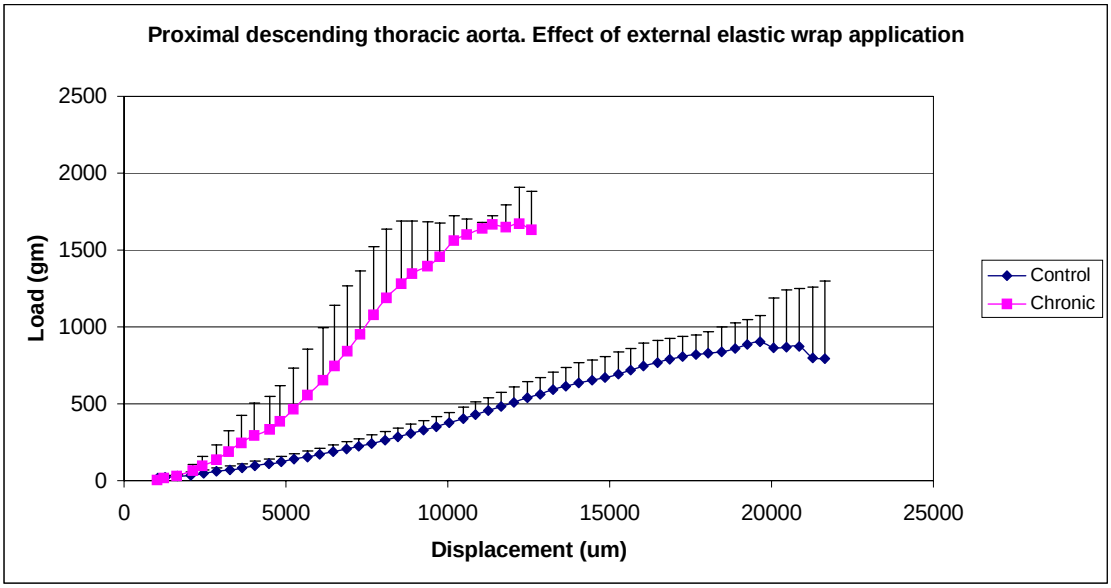


Figure 103 Alterations in load displacement curves of the ovine proximal descending thoracic aorta with application of the elastic wrap for 10 weeks.

Wrap material

There was no significant difference in stiffness 1 and stiffness 2 between the control material and the implanted material. The peak load (load at displacement 15,000 um) and the tensile energy of the implanted material were significantly less than the control material.

Elastic wrap (12% stiffness)	Control material (N = 4)	Implanted material (N= 2)	Significance
Stiffness 1 (gm/um)	0.0290 +/- 0.0006	0.0251 +/- 0.0049	N/S
Stiffness 2 (gm/um)	0.0087 +/- 0.0010	0.0083 +/- 0.0011	N/S
Energy (gm.um)	2.24×10^6 +/- 6.08×10^4	1.89×10^6 +/- 2.05×10^5	$P < 0.05$
Peak load (gm)	226.62 +/- 10.75	198.48 +/- 10.21	$P < 0.05$

Table 36 Alterations in stiffness, energy, and peak load of the elastic wrap with application to the ovine proximal descending thoracic aorta for 10 weeks.

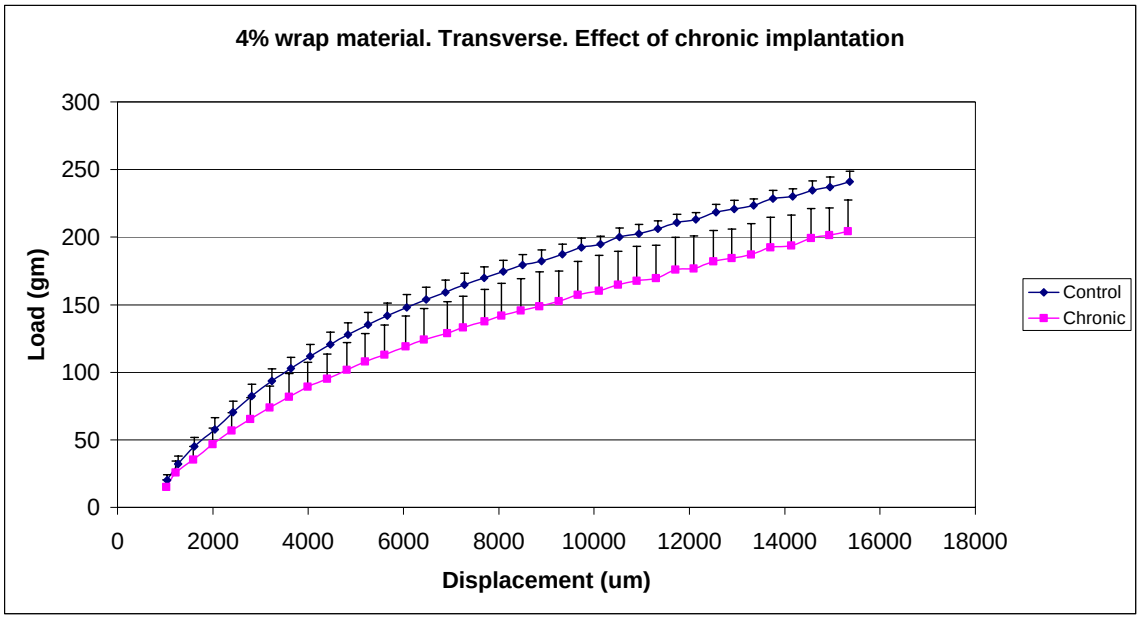


Figure 104 Alterations in load displacement curves of the elastic wrap with application to the ovine proximal descending thoracic aorta for 10 weeks.

7.3.3 Histology

There were no visible differences in the tunica intima of the wrapped segments (treated animals) and the tunica intima of the control animals. The tunica media was thinner in the wrapped segments of the treated animals when compared to the control animals.

The elastic fibres and lamellae appeared more densely packed within the aortic media in the wrapped segments of treated animals. There was atrophy of muscle in the aortic musculo-elastic fascicles in the wrapped segments of treated animals. There was no visible difference in interstitial cell composition in the aortic media between the wrapped segments (treated animals) and the control animals. There was no evidence of infarction of the aortic media in the wrapped segments in the treated animals.

The adventitia was also thinner in the wrapped segments of the treated animals when compared to the control animals.

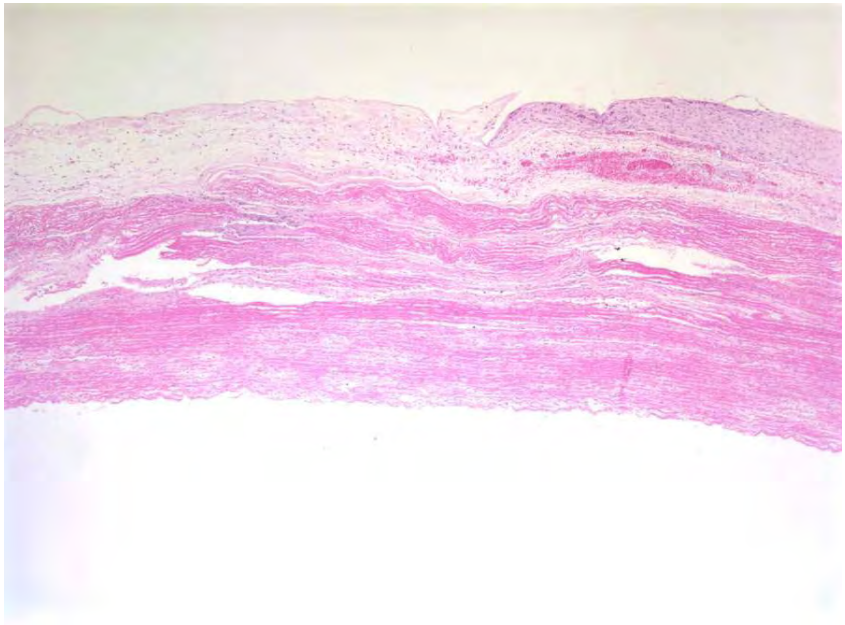


Figure 105 Cross section of wrapped segment of aorta from animal 1 (Hematoxylin-eosin stain, x4).

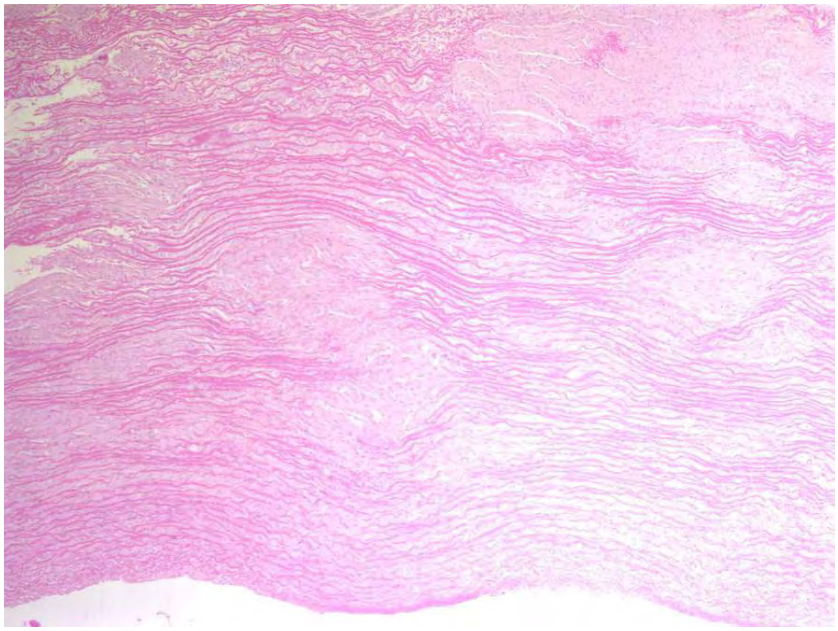


Figure 106 Cross section of control aorta (Hematoxylin-eosin stain, x4).

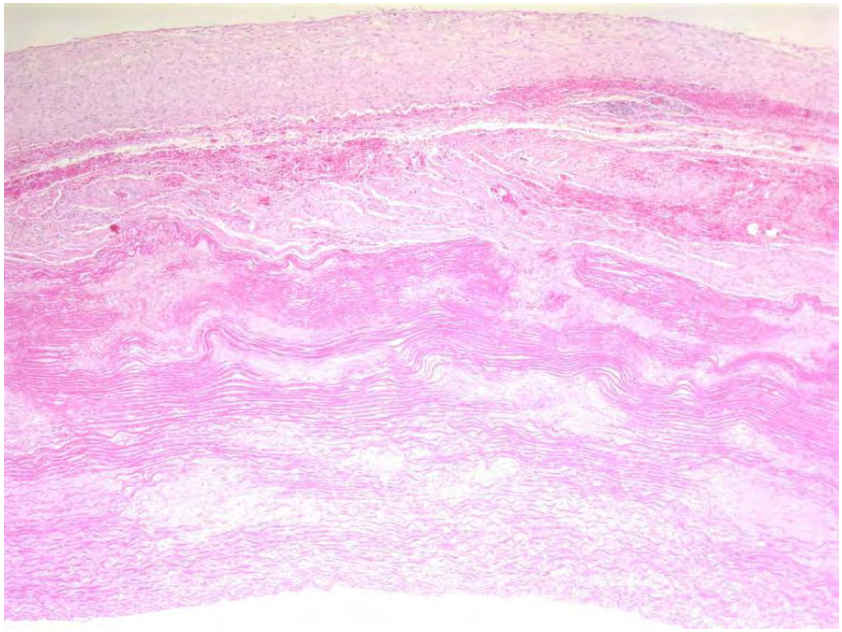


Figure 107 Cross section of wrapped segment of aorta from animal 2 (Hematoxylin-eosin stain, x4).

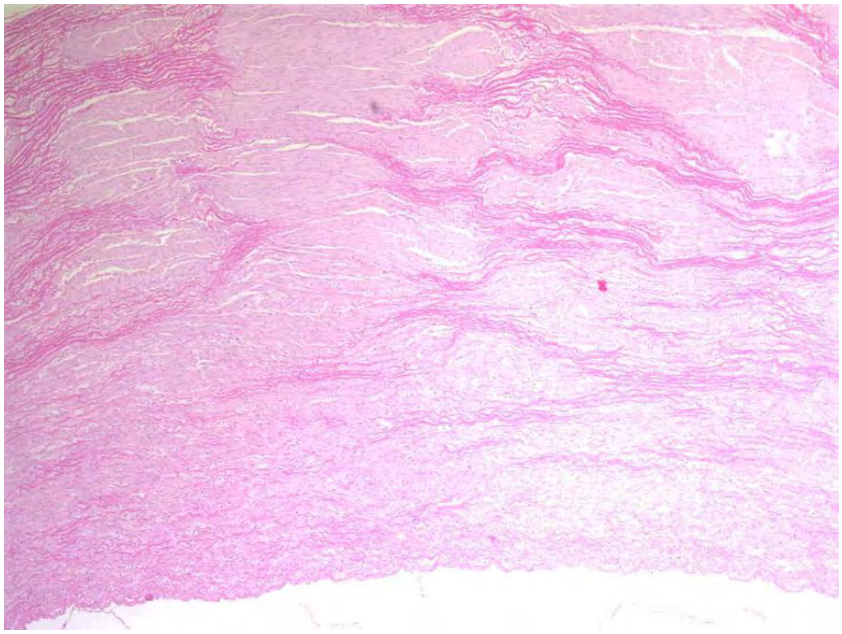


Figure 108 Cross section of control aorta (Hematoxylin-eosin stain, x4).

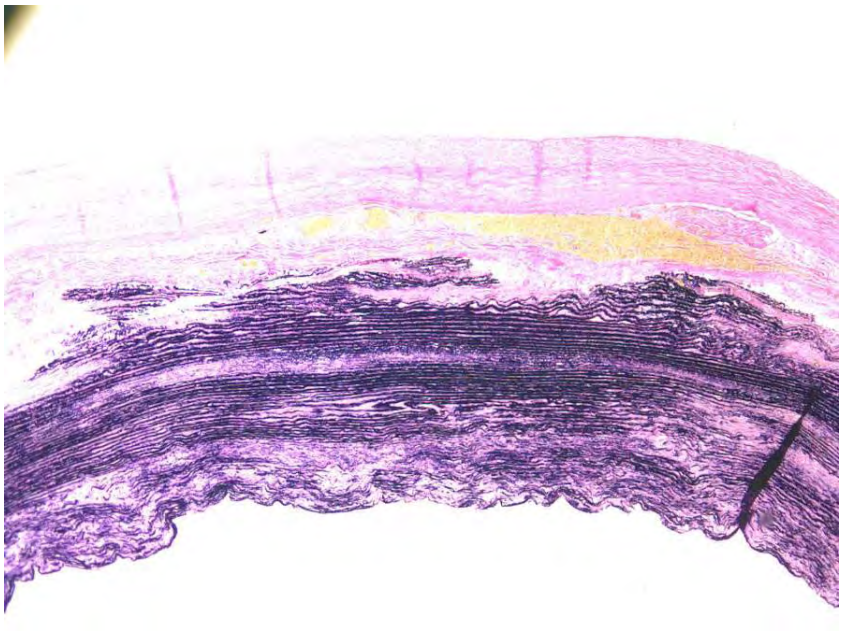


Figure 109 Cross section of wrapped segment of aorta from animal 1 (Verhoeff's elastica, x4).

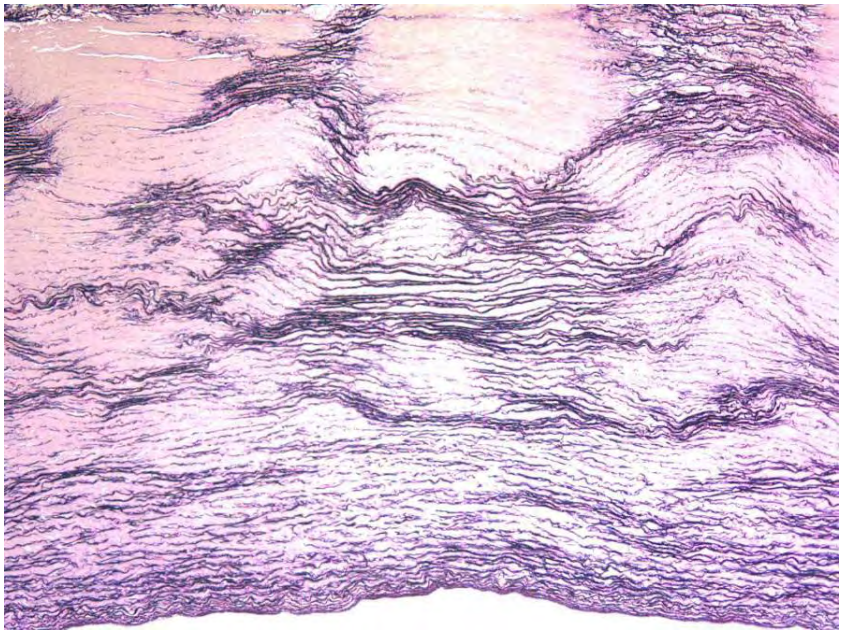


Figure 110 Cross section of control aorta (Verhoeff's elastica, x4).

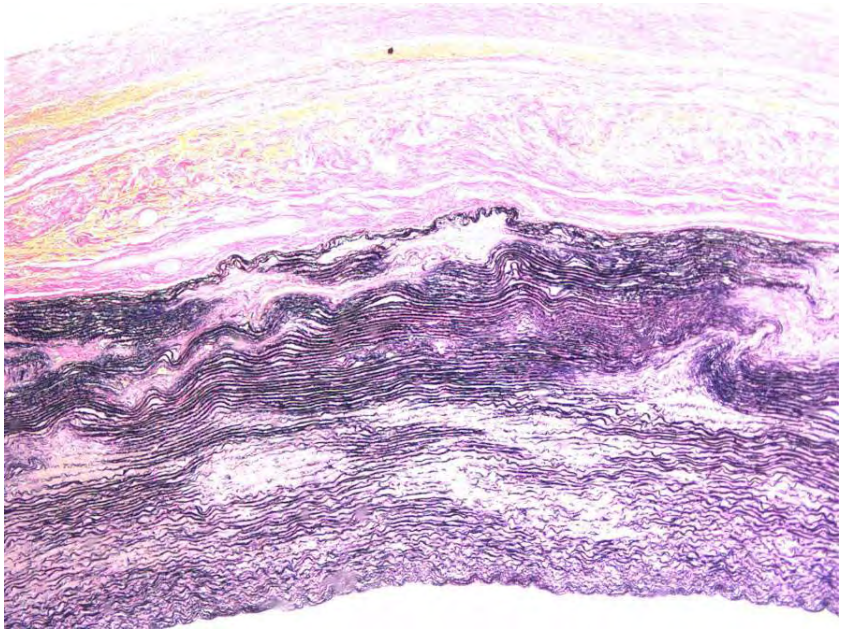


Figure 111 Cross section of wrapped segment of aorta from animal 1 (Verhoeff's elastica, x4).

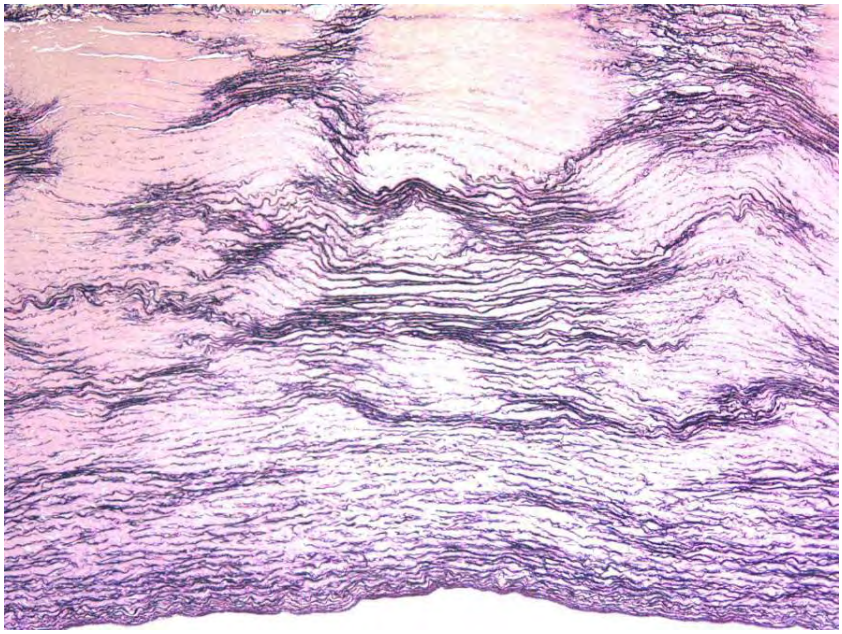


Figure 112 Cross section of control aorta (Verhoeff's elastica, x4).

For each instrumented animal, there were no visible differences in the aortic intima between the wrapped segment and the proximal non-wrapped segment. The aortic media of the wrapped segment was thinner than the media of the proximal non-wrapped segment. The elastic fibres appeared more densely packed within the aortic media in the wrapped segments. There was atrophy of muscle in the aortic musculo-elastic fascicles in the wrapped segments. There was no visible difference in interstitial cell composition in the aortic media between the wrapped and non-wrapped segments.

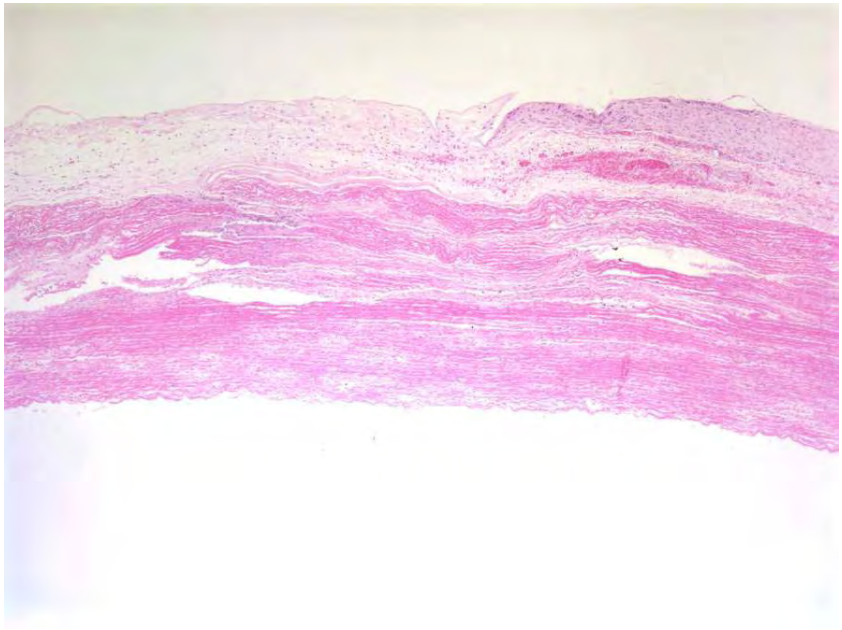


Figure 113 Cross section of wrapped segment of aorta from animal 1 (Hematoxylin-eosin stain, x4).

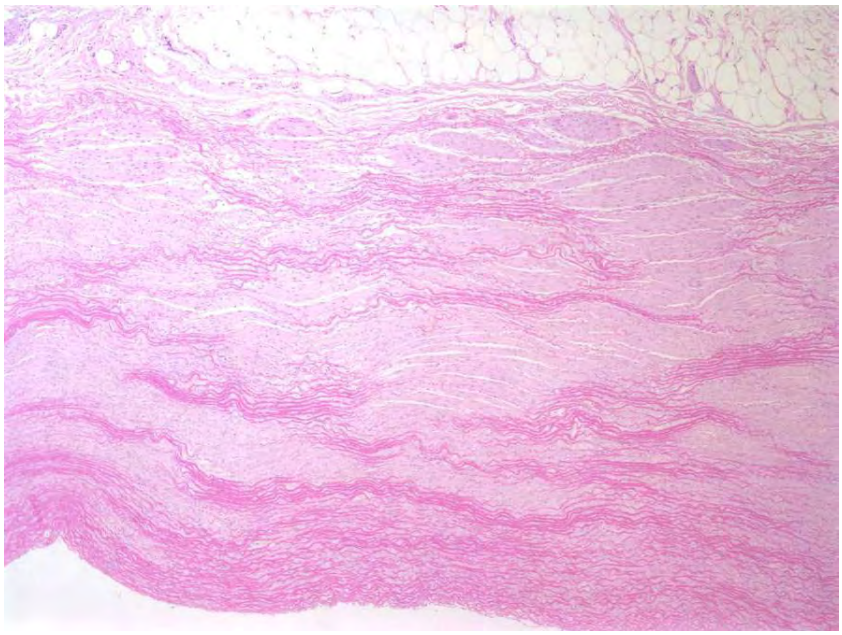


Figure 114 Cross section of region of aorta proximal to wrapped segment from animal 1 (Hematoxylin-eosin stain, x4).

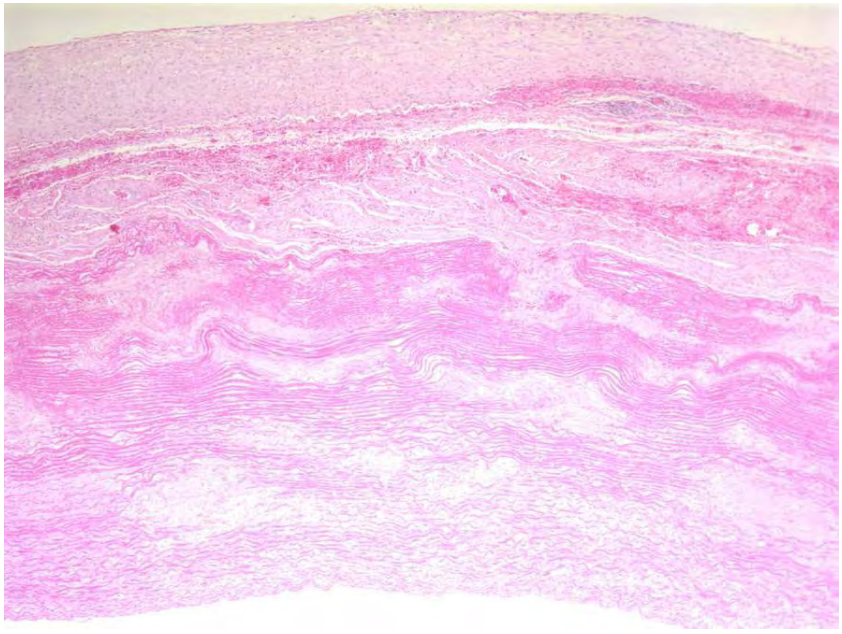


Figure 115 Cross section of wrapped segment of aorta from animal 2 (Hematoxylin-eosin stain, x4).

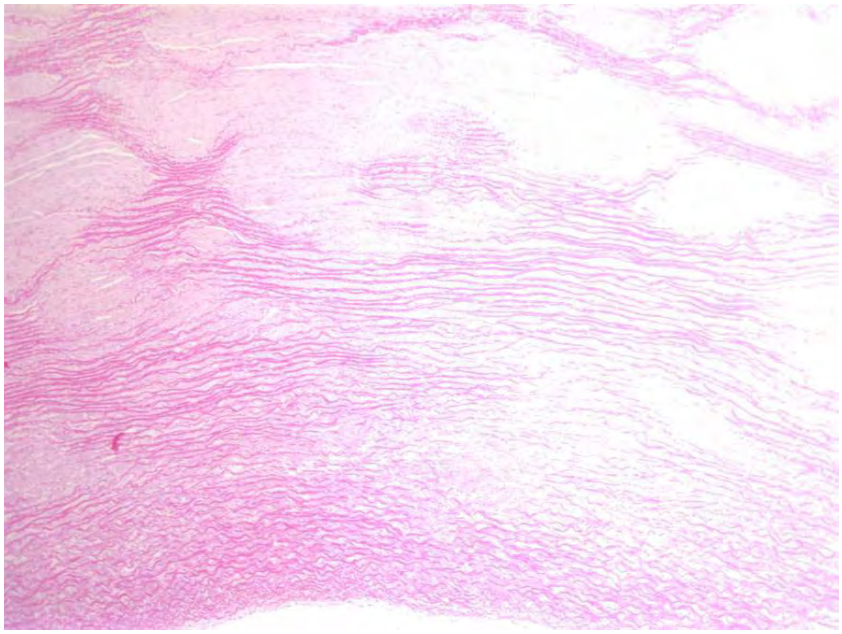


Figure 116 Cross section of region of aorta proximal to wrapped segment from animal 2 (Hematoxylin-eosin stain, x4).

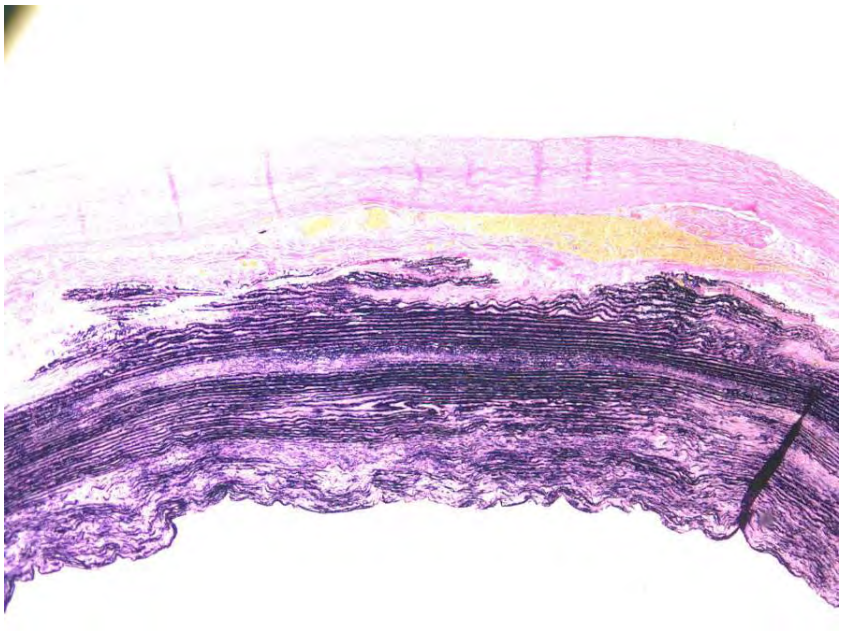


Figure 117 Cross section of wrapped segment of aorta from animal 1 (Verhoeff's elastica, x4).

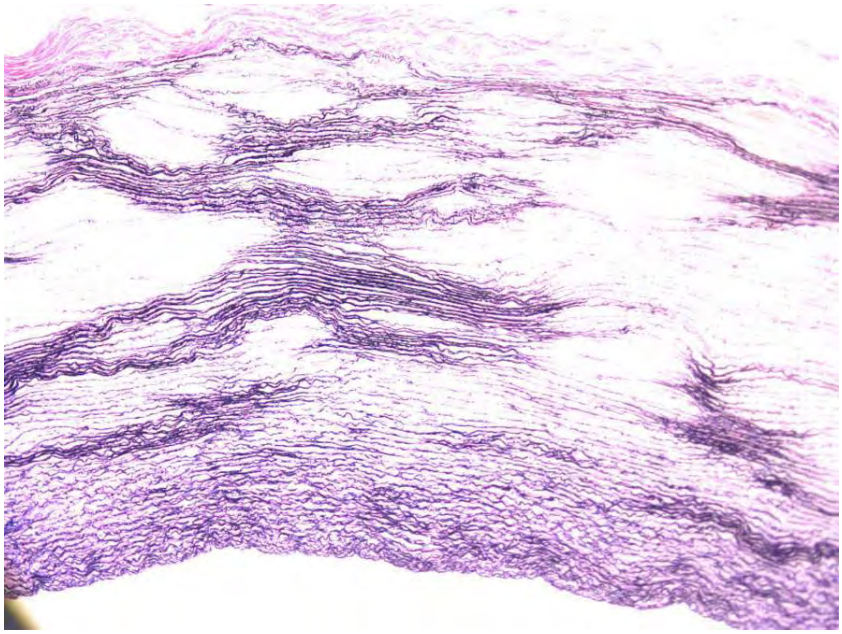


Figure 118 Cross section of region of aorta proximal to wrapped segment from animal 1 (Verhoeff's elastica, x4).

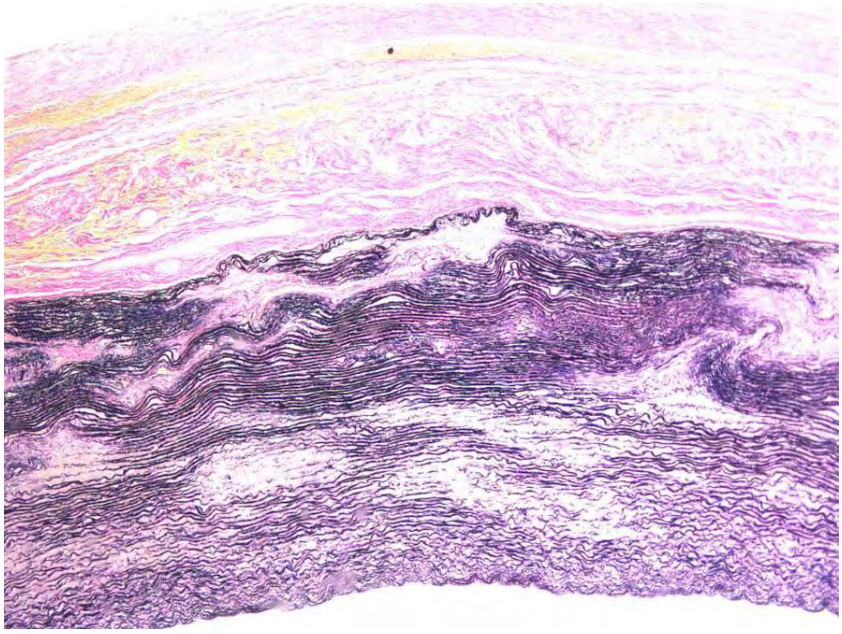


Figure 119 Cross section of wrapped segment of aorta from animal 2 (Verhoeff's elastica, x4).

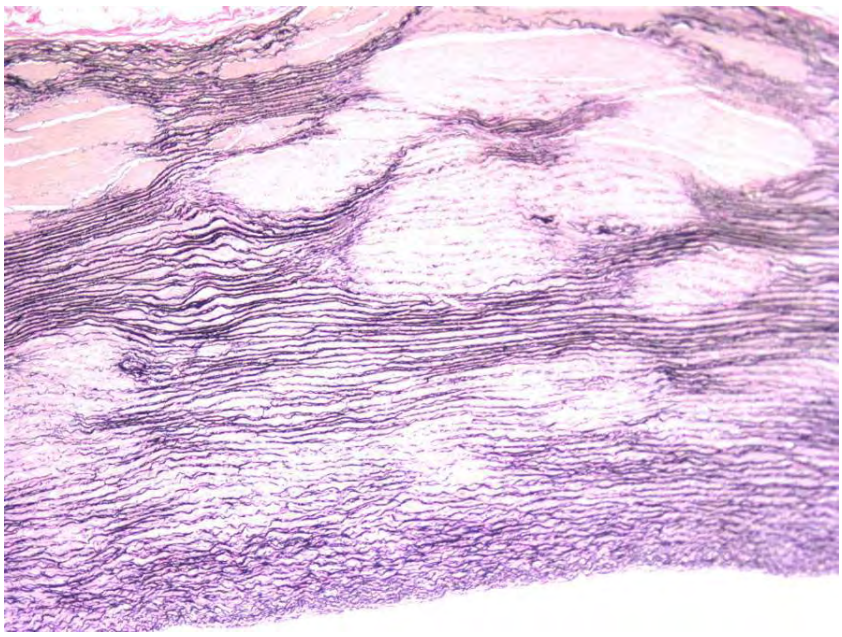


Figure 120 Cross section of region of aorta proximal to wrapped segment from animal 2 (Verhoeff's elastica, x4).

There were no visible differences in the aortas from the control animals and the non-wrapped proximal segments of aorta in the treated animals.

The wrapped aortas showed evidence of fibrous capsule formation that surrounded the wrap material. The fibrous capsule was adherent to the aorta at the edges of the wrap material. There were no adhesions between the wrap material and the aorta, or between the wrap material and fibrous capsule.

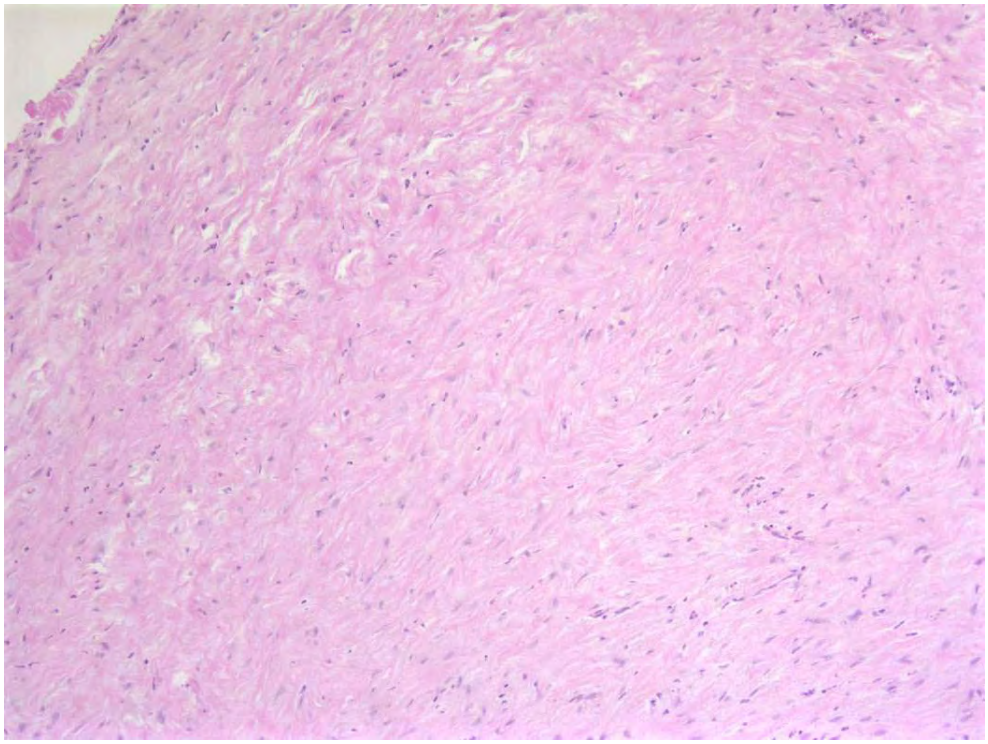


Figure 121 'Neo-capsule' surrounding aortic wrap (Hematoxylin-eosin stain, x10).

7.4 DISCUSSION

7.4.1 Animal model

Application of stiff external wraps to the thoracic aorta and descending thoracic aorta has been used in experimental animals to limit aortic wall motion, induce hypertension and increase cardiac load (Watanabe, Ohtsuka et al. 1993; Tropea, Huie et al. 1996; Tropea, Schwarzacher et al. 2000; Ioannou, Stergiopulos et al. 2003). The effect of chronic application of a stiff wrap on the structure of the aorta in experimental animals has been described by Tropea (2000). The descending thoracic aorta of rabbits was wrapped with a stiff material (PTFE) to limit wall motion for 3 weeks. There was no alteration in the structure or thickness of the intima of the wrapped segments of the aorta when compared to controls. There was also no alteration in the thickness of the media of the wrapped segments when compared to controls; however, alterations in the structure of the media were not discussed. There was no evidence of dislocation of the wrap at 3 weeks. In this study, an ovine model was used to investigate the alterations in thoracic aortic structure and mechanical properties with chronic application of an elastic wrap. An elastic wrap was applied to the ovine proximal descending thoracic aorta to reduce its diameter through a minimal access incision.

A thoracotomy was carried out through the 4th intercostal space. The incision was only 7 cm long and avoided incision of the chest wall muscles. An intercostal nerve block was used to provide intra-operative and post-operative anaesthesia. An excellent view and surgical access was provided to the descending thoracic aorta. The use of a short incision, avoidance of damage to the chest wall muscles, and use of an intercostal nerve block were

used to (Baue, Geha et al. 1996; McRae, Slinger et al. 2002; Murthy and Rice 2002; Concha, Dagnino et al. 2004; Osinowo, Zahrani et al. 2004; Taylor, Massey et al. 2004):

1. Reduce postoperative respiratory dysfunction
2. Facilitate early postoperative mobilisation
3. Facilitate early drinking and eating
4. Reduce postoperative analgesia

Use of a muscle sparing minimal access thoracotomy is associated with reduced rates of wound infection, respiratory complication, and analgesia dysfunction in human subjects undergoing thoracic surgery (Baue, Geha et al. 1996; Murthy and Rice 2002). Both animals used in the study recovered rapidly with no evidence of respiratory or wound complication, early mobilization and return to normal behaviour.

7.4.2 Alterations in aortic structure and function

The wrapped aortas were stiffened at 10 weeks when compared to controls. Histologically there was evidence of compression of the aortic wall that was thinned, with closer apposition of elastin fibres and lamellae. There was also atrophy of muscle in the aortic musculo-elastic fascicles. The exact mechanism of the increase in stiffness was unclear. Possible causes of increased stiffness may be:

1. Increased cross link formation between compressed elastin fibres
2. Fibrosis in the wrapped aortic media
3. Alterations in the mechanical properties of the aorta secondary to compression of elastic lamellae.

Whereas these studies were performed on animals with normal aortas, the target clinical group will be elderly human subjects with stiffened and dilated aortas. The

alteration in aortic stiffness in these subjects is expected to be less marked. In these subjects, there is alteration in elastin fibre structure, increase in collagen content, and decrease in elastin fibres content (Schlatmann and Becker 1977; Virmani, Avolio et al. 1991; Nichols and O'Rourke 2005; O'Rourke and Nichols 2005). Aortic stiffening is already present and may not increase markedly with wrap application. The previous studies have shown that when an elastic wrap is applied to a stiffened and dilated vessel or graft to reduce its diameter, the mechanical properties of the elastic wrap are the major factors determining the stiffness of the wrapped vessel or graft (see Chapters 3 to 5).

There are no animal models of ascending aortic dilatation and stiffness that simulate the alterations in aortic structure and function with aging. The chronic effects of elastic wrap application onto an aorta with structural changes seen in aging cannot be modelled in-vivo.

7.4.3 Elastic material and clamp

Application of stiff wraps to the ascending aorta is used to treat aneurysmal disease in patients where replacement of the ascending aorta is not indicated (e.g. diameter less than 6cm) and/or when the patient is not suitable for replacement (i.e. is medically unfit or has a contraindication to replacement) (Robicsek 1982; Bauer, Pasic et al. 2002; Arsan, Akgun et al. 2004; Robicsek, Cook et al. 2004). Good long term results have been reported, however the procedure may rarely be complicated by dislocation of the wrap, erosion of the aortic wall, false aneurysm formation, and rupture of the aortic wall (Bauer, Grauhan et al. 2003; Robicsek, Cook et al. 2004).

In this study, there was no evidence of dilatation of the aorta proximal or distal to the elastic wrap, or macroscopic damage (such as erosion or hematoma) to the aorta. There was also no macroscopic evidence of slippage of the wrap from the clasping mechanism.

The wrap material and clamp were surrounded by formation of a thin fibrous capsule. There was no evidence of adhesion formation between the wrap material and the aorta, or between the wrap material and the fibrous layer. Macroscopically, the fibrous layer did not appear to impinge the functioning of the wrap material. Application of a rigid band onto the pulmonary artery in experimental animals similarly results in formation of a fibrous capsule that surrounds the rigid wrap (Leeuwenburgh, Schoof et al. 2003).

There was no significant alteration in the stiffness of the material with implantation for 10 weeks. The alterations in the load displacement curves of the material with chronic implantation are consistent with preconditioning (Fung 1981). Macroscopically the clamp was unchanged and there was no evidence of fracturing or failure of the wrap material at the point of engagement with the clamp. There was no evidence of failure of the clamp mechanism or dislocation of the wrap.

The elastic wrap is composed of a silicon polymer. Silicon polymers have been widely used for biomedical and surgical applications and have good biocompatibility (Park and Lakes 1992; Wynne and Lambert 2004). Chronically implanted silicon devices show little structural deterioration with implantation (and loading).

7.5 Conclusions

In conclusion, application of an elastic wrap to the normal ovine descending thoracic aorta produced thinning of the aortic wall and an increase in the stiffness of the aortic wall. The exact mechanism for this remains unclear. These effects of chronic elastic

wrap application on dilated and stiffened aortas in human subjects are expected to differ and be less striking as there are marked differences in aortic wall structure between these two groups. Furthermore, the mechanical properties of the wrap material have been shown to be the major determinant of the final stiffness of the wrapped vessel.

The wrap material and clamp were undamaged at 10 weeks and the alterations in the uniaxial tensile properties of the wrap material are consistent with preconditioning. The elastic wrap and clamp were variably surrounded by a thin fibrous capsule that did not impinge wrap function. There was no evidence of damage to the elastic wrap or clamp, or aneurysmal dilatation or erosion of the aorta.

More extensive biocompatibility studies, in terms of animal numbers and duration of implantation will be required prior to implantation in humans. There is no animal model of aortic dilatation and stiffening that simulates the alterations in ascending aortic structure with aging. Further biocompatibility studies will therefore be limited to normal animal models of the aorta.

CHAPTER 8: UNIAXIAL TENSILE TESTING OF THE OVINE DESCENDING THORACIC AORTA AND THE ELASTIC WRAP MATERIAL.

8.1 INTRODUCTION

The aorta acts as an elastic conduit that converts abrupt pressure changes due to ventricular contraction to a smoother pressure pattern with a higher diastolic value (Berne and Levy 1977; Boudoulas and Wooley 1996; Li 2004). The mechanical properties of the thoracic aorta are important factors influencing arterial haemodynamics, and are altered in a number of disease states, as well as in normal aging (Milnor 1989; Nichols and O'Rourke 2005). An understanding of the mechanical properties of the aorta is essential to the understanding of these states as well as for the development of compliant aortic grafts and elastic wrap materials.

The simplest mechanical test that can be done on a biologic or artificial material is the uniaxial tensile test (Fung 1981; Park and Lakes 1992). A strip of material is lengthened while the lateral sides are left free. Uniaxial tensile testing of a material generates a load displacement curve that allows comparison of the mechanical properties of different materials.

A period of repeated cyclic stretching (preconditioning) is required prior to mechanical testing of biologic materials to establish a repeatable steady state (Fung 1981). A number of different preconditioning protocols have been used in the literature, and it is

unclear whether this results in variation in the experimental data (load displacement curves) generated.

The objectives of this study were to:

1. To determine the effect of the amplitude and frequency of preconditioning on the load-displacement curve of the ovine descending thoracic aorta.
2. To generate and compare load displacement curves for the proximal and distal ovine descending thoracic aorta in the transverse (circumferential) and longitudinal orientation.
3. To generate and compare load displacement curves for the elastic wrap material used in the animal and in-vitro studies.
4. To compare the load displacement curves of the sheep descending thoracic aorta and the elastic wrap material.

8.2 MATERIALS AND METHODS

8.2.1 Specimen preparation

Aorta

Sixteen neutered adult male sheep were used in this study. The animals were humanely killed by an intravenous overdose of barbiturate (Pentobarbitone 90mg/kg). The descending thoracic aorta was excised from the level of the ligamentum arteriosum to the diaphragm, and immediately placed in normal saline at room temperature.

Each aorta was opened longitudinally along the posterior midline of the vessel (i.e. along the line of origin of the intercostal arteries). Eight rectangular strips (10mm x 35mm)

were cut from each aorta using Vernier callipers and surgical loupes. The position and orientation of each strip is illustrated in figure 95.

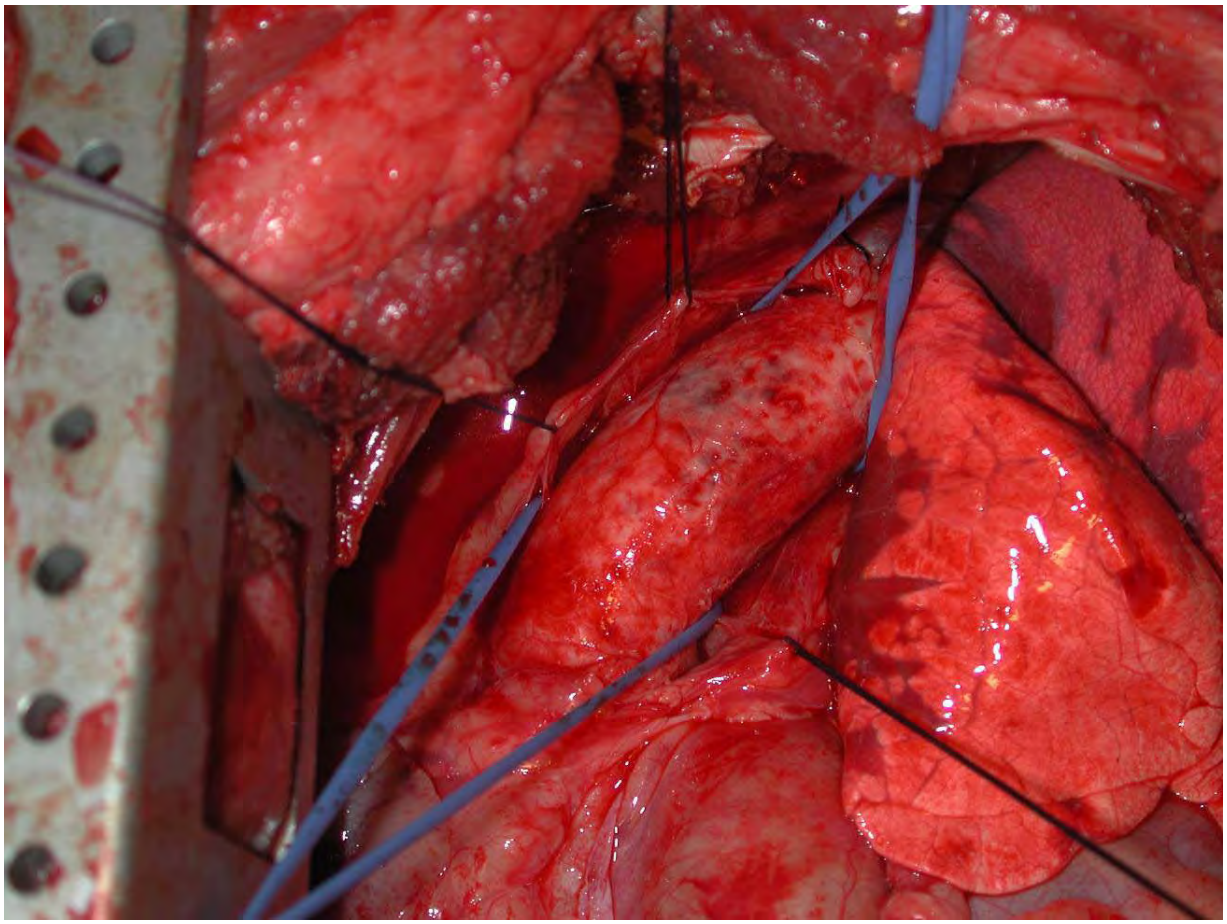


Figure 122 The ovine descending thoracic aorta exposed through a left thoracotomy.

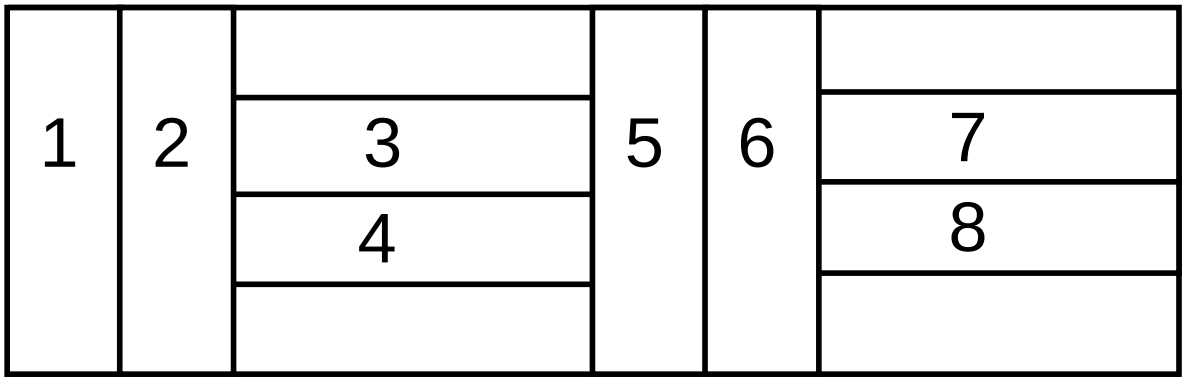


Figure 123 Schematic illustrating the position and orientation of the strips cut from the ovine descending thoracic aorta. The left side is proximal and the right side distal.

1. Position 1: Proximal descending thoracic aorta; transverse (circumferential) orientation.
2. Position 2: Proximal descending thoracic aorta; transverse (circumferential) orientation.
3. Position 3: Proximal descending thoracic aorta; longitudinal orientation.
4. Position 4: Proximal descending thoracic aorta; longitudinal orientation.
5. Position 5: Distal descending thoracic aorta; transverse (circumferential) orientation.
6. Position 6: Distal descending thoracic aorta; transverse (circumferential) orientation.
7. Position 7: Distal descending thoracic aorta; longitudinal orientation.
8. Position 8: Distal descending thoracic aorta; longitudinal orientation.

Elastic material

The elastic silicon polymer used as the elastic wrap material in the in-vivo and in-vitro studies was tested in this study. Both the 4% stiffness material and the 12% stiffness material were tested in this study.

The materials come in prefabricated cylindrical lengths (diameter 30mm, 25mm, and 20mm). Four cylindrical lengths of each 4% and 12% material (internal diameter 25mm, length 3cm) were divided along the longitudinal axis at one point to form a rectangular piece of material. A 35 mm by 10mm transverse (circumferential) strip and a 35 mm by 10mm longitudinal strip were cut from each elastic wrap using Vernier callipers and surgical loupes.

8.2.3 Mechanical testing

Uniaxial tensile testing of the strips of aorta and elastic wrap was performed using a Mach-1 micromechanical testing machine (Biosyntech Canada Inc., Quebec, Canada) fitted with a 10N load-cell. The strips were mounted onto screw tightened stainless steel grips that were lined with sandpaper for added grip.

The strips were loaded in air at room temperature at a stress free gauge length of 8mm. The strips were tested in normal saline at room temperature. Each strip once mounted was lengthened until there was a development of load.

Figure 124 Mach-1 micromechanical testing machine (Biosyntech Canada Inc., Quebec, Canada).

8.2.4 Testing protocol

Aorta

Prior to testing aortic strips were preconditioned using dynamic sinusoids in displacement control. Strips from eight aortas were preconditioned at a frequency of 0.1Hz and strips from the remaining eight aortas were preconditioned at a frequency of 0.3Hz.

Positions 1, 3, 5, and 7 were preconditioned using dynamic sinusoidal displacements of amplitude 2000um for 30 cycles. Positions 2, 4, 6, and 8 were preconditioned using dynamic sinusoidal displacements of amplitude 4000um for 30 cycles. The strips were then subjected to a uniaxial tensile test to failure. The strips were stretched at a constant rate of 4mm/sec to failure, while the load and displacement were measured simultaneously.

Elastic wrap strips

The elastic wrap strips were preconditioned using dynamic sinusoidal displacements of amplitude 2000um and frequency 0.1Hz. The elastic wrap strips were then subjected to a sub-failure uniaxial tensile test. The strips were stretched at a constant rate of 4mm/sec to a displacement of 30000 um, while the load and displacement were measured simultaneously.

8.2.5 Data analysis

During testing, load and displacement were logged on to a PC at a sampling rate of 10 Hz. A load (grams) versus displacement curve (micrometres) was obtained using Microsoft Excel (Office 2000; Microsoft Corporation). Four parameters were calculated for each specimen from its load displacement curve:

5. Stiffness (gm/um): the slopes of the load displacement curve
6. Ultimate/maximum tensile strength (peak load): the load at failure (aortic strips) or the maximum load (elastic material)
7. Failure or tensile energy (gm.um): the area between the load displacement curve and the x-axis at the peak load for the aortic strips (failure energy) or elastic material (tensile energy)
8. Ultimate/maximum tensile displacement (peak displacement)

The elastic material was not tested to failure, as this occurs at strains that are beyond the testing capability of the testing apparatus and beyond strains that would be encountered in vivo.

The stiffness of the strips (aorta and elastic material) was calculated using Matlab. The load-displacement curves of the aortic strips and elastic material are characteristically biphasic. The stiffness was determined by calculating the slope of the load-displacement curve in each phase of the curve (stiffness 1 and stiffness 2).

Mechanical testing data are presented as mean +/- standard deviation. Data was analysed using a one-way analysis of variance (ANOVA) followed by a Tukey Honest significant difference post-hoc test using SPPS for Windows (SPSS Inc, Chicago, Illinois). Statistical significance was set at a level of $p < 0.05$.

For each aorta and elastic wrap group, an averaged load displacement curve was generated and compared graphically using Microsoft Excel (Office 2000; Microsoft Corporation).

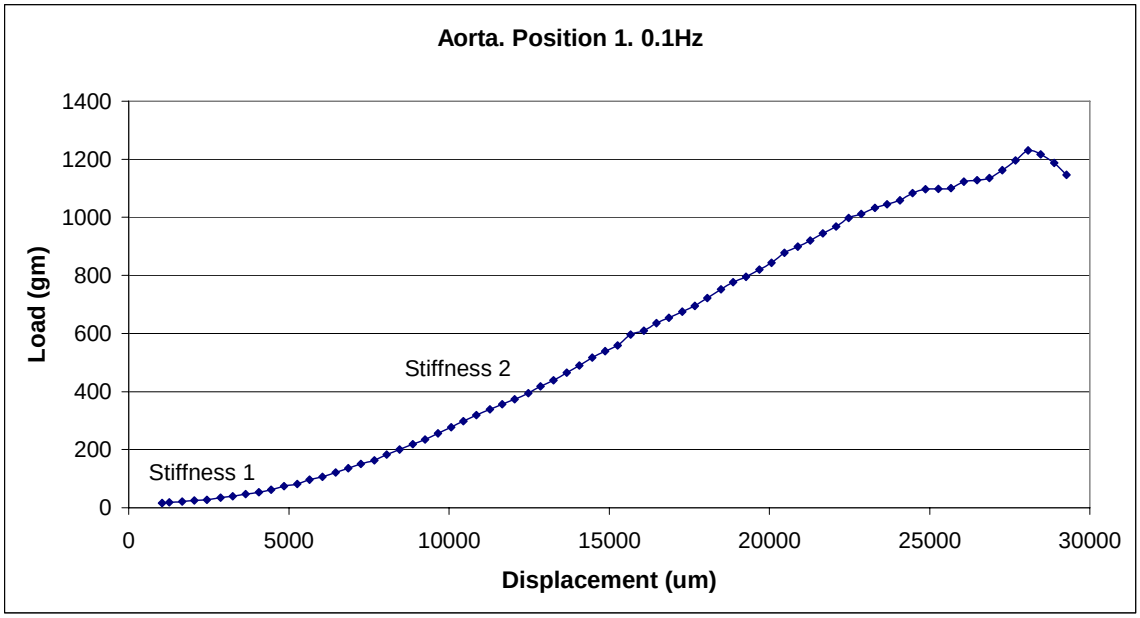


Figure 125 Representative load displacement curve for an aortic strip illustrating its biphasic appearance. Stiffness 1 is the stiffness of the more horizontal part of the load displacement curve, and Stiffness 2 is the stiffness of the subsequent more vertical part of the curve.

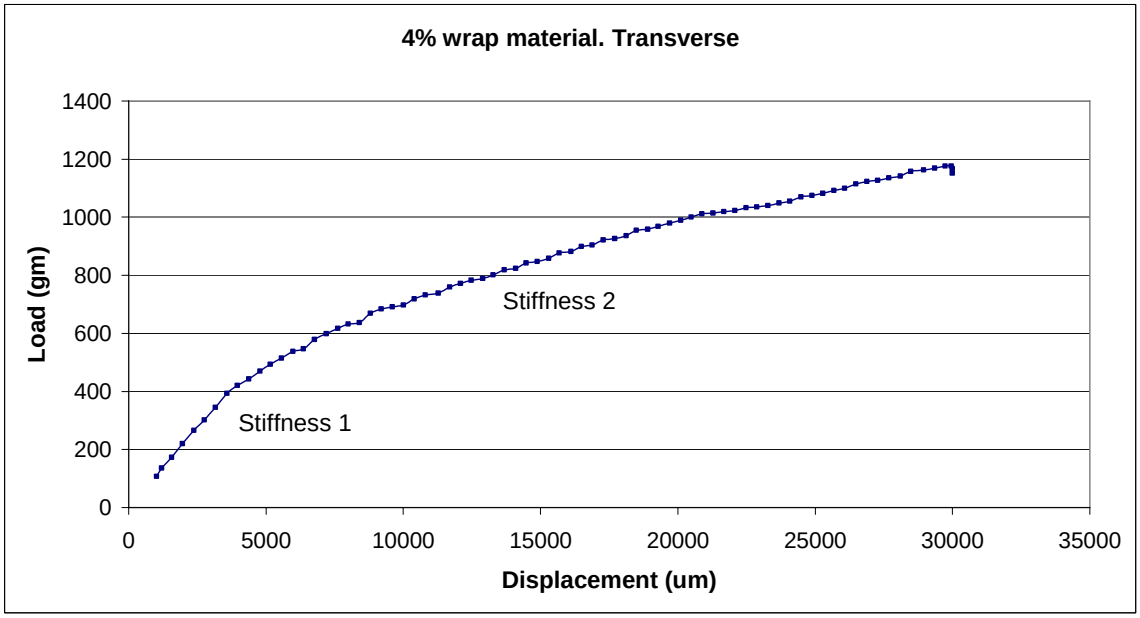


Figure 126 Representative load displacement curve for an elastic wrap strip illustrating its biphasic appearance. Stiffness 1 is the stiffness of the more vertical part of the load displacement curve, and Stiffness 2 is the stiffness of the subsequent more horizontal part of the curve.

8.3 RESULTS

8.3.1 Aortic strips (all data)

Position (n=8)	Frequency	Amplitude	Orientation	Stiffness 1 (gm/um)	Stiffness 2 (gm/um)
1	0.1Hz	2000um	Transverse	0.0271 +/- 0.0062	0.0723 +/- 0.0080
1	0.3Hz	2000um	Transverse	0.0234 +/- 0.0063	0.0688 +/- 0.0222
2	0.1Hz	4000um	Transverse	0.0263 +/- 0.0048	0.0728 +/- 0.0233
2	0.3Hz	4000um	Transverse	0.0285 +/- 0.0079	0.0681 +/- 0.0237
3	0.1Hz	2000um	Longitudinal	0.0197 +/- 0.0056	0.0581 +/- 0.0130
3	0.3Hz	2000um	Longitudinal	0.0250 +/- 0.0105	0.0639 +/- 0.0193
4	0.1Hz	4000um	Longitudinal	0.0161 +/- 0.0044	0.0567 +/- 0.0128
4	0.3Hz	4000um	Longitudinal	0.0185 +/- 0.0051	0.0561 +/- 0.0166
5	0.1Hz	2000um	Transverse	0.0251 +/- 0.0097	0.0823 +/- 0.0115
5	0.3Hz	2000um	Transverse	0.0268 +/- 0.0097	0.0863 +/- 0.0266
6	0.1Hz	4000um	Transverse	0.0274 +/- 0.0058	0.0924 +/- 0.0169
6	0.3Hz	4000um	Transverse	0.0287 +/- 0.0056	0.0894 +/- 0.0150
7	0.1Hz	2000um	Longitudinal	0.0265 +/- 0.0095	0.0674 +/- 0.0118
7	0.3Hz	2000um	Longitudinal	0.0237 +/- 0.0129	0.0738 +/- 0.0299
8	0.1Hz	4000um	Longitudinal	0.0175 +/- 0.0935	0.0935 +/- 0.0420
8	0.3Hz	4000um	Longitudinal	0.0212 +/- 0.0129	0.1076 +/- 0.0497

Table 37 Stiffness 1 and stiffness 2 of strips of ovine descending thoracic aorta

Position (n=8)	Frequency	Amplitude	Orientation	Peak Load (gm)	Peak Displacement (um)
1	0.1Hz	2000um	Transverse	1155.45 +/- 184.22	22670.85 +/- 4335.55
1	0.3Hz	2000um	Transverse	1030.38 +/- 297.99	21124.43 +/- 4100.14
2	0.1Hz	4000um	Transverse	1245.66 +/- 240.92	25958.10 +/- 6208.62
2	0.3Hz	4000um	Transverse	1117.02 +/- 100.02	22700.93 +/- 3015.74
3	0.1Hz	2000um	Longitudinal	581.45 +/- 188.40	15148.58 +/- 5156.45
3	0.3Hz	2000um	Longitudinal	595.82 +/- 213.23	14198.03 +/- 4009.02
4	0.1Hz	4000um	Longitudinal	487.85 +/- 82.97	13413.83 +/- 2290.00
4	0.3Hz	4000um	Longitudinal	586.79 +/- 289.51	14968.50 +/- 4373.83
5	0.1Hz	2000um	Transverse	1095.19 +/- 227.45	20712.38 +/- 5681.32
5	0.3Hz	2000um	Transverse	1110.86 +/- 236.01	19653.09 +/- 3313.76
6	0.1Hz	4000um	Transverse	1173.88 +/- 167.59	20016.68 +/- 4927.60
6	0.3Hz	4000um	Transverse	1080.03 +/- 189.74	18462.38 +/- 2480.32
7	0.1Hz	2000um	Longitudinal	648.87 +/- 248.67	15112.95 +/- 4581.69
7	0.3Hz	2000um	Longitudinal	677.61 +/- 205.25	15442.05 +/- 1729.06
8	0.1Hz	4000um	Longitudinal	572.97 +/- 141.42	13268.93 +/- 2193.56
8	0.3Hz	4000um	Longitudinal	590.43 +/- 165.01	13219.58 +/- 3465.63

Table 38 Peak load and peak displacement of strips of ovine descending thoracic aorta

Position (n=8)	Frequency	Amplitude	Orientation	Failure energy (gm.um)
1	0.1Hz	2000um	Transverse	1.24×10^7 +/- 3.93×10^6
1	0.3Hz	2000um	Transverse	1.01×10^7 +/- 3.88×10^6
2	0.1Hz	4000um	Transverse	1.69×10^7 +/- 6.65×10^6
2	0.3Hz	4000um	Transverse	1.23×10^7 +/- 2.44×10^6
3	0.1Hz	2000um	Longitudinal	4.96×10^6 +/- 3.54×10^6
3	0.3Hz	2000um	Longitudinal	4.56×10^6 +/- 2.85×10^6
4	0.1Hz	4000um	Longitudinal	3.36×10^6 +/- 9.82×10^5
4	0.3Hz	4000um	Longitudinal	4.84×10^6 +/- 3.61×10^6
5	0.1Hz	2000um	Transverse	1.13×10^7 +/- 6.05×10^6
5	0.3Hz	2000um	Transverse	1.01×10^7 +/- 3.07×10^6
6	0.1Hz	4000um	Transverse	1.19×10^7 +/- 4.56×10^6
6	0.3Hz	4000um	Transverse	9.80×10^6 +/- 2.72×10^6
7	0.1Hz	2000um	Longitudinal	6.10×10^6 +/- 5.03×10^6
7	0.3Hz	2000um	Longitudinal	5.56×10^6 +/- 1.72×10^6
8	0.1Hz	4000um	Longitudinal	4.39×10^6 +/- 9.26×10^5
8	0.3Hz	4000um	Longitudinal	4.94×10^6 +/- 3.20×10^6

Table 39 Failure energy of strips of ovine descending thoracic aorta

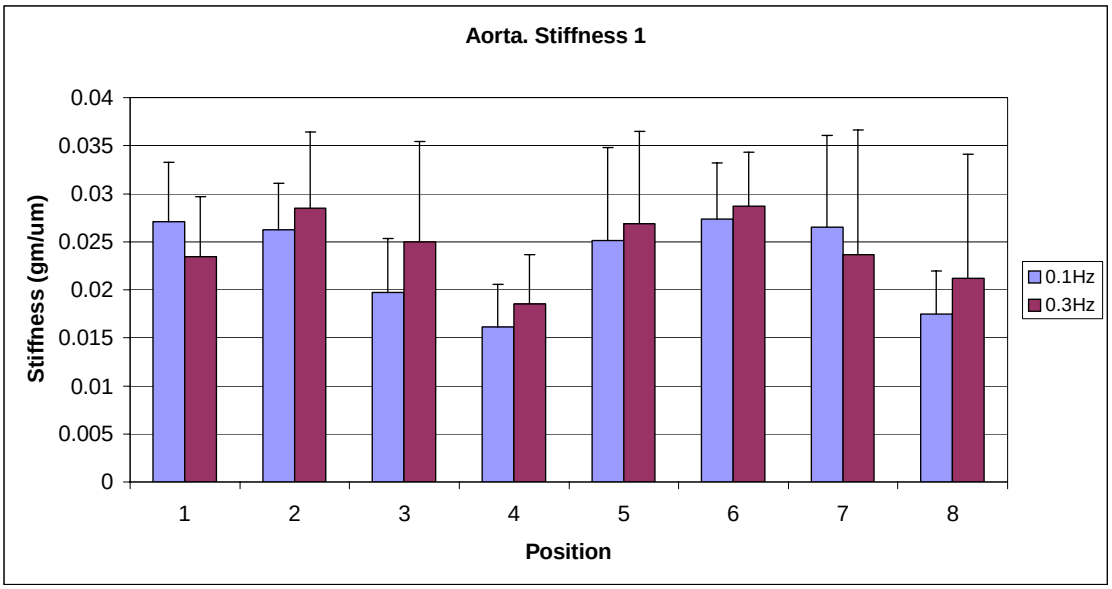


Figure 127 Stiffness 1 of strips of ovine descending thoracic aorta

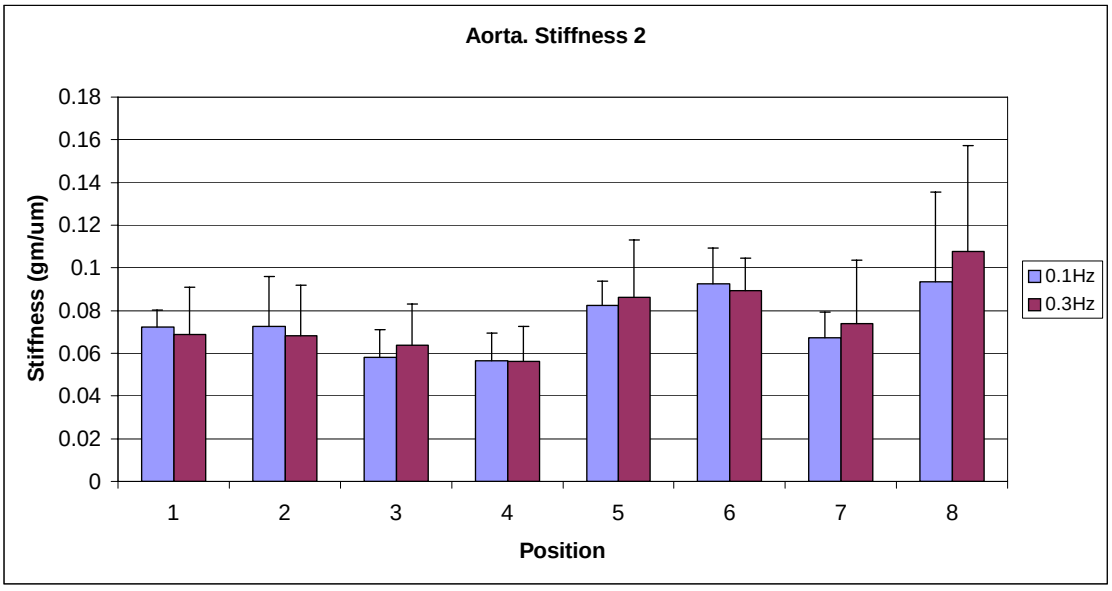


Figure 128 Stiffness 2 of strips of ovine descending thoracic aorta

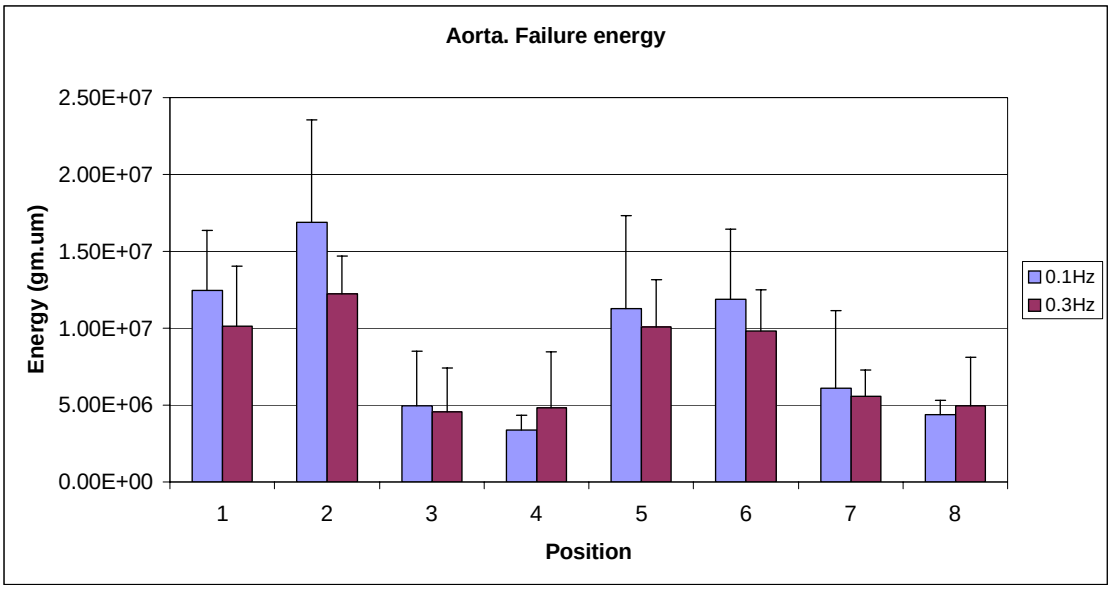


Figure 129 Failure energy of strips of ovine descending thoracic aorta

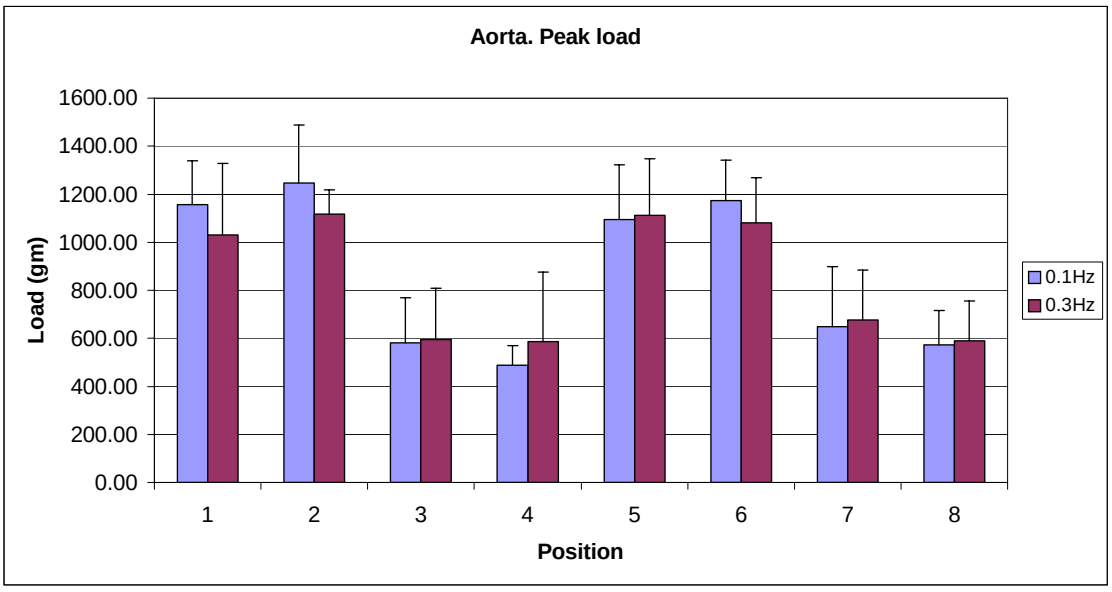


Figure 130 Peak load of strips of ovine descending thoracic aorta

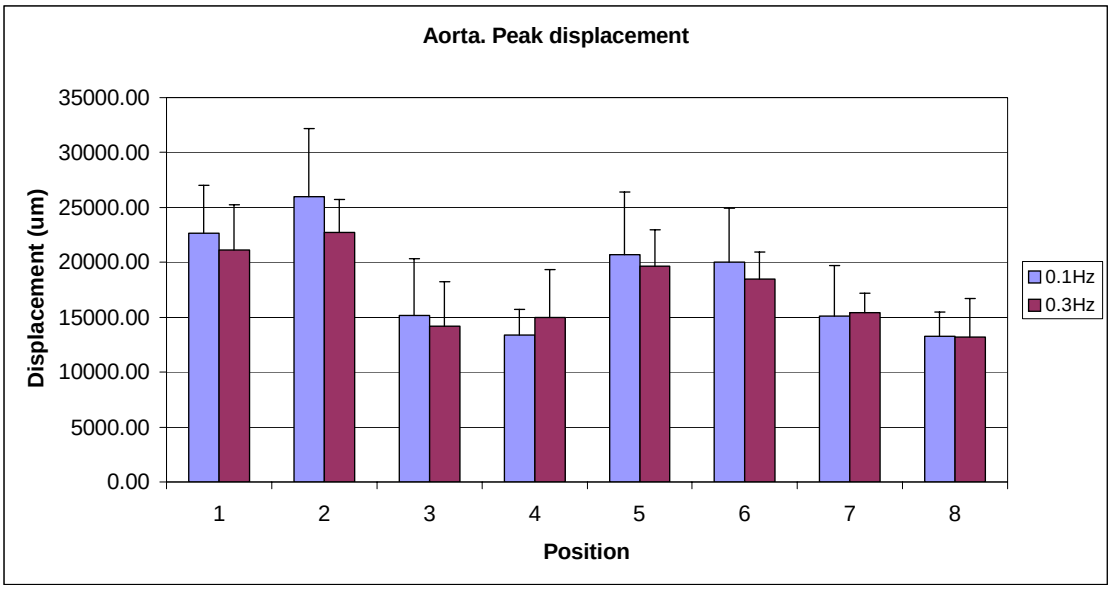


Figure 131 Peak displacement of strips of ovine descending thoracic aorta

8.3.2 Frequency of preconditioning

There were no significant differences in stiffness 1, stiffness 2, failure energy, rupture load, or rupture displacement for aortic strips preconditioned at a frequency of 0.1Hz and aortic strips preconditioned at a frequency of 0.3Hz.

Position (n=8)	Amplitude of preconditioning	Orientation	Frequency of preconditioning 0.1Hz **Stiffness 1 (gm/um)**	Frequency of preconditioning 0.3Hz **Stiffness 1 (gm/um)**	Significance
1	2000um	Transverse	0.0271 +/- 0.0062	0.0234 +/- 0.0063	N/S
2	4000um	Transverse	0.0263 +/- 0.0048	0.0285 +/- 0.0079	N/S
3	2000um	Longitudinal	0.0197 +/- 0.0056	0.0250 +/- 0.0105	N/S
4	4000um	Longitudinal	0.0161 +/- 0.0044	0.0185 +/- 0.0051	N/S
5	2000um	Transverse	0.0251 +/- 0.0097	0.0268 +/- 0.0097	N/S
6	4000um	Transverse	0.0274 +/- 0.0058	0.0287 +/- 0.0056	N/S
7	2000um	Longitudinal	0.0265 +/- 0.0095	0.0237 +/- 0.0129	N/S
8	4000um	Longitudinal	0.0175 +/- 0.0935	0.0212 +/- 0.0129	N/S

Table 40 Comparison of stiffness 1 for strips of ovine descending thoracic aorta preconditioned at 0.1Hz and 0.3Hz.

Position (n=8)	Amplitude of preconditioning	Orientation	Frequency of preconditioning 0.1Hz **Stiffness 2 (gm/um)**	Frequency of preconditioning 0.3Hz **Stiffness 2 (gm/um)**	Significance
1	2000um	Transverse	0.0723 +/- 0.0080	0.0688 +/- 0.0222	N/S
2	4000um	Transverse	0.0728 +/- 0.0233	0.0681 +/- 0.0237	N/S
3	2000um	Longitudinal	0.0581 +/- 0.0130	0.0639 +/- 0.0193	N/S
4	4000um	Longitudinal	0.0567 +/- 0.0128	0.0561 +/- 0.0166	N/S
5	2000um	Transverse	0.0823 +/- 0.0115	0.0863 +/- 0.0266	N/S
6	4000um	Transverse	0.0924 +/- 0.0169	0.0894 +/- 0.0150	N/S
7	2000um	Longitudinal	0.0674 +/- 0.0118	0.0738 +/- 0.0299	N/S
8	4000um	Longitudinal	0.0935 +/- 0.0420	0.1076 +/- 0.0497	N/S

Table 41 Comparison of stiffness 2 for strips of ovine descending thoracic aorta preconditioned at 0.1Hz and 0.3Hz.

Position (n=8)	Amplitude of preconditioning	Orientation	Frequency of preconditioning 0.1Hz **Failure energy (gm.um)**	Frequency of preconditioning 0.3Hz **Failure energy (gm.um)**	Significance
1	2000um	Transverse	1.24×10^7 +/- 3.93×10^6	1.01×10^7 +/- 3.88×10^6	N/S
2	4000um	Transverse	1.69×10^7 +/- 6.65×10^6	1.23×10^7 +/- 2.44×10^6	N/S
3	2000um	Longitudinal	4.96×10^6 +/- 3.54×10^6	4.56×10^6 +/- 2.85×10^6	N/S
4	4000um	Longitudinal	3.36×10^6 +/- 9.82×10^5	4.84×10^6 +/- 3.61×10^6	N/S
5	2000um	Transverse	1.13×10^7 +/- 6.05×10^6	1.01×10^7 +/- 3.07×10^6	N/S
6	4000um	Transverse	1.19×10^7 +/- $4.56x\ 10^6$	9.80×10^6 +/- 2.72×10^6	N/S
7	2000um	Longitudinal	6.10×10^6 +/- 5.03×10^6	5.56×10^6 +/- 1.72×10^6	N/S
8	4000um	Longitudinal	4.39×10^6 +/- 9.26×10^5	4.94×10^6 +/- 3.20×10^6	N/S

Table 42 Comparison of failure energy for strips of ovine descending thoracic aorta preconditioned at 0.1Hz and 0.3Hz.

Position (n=8)	Amplitude of preconditioning	Orientation	Frequency of preconditioning 0.1Hz **Peak load (gm)**	Frequency of preconditioning 0.3Hz **Peak load (gm)**	Significance
1	2000um	Transverse	1155.45 +/- 184.22	1030.38 +/- 297.99	N/S
2	4000um	Transverse	1245.66 +/- 240.92	1117.02 +/- 100.02	N/S
3	2000um	Longitudinal	581.45 +/- 188.40	595.82 +/- 213.23	N/S
4	4000um	Longitudinal	487.85 +/- 82.97	586.79 +/- 289.51	N/S
5	2000um	Transverse	1095.19 +/- 227.45	1110.86 +/- 236.01	N/S
6	4000um	Transverse	1173.88 +/- 167.59	1080.03 +/- 189.74	N/S
7	2000um	Longitudinal	648.87 +/- 248.67	677.61 +/- 205.25	N/S
8	4000um	Longitudinal	572.97 +/- 141.42	590.43 +/- 165.01	N/S

Table 43 Comparison of peak load for strips of ovine descending thoracic aorta preconditioned at 0.1Hz and 0.3Hz

Position (n=8)	Amplitude of preconditioning	Orientation	Frequency of preconditioning 0.1Hz **Peak displacement (um)**	Frequency of preconditioning 0.3Hz **Peak displacement (um)**	Significance
1	2000um	Transverse	22670.85 +/- 4335.55	21124.43 +/- 4100.14	N/S
2	4000um	Transverse	25958.10 +/- 6208.62	22700.93 +/- 3015.74	N/S
3	2000um	Longitudinal	15148.58 +/- 5156.45	14198.03 +/- 4009.02	N/S
4	4000um	Longitudinal	13413.83 +/- 2290.00	14968.50 +/- 4373.83	N/S
5	2000um	Transverse	20712.38 +/- 5681.32	19653.09 +/- 3313.76	N/S
6	4000um	Transverse	20016.68 +/- 4927.60	18462.38 +/- 2480.32	N/S
7	2000um	Longitudinal	15112.95 +/- 4581.69	15442.05 +/- 1729.06	N/S
8	4000um	Longitudinal	13268.93 +/- 2193.56	13219.58 +/- 3465.63	N/S

Table 44 Comparison of peak displacement for strips of ovine descending thoracic aorta preconditioned at 0.1Hz and 0.3Hz.

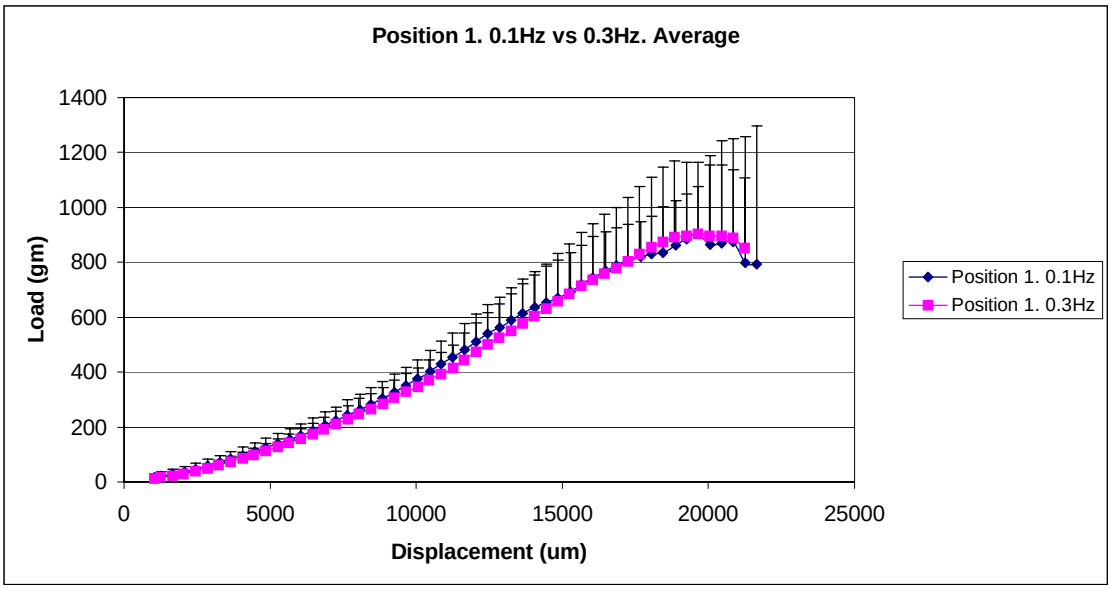


Figure 132 Comparison of strips of ovine descending thoracic aorta from position 1 (amplitude of preconditioning 2000um; proximal; transverse) preconditioned at 0.1Hz and 0.3Hz.

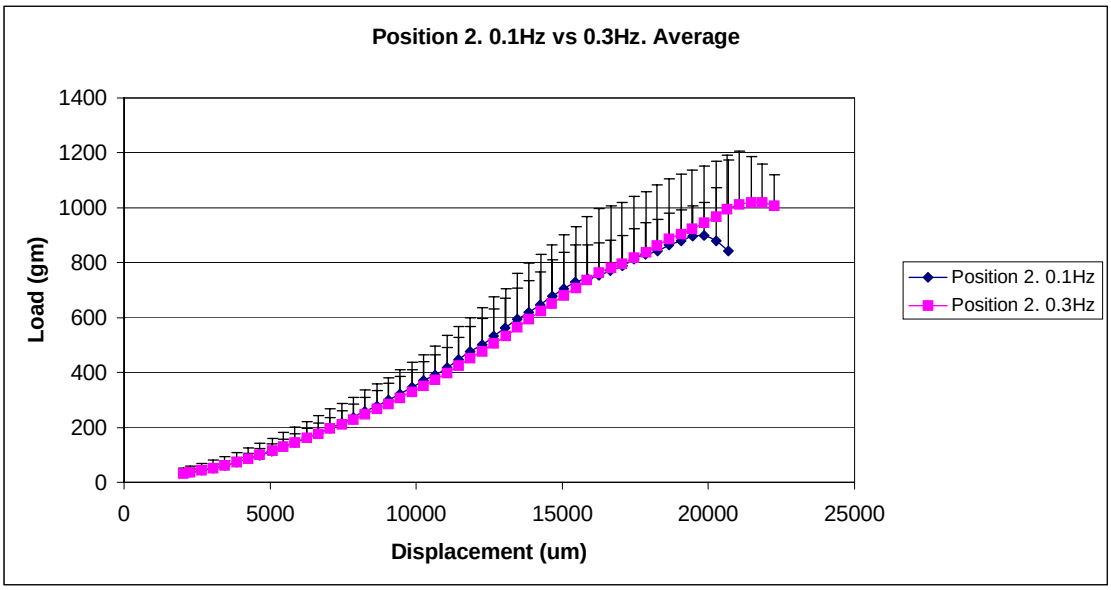


Figure 133 Comparison of strips of ovine descending thoracic aorta from position 2 (amplitude of preconditioning 4000um; proximal; transverse) preconditioned at 0.1Hz and 0.3Hz.

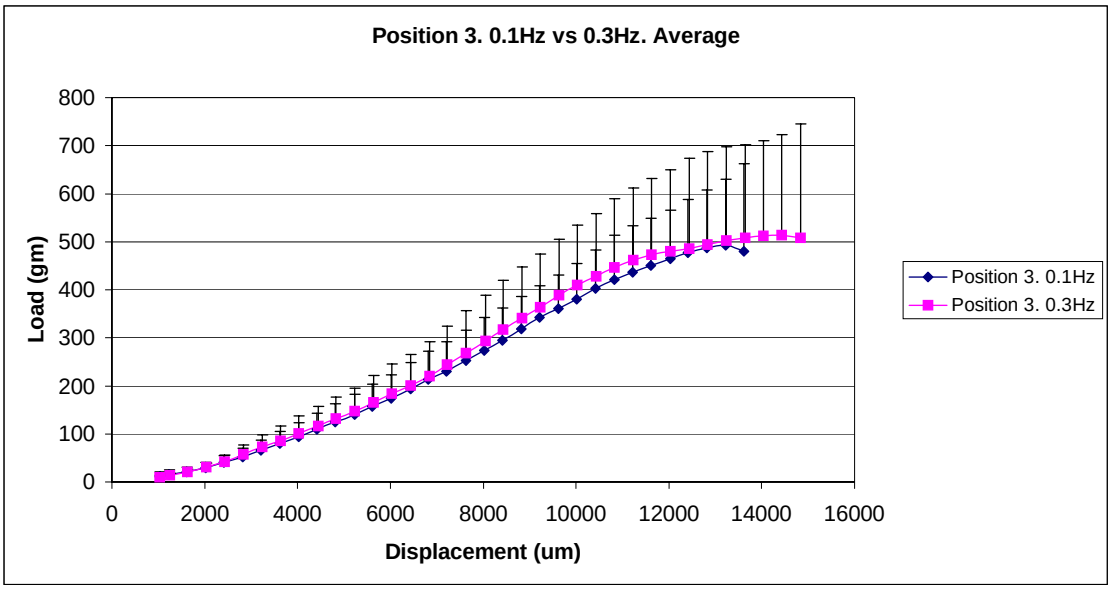


Figure 134 Comparison of strips of ovine descending thoracic aorta from position 3 (amplitude of preconditioning 2000um; proximal; longitudinal) preconditioned at 0.1Hz and 0.3Hz.

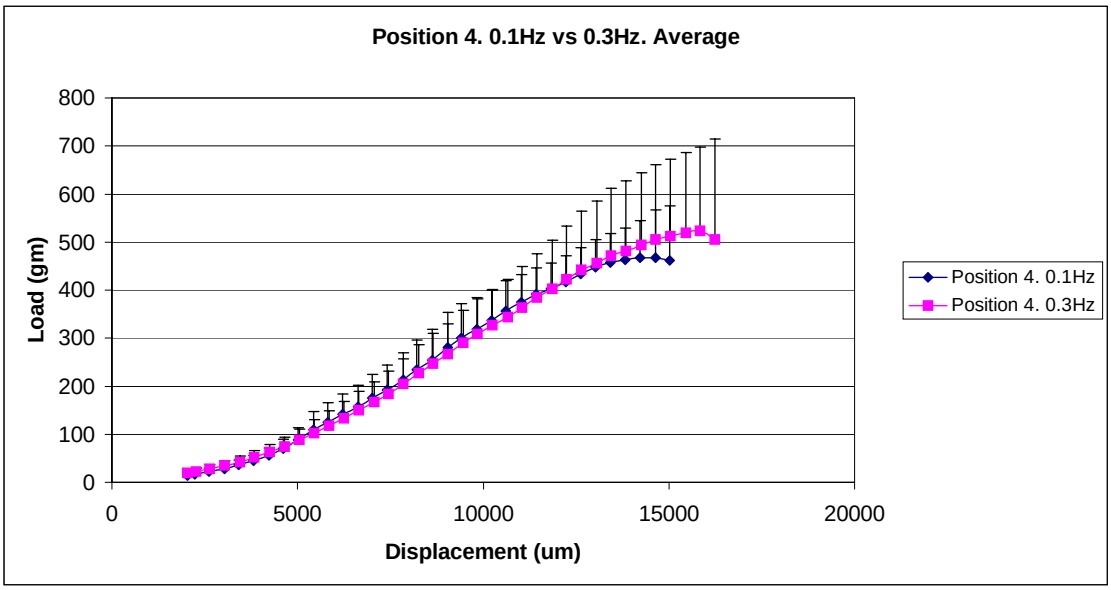


Figure 135 Comparison of strips of ovine descending thoracic aorta from position 4 (amplitude of preconditioning 4000um; proximal; longitudinal) preconditioned at 0.1Hz and 0.3Hz.

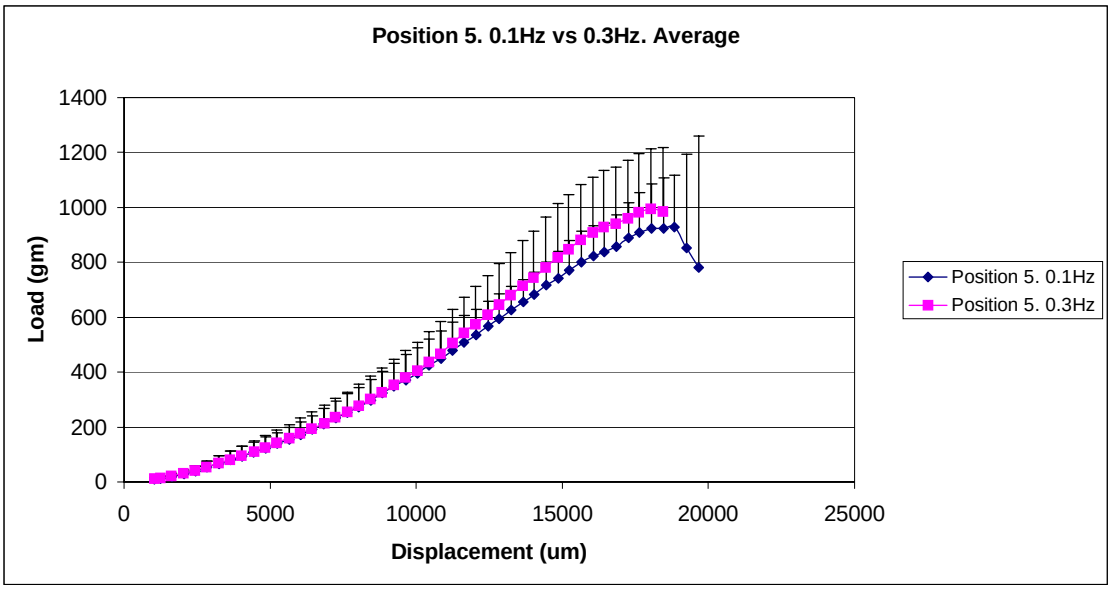


Figure 136 Comparison of strips of ovine descending thoracic aorta from position 5 (amplitude of preconditioning 2000um; distal; transverse) preconditioned at 0.1Hz and 0.3Hz.

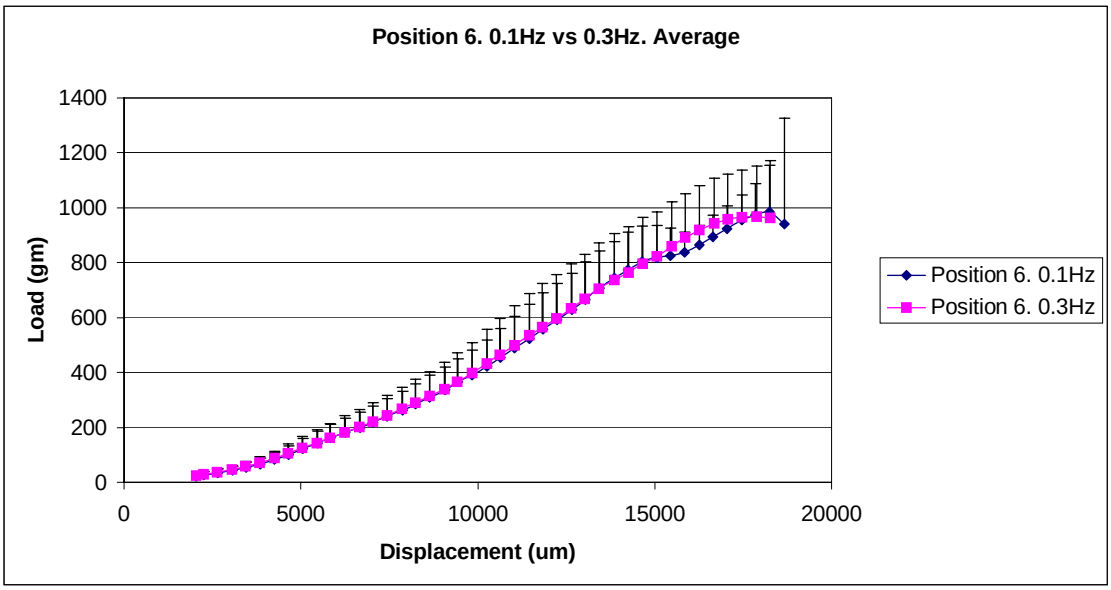


Figure 137 Comparison of strips of ovine descending thoracic aorta from position 6 (amplitude of preconditioning 4000um; distal; transverse) preconditioned at 0.1Hz and 0.3Hz.

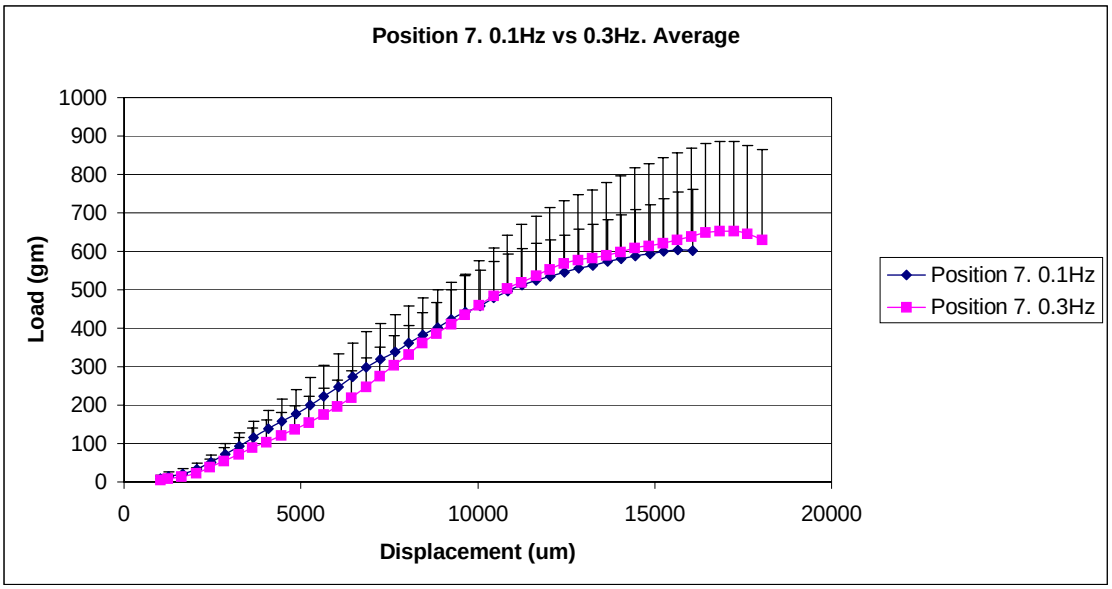


Figure 138 Comparison of strips of ovine descending thoracic aorta from position 7 (amplitude of preconditioning 2000um; distal; longitudinal) preconditioned at 0.1Hz and 0.3Hz.

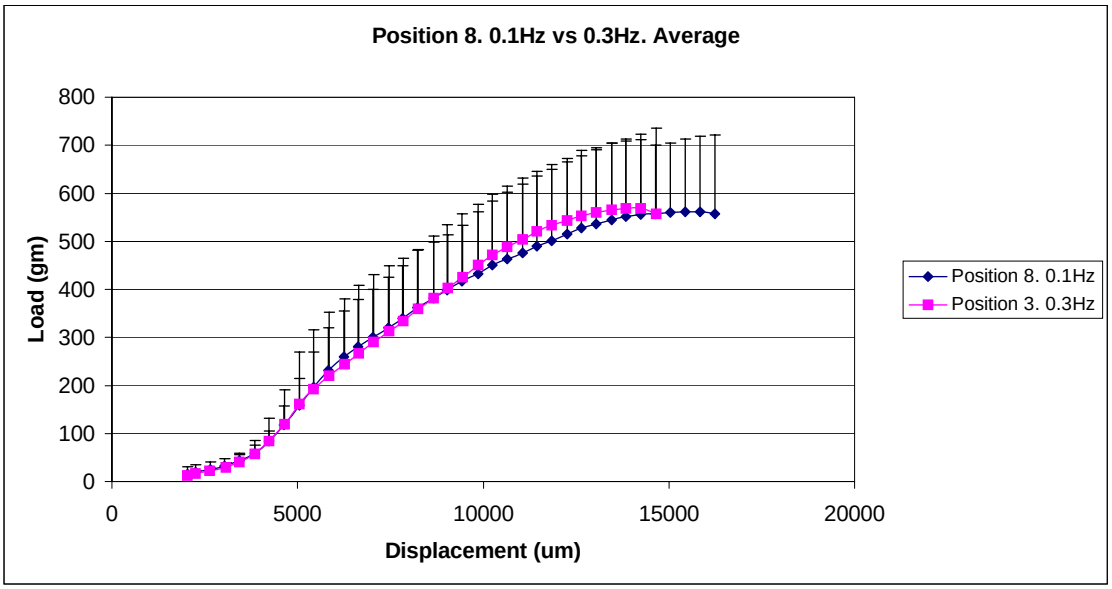


Figure 139 Comparison of strips of ovine descending thoracic aorta from position 7 (amplitude of preconditioning 4000um; distal; longitudinal) preconditioned at 0.1Hz and 0.3Hz.

8.3.3 Amplitude of preconditioning

There were no significant differences in stiffness 1, stiffness 2, failure energy, rupture load, or rupture displacement for aortic strips preconditioned at amplitude of 2000um and aortic strips preconditioned at amplitude of 4000um.

Position (n=8)	Frequency of preconditioning	Orientation	Amplitude of preconditioning 2000um **Stiffness 1 (gm/um)**	Amplitude of preconditioning 4000um **Stiffness 1 (gm/um)**	Significance
1 versus 2	0.1Hz	Transverse	0.0271 +/- 0.0062	0.0263 +/- 0.0048	N/S
1 versus 2	0.3Hz	Transverse	0.0234 +/- 0.0063	0.0285 +/- 0.0079	N/S
3 versus 4	0.1Hz	Longitudinal	0.0197 +/- 0.0056	0.0161 +/- 0.0044	N/S
3 versus 4	0.3Hz	Longitudinal	0.0250 +/- 0.0105	0.0185 +/- 0.0051	N/S
5 versus 6	0.1Hz	Transverse	0.0251 +/- 0.0097	0.0274 +/- 0.0058	N/S
5 versus 6	0.3Hz	Transverse	0.0268 +/- 0.0097	0.0287 +/- 0.0056	N/S
7 versus 8	0.1Hz	Longitudinal	0.0265 +/- 0.0095	0.0175 +/- 0.0935	N/S
7 versus 8	0.3Hz	Longitudinal	0.0237 +/- 0.0129	0.0212 +/- 0.0129	N/S

Table 45 Comparison of stiffness 1 for strips of ovine descending thoracic aorta preconditioned at 2000um and 4000um.

Position (n=8)	Frequency of preconditioning	Orientation	Amplitude of preconditioning 2000um **Stiffness 2 (gm/um)**	Amplitude of preconditioning 4000um **Stiffness 2 (gm/um)**	Significance
1 versus 2	0.1Hz	Transverse	0.0723 +/- 0.0080	0.0728 +/- 0.0233	N/S
1 versus 2	0.3Hz	Transverse	0.0688 +/- 0.0222	0.0681 +/- 0.0237	N/S
3 versus 4	0.1Hz	Longitudinal	0.0581 +/- 0.0130	0.0567 +/- 0.0128	N/S
3 versus 4	0.3Hz	Longitudinal	0.0639 +/- 0.0193	0.0561 +/- 0.0166	N/S
5 versus 6	0.1Hz	Transverse	0.0823 +/- 0.0115	0.0924 +/- 0.0169	N/S
5 versus 6	0.3Hz	Transverse	0.0863 +/- 0.0266	0.0894 +/- 0.0150	N/S
7 versus 8	0.1Hz	Longitudinal	0.0674 +/- 0.0118	0.0935 +/- 0.0420	N/S
7 versus 8	0.3Hz	Longitudinal	0.0738 +/- 0.0299	0.1076 +/- 0.0497	N/S

Table 46 Comparison of stiffness 2 for strips of ovine descending thoracic aorta preconditioned at 2000um and 4000um.

Position (n=8)	Frequency of preconditioning	Orientation	Amplitude of preconditioning 2000um **Failure energy (gm.um)**	Amplitude of preconditioning 4000um **Failure energy (gm.um)**	Significance
1 versus 2	0.1Hz	Transverse	1.24×10^7 +/- 3.93×10^6	1.69×10^7 +/- 6.65×10^6	N/S
1 versus 2	0.3Hz	Transverse	1.01×10^7 +/- 3.88×10^6	1.23×10^7 +/- 2.44×10^6	N/S
3 versus 4	0.1Hz	Longitudinal	4.96×10^6 +/- 3.54×10^6	3.36×10^6 +/- 9.82×10^5	N/S
3 versus 4	0.3Hz	Longitudinal	4.56×10^6 +/- 2.85×10^6	4.84×10^6 +/- 3.61×10^6	N/S
5 versus 6	0.1Hz	Transverse	1.13×10^7 +/- 6.05×10^6	1.19×10^7 +/- $4.56x\ 10^6$	N/S
5 versus 6	0.3Hz	Transverse	1.01×10^7 +/- 3.07×10^6	9.80×10^6 +/- 2.72×10^6	N/S
7 versus 8	0.1Hz	Longitudinal	6.10×10^6 +/- 5.03×10^6	4.39×10^6 +/- 9.26×10^5	N/S
7 versus 8	0.3Hz	Longitudinal	5.56×10^6 +/- 1.72×10^6	4.94×10^6 +/- 3.20×10^6	N/S

Table 47 Comparison of failure energy for strips of ovine descending thoracic aorta preconditioned at 2000um and 4000um.

Position (n=8)	Frequency of preconditioning	Orientation	Amplitude of preconditioning 2000um **Peak load (gm)**	Amplitude of preconditioning 4000um **Peak load (gm)**	Significance
1 versus 2	0.1Hz	Transverse	1155.45 +/- 184.22	1245.66 +/- 240.92	N/S
1 versus 2	0.3Hz	Transverse	1030.38 +/- 297.99	1117.02 +/- 100.02	N/S
3 versus 4	0.1Hz	Longitudinal	581.45 +/- 188.40	487.85 +/- 82.97	N/S
3 versus 4	0.3Hz	Longitudinal	595.82 +/- 213.23	586.79 +/- 289.51	N/S
5 versus 6	0.1Hz	Transverse	1095.19 +/- 227.45	1173.88 +/- 167.59	N/S
5 versus 6	0.3Hz	Transverse	1110.86 +/- 236.01	1080.03 +/- 189.74	N/S
7 versus 8	0.1Hz	Longitudinal	648.87 +/- 248.67	572.97 +/- 141.42	N/S
7 versus 8	0.3Hz	Longitudinal	677.61 +/- 205.25	590.43 +/- 165.01	N/S

Table 48 Comparison of peak load for strips of ovine descending thoracic aorta preconditioned at 2000um and 4000um.

Position (n=8)	Frequency of preconditioning	Orientation	Amplitude of preconditioning 2000um **Peak displacement (um)**	Amplitude of preconditioning 4000um **Peak displacement (um)**	Significance
1 versus 2	0.1Hz	Transverse	22670.85 +/- 4335.55	25958.10 +/- 6208.62	N/S
1 versus 2	0.3Hz	Transverse	21124.43 +/- 4100.14	22700.93 +/- 3015.74	N/S
3 versus 4	0.1Hz	Longitudinal	15148.58 +/- 5156.45	13413.83 +/- 2290.00	N/S
3 versus 4	0.3Hz	Longitudinal	14198.03 +/- 4009.02	14968.50 +/- 4373.83	N/S
5 versus 6	0.1Hz	Transverse	20712.38 +/- 5681.32	20016.68 +/- 4927.60	N/S
5 versus 6	0.3Hz	Transverse	19653.09 +/- 3313.76	18462.38 +/- 2480.32	N/S
7 versus 8	0.1Hz	Longitudinal	15112.95 +/- 4581.69	13268.93 +/- 2193.56	N/S
7 versus 8	0.3Hz	Longitudinal	15442.05 +/- 1729.06	13219.58 +/- 3465.63	N/S

Table 49 Comparison of peak displacement for strips of ovine descending thoracic aorta preconditioned at 2000um and 4000um.

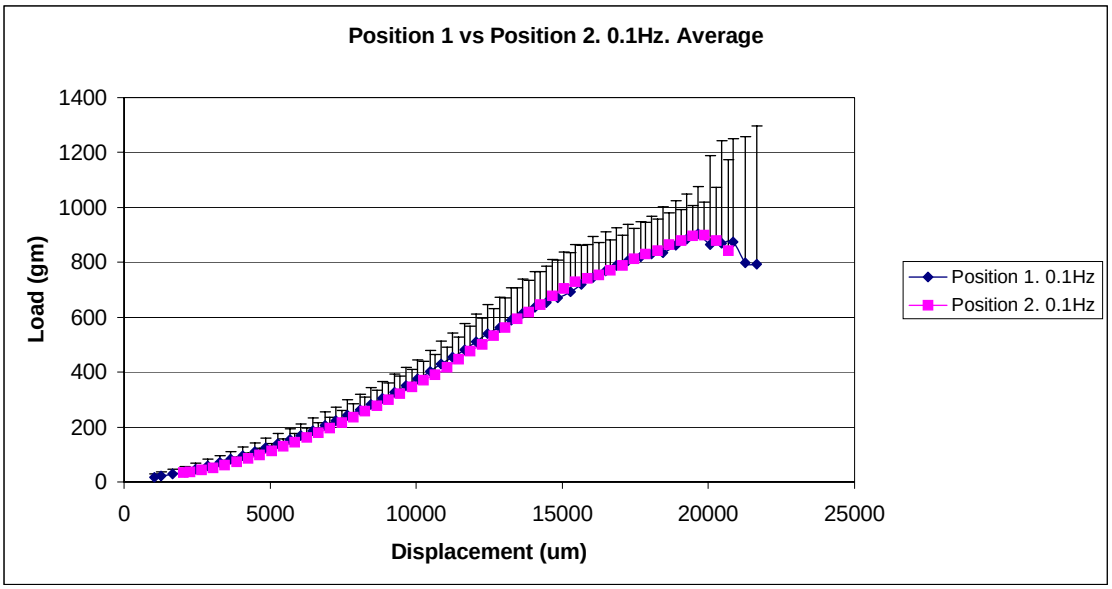


Figure 140 Comparison of strips of ovine descending thoracic aorta from position 1 (amplitude of preconditioning 2000um; frequency of preconditioning 0.1Hz; proximal; transverse) and position 2 (amplitude of preconditioning 4000um; frequency of preconditioning 0.1Hz; proximal; transverse).

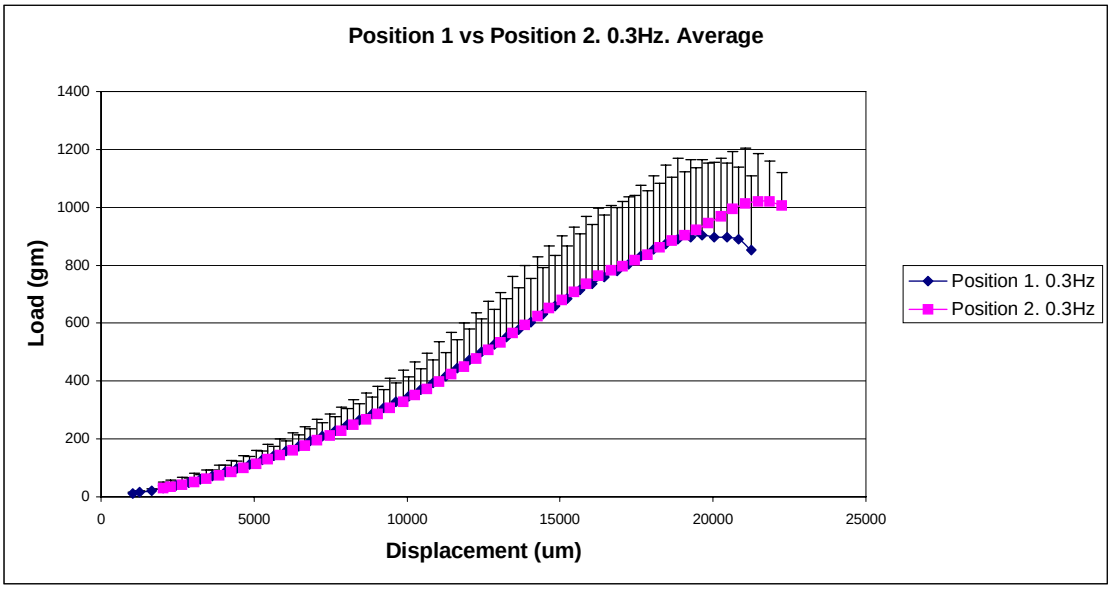


Figure 141 Comparison of strips of ovine descending thoracic aorta from position 1 (amplitude of preconditioning 2000um; frequency of preconditioning 0.3Hz; proximal; transverse) and position 2 (amplitude of preconditioning 4000um; frequency of preconditioning 0.3Hz; proximal; transverse).

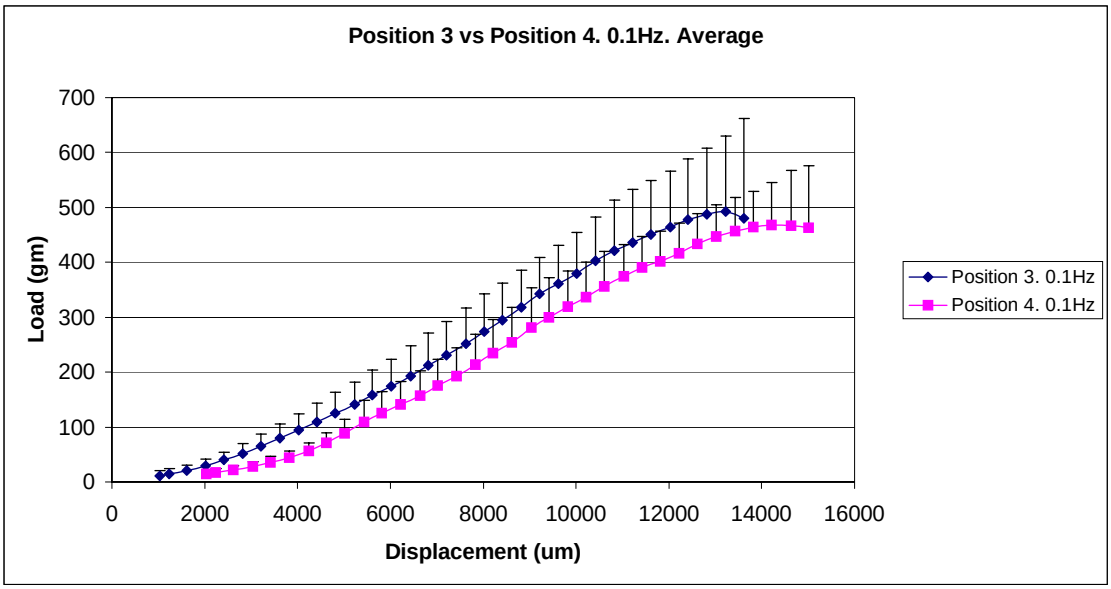


Figure 142 Comparison of strips of ovine descending thoracic aorta from position 3 (amplitude of preconditioning 2000um; frequency of preconditioning 0.1Hz; proximal; longitudinal) and position 4 (amplitude of preconditioning 4000um; frequency of preconditioning 0.1Hz; proximal; longitudinal).

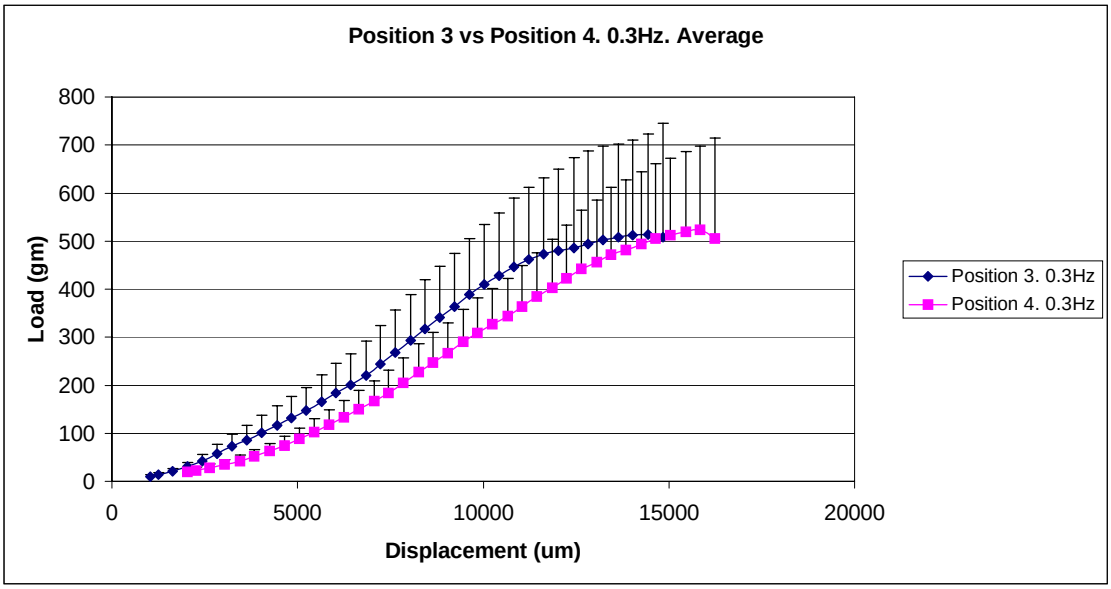


Figure 143 Comparison of strips of ovine descending thoracic aorta from position 3 (amplitude of preconditioning 2000um; frequency of preconditioning 0.3Hz; proximal; longitudinal) and position 4 (amplitude of preconditioning 4000um; frequency of preconditioning 0.3Hz; proximal; longitudinal).

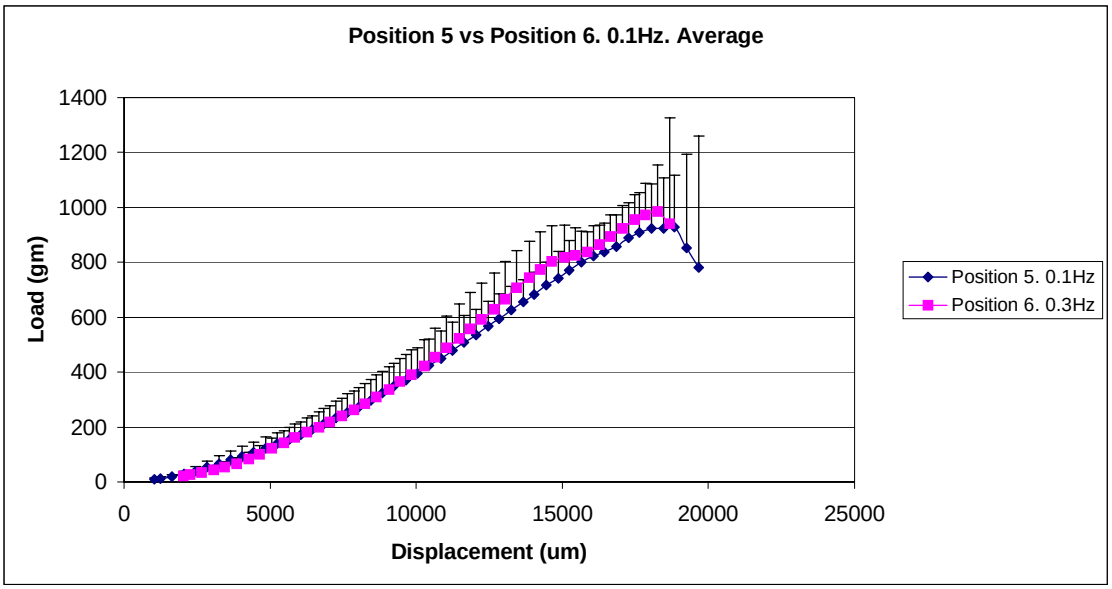


Figure 144 Comparison of strips of ovine descending thoracic aorta from position 5 (amplitude of preconditioning 2000um; frequency of preconditioning 0.1Hz; distal; transverse) and position 6 (amplitude of preconditioning 4000um; frequency of preconditioning 0.1Hz; distal; transverse).

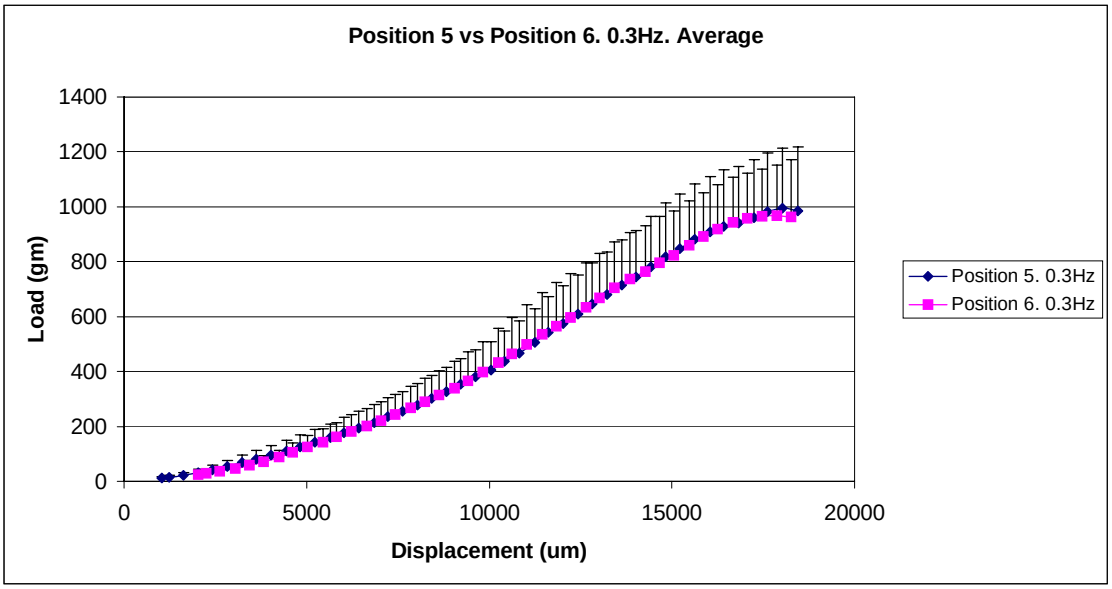


Figure 145 Comparison of strips of ovine descending thoracic aorta from position 5 (amplitude of preconditioning 2000um; frequency of preconditioning 0.3Hz; distal; transverse) and position 6 (amplitude of preconditioning 4000um; frequency of preconditioning 0.3Hz; distal; transverse).

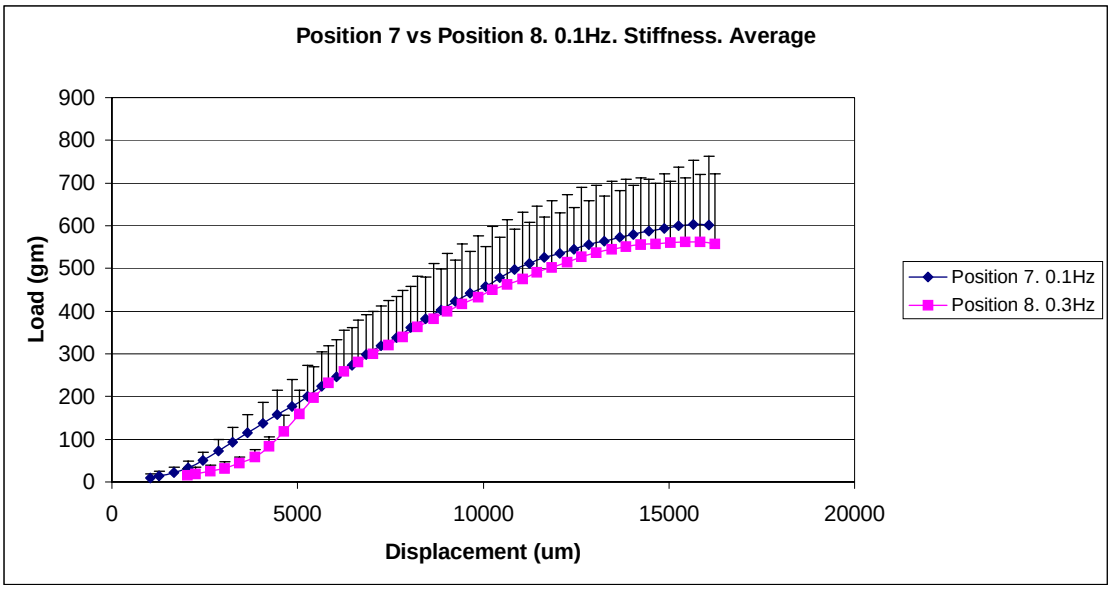


Figure 146 Comparison of strips of ovine descending thoracic aorta from position 7 (amplitude of preconditioning 2000um; frequency of preconditioning 0.1Hz; distal; longitudinal) and position 8 (amplitude of preconditioning 4000um; frequency of preconditioning 0.1Hz; distal; longitudinal).

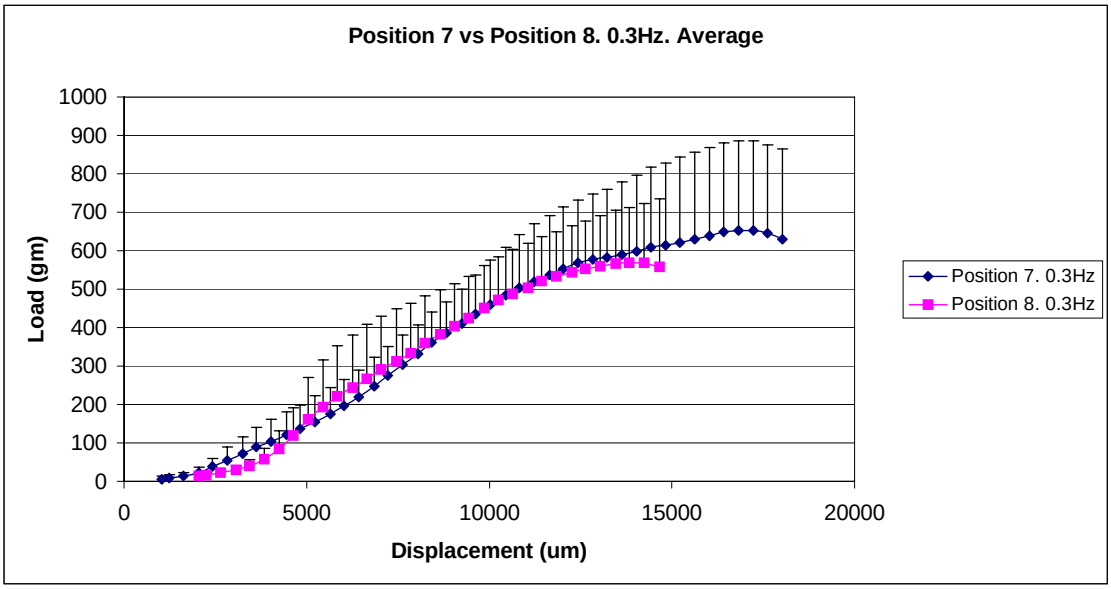


Figure 147 Comparison of strips of ovine descending thoracic aorta from position 7 (amplitude of preconditioning 2000um; frequency of preconditioning 0.1Hz; distal; longitudinal) and position 8 (amplitude of preconditioning 4000um; frequency of preconditioning 0.1Hz; distal; longitudinal).

8.3.4 Position of aortic strip

Stiffness 2 was greater in aortic strips from the distal descending thoracic aorta than the proximal descending thoracic aorta. Stiffness 2 was significantly greater in the between group comparison for group 4 (0.3Hz) versus group 8 (0.3 Hz) ($p < 0.005$). Stiffness 2 was greater in the distal groups than the proximal groups for all other between group comparisons; however this did not reach statistical significance.

There were no significant differences in stiffness 1, failure energy, rupture load, or rupture displacement between aortic strips from the proximal descending thoracic aorta and aortic strips from the distal descending thoracic aorta.

Position (n=8)	Frequency of preconditioning	Amplitude of preconditioning	Orientation	Proximal **Stiffness 1 (gm/um)**	Distal **Stiffness 1 (gm/um)**	Significance
1 versus 5	0.1Hz	2000um	Transverse	0.0271 +/- 0.0062	0.0251 +/- 0.0097	N/S
1 versus 5	0.3Hz	2000um	Transverse	0.0234 +/- 0.0063	0.0268 +/- 0.0097	N/S
2 versus 6	0.1Hz	4000um	Transverse	0.0263 +/- 0.0048	0.0274 +/- 0.0058	N/S
2 versus 6	0.3Hz	4000um	Transverse	0.0285 +/- 0.0079	0.0287 +/- 0.0056	N/S
3 versus 7	0.1Hz	2000um	Longitudinal	0.0197 +/- 0.0056	0.0265 +/- 0.0095	N/S
3 versus 7	0.3Hz	2000um	Longitudinal	0.0250 +/- 0.0105	0.0237 +/- 0.0129	N/S
4 versus 8	0.1Hz	4000um	Longitudinal	0.0161 +/- 0.0044	0.0175 +/- 0.0935	N/S
4 versus 8	0.3Hz	4000um	Longitudinal	0.0185 +/- 0.0051	0.0212 +/- 0.0129	N/S

Table 50 Comparison of stiffness 1 for strips from the proximal and distal ovine descending thoracic aorta.

Position (n=8)	Frequency of preconditioning	Amplitude of preconditioning	Orientation	Proximal **Stiffness 2 (gm/um)**	Distal **Stiffness 2 (gm/um)**	Significance
1 versus 5	0.1Hz	2000um	Transverse	0.0723 +/- 0.0080	0.0823 +/- 0.0115	N/S
1 versus 5	0.3Hz	2000um	Transverse	0.0688 +/- 0.0222	0.0863 +/- 0.0266	N/S
2 versus 6	0.1Hz	4000um	Transverse	0.0728 +/- 0.0233	0.0924 +/- 0.0169	N/S
2 versus 6	0.3Hz	4000um	Transverse	0.0681 +/- 0.0237	0.0894 +/- 0.0150	N/S
3 versus 7	0.1Hz	2000um	Longitudinal	0.0581 +/- 0.0130	0.0674 +/- 0.0118	N/S
3 versus 7	0.3Hz	2000um	Longitudinal	0.0639 +/- 0.0193	0.0738 +/- 0.0299	N/S
4 versus 8	0.1Hz	4000um	Longitudinal	0.0567 +/- 0.0128	0.0935 +/- 0.0420	N/S
4 versus 8	0.3Hz	4000um	Longitudinal	0.0561 +/- 0.0166	0.1076 +/- 0.0497	$P < 0.005$

Table 51 Comparison of stiffness 2 for strips from the proximal and distal ovine descending thoracic aorta.

Position (n=8)	Frequency of preconditioning	Amplitude of preconditioning	Orientation	Proximal **Failure energy (gm.um)**	Distal **Failure energy (gm.um)**	Significance
1 versus 5	0.1Hz	2000um	Transverse	1.24×10^7 +/- 3.93×10^6	1.13×10^7 +/- 6.05×10^6	N/S
1 versus 5	0.3Hz	2000um	Transverse	1.01×10^7 +/- 3.88×10^6	1.01×10^7 +/- 3.07×10^6	N/S
2 versus 6	0.1Hz	4000um	Transverse	1.69×10^7 +/- 6.65×10^6	1.19×10^7 +/- 4.56×10^6	N/S
2 versus 6	0.3Hz	4000um	Transverse	1.23×10^7 +/- 2.44×10^6	9.80×10^6 +/- 2.72×10^6	N/S
3 versus 7	0.1Hz	2000um	Longitudinal	4.96×10^6 +/- 3.54×10^6	6.10×10^6 +/- 5.03×10^6	N/S
3 versus 7	0.3Hz	2000um	Longitudinal	4.56×10^6 +/- 2.85×10^6	5.56×10^6 +/- 1.72×10^6	N/S
4 versus 8	0.1Hz	4000um	Longitudinal	3.36×10^6 +/- 9.82×10^5	4.39×10^6 +/- 9.26×10^5	N/S
4 versus 8	0.3Hz	4000um	Longitudinal	4.84×10^6 +/- 3.61×10^6	4.94×10^6 +/- 3.20×10^6	N/S

Table 52 Comparison of failure energy for strips from the proximal and distal ovine descending thoracic aorta.

Position (n=8)	Frequency of preconditioning	Amplitude of preconditioning	Orientation	Proximal **Peak load (gm)**	Distal **Peak load (gm)**	Significance
1 versus 5	0.1Hz	2000um	Transverse	1155.45 +/- 184.22	1095.19 +/- 227.45	N/S
1 versus 5	0.3Hz	2000um	Transverse	1030.38 +/- 297.99	1110.86 +/- 236.01	N/S
2 versus 6	0.1Hz	4000um	Transverse	1245.66 +/- 240.92	1173.88 +/- 167.59	N/S
2 versus 6	0.3Hz	4000um	Transverse	1117.02 +/- 100.02	1080.03 +/- 189.74	N/S
3 versus 7	0.1Hz	2000um	Longitudinal	581.45 +/- 188.40	648.87 +/- 248.67	N/S
3 versus 7	0.3Hz	2000um	Longitudinal	595.82 +/- 213.23	677.61 +/- 205.25	N/S
4 versus 8	0.1Hz	4000um	Longitudinal	487.85 +/- 82.97	572.97 +/- 141.42	N/S
4 versus 8	0.3Hz	4000um	Longitudinal	586.79 +/- 289.51	590.43 +/- 165.01	N/S

Table 53 Comparison of peak load for strips from the proximal and distal ovine descending thoracic aorta

Position (n=8)	Frequency of preconditioning	Amplitude of preconditioning	Orientation	Proximal **Peak displacement (um)**	Distal **Peak displacement (um)**	Significance
1 versus 5	0.1Hz	2000um	Transverse	22670.85 +/- 4335.55	20712.38 +/- 5681.32	N/S
1 versus 5	0.3Hz	2000um	Transverse	21124.43 +/- 4100.14	19653.09 +/- 3313.76	N/S
2 versus 6	0.1Hz	4000um	Transverse	25958.10 +/- 6208.62	20016.68 +/- 4927.60	N/S
2 versus 6	0.3Hz	4000um	Transverse	22700.93 +/- 3015.74	18462.38 +/- 2480.32	N/S
3 versus 7	0.1Hz	2000um	Longitudinal	15148.58 +/- 5156.45	15112.95 +/- 4581.69	N/S
3 versus 7	0.3Hz	2000um	Longitudinal	14198.03 +/- 4009.02	15442.05 +/- 1729.06	N/S
4 versus 8	0.1Hz	4000um	Longitudinal	13413.83 +/- 2290.00	13268.93 +/- 2193.56	N/S
4 versus 8	0.3Hz	4000um	Longitudinal	14968.50 +/- 4373.83	13219.58 +/- 3465.63	N/S

Table 54 Comparison of peak displacement for strips from the proximal and distal ovine descending thoracic aorta.

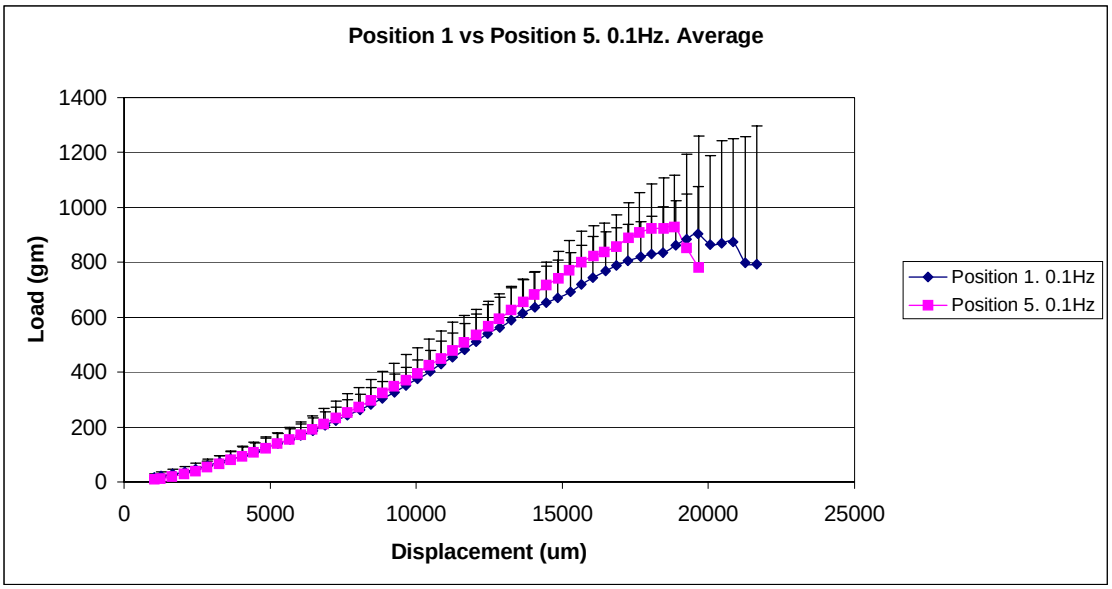


Figure 148 Comparison of strips of ovine descending thoracic aorta from position 1 (amplitude of preconditioning 2000um; frequency of preconditioning 0.1Hz; proximal; transverse) and position 5 (amplitude of preconditioning 2000um; frequency of preconditioning 0.1Hz; distal; transverse).

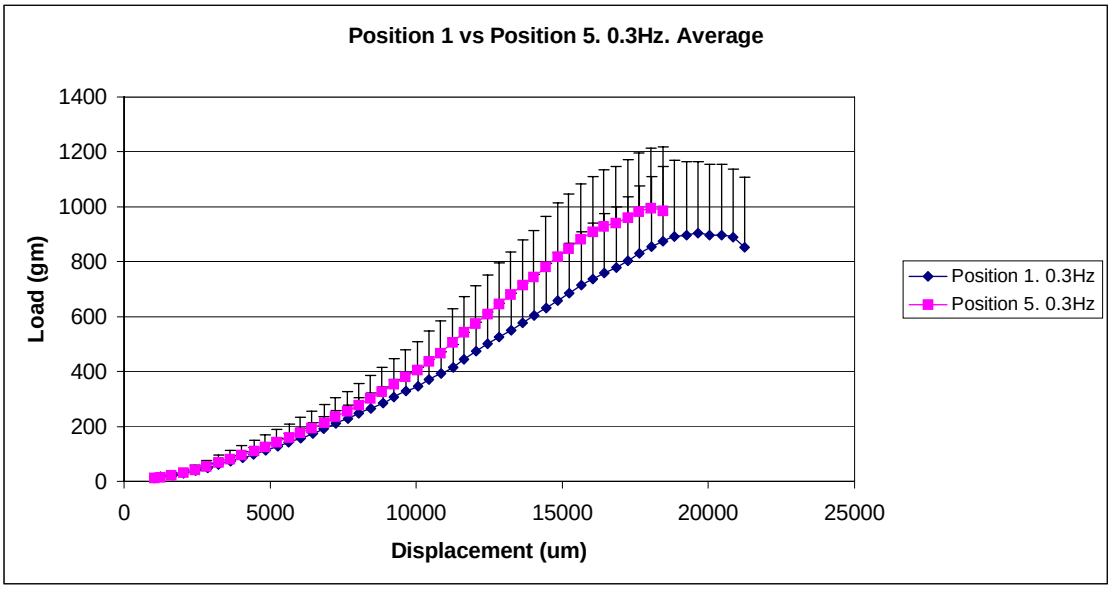


Figure 149 Comparison of strips of ovine descending thoracic aorta from position 1 (amplitude of preconditioning 2000um; frequency of preconditioning 0.3Hz; proximal; transverse) and position 5 (amplitude of preconditioning 2000um; frequency of preconditioning 0.3Hz; distal; transverse).

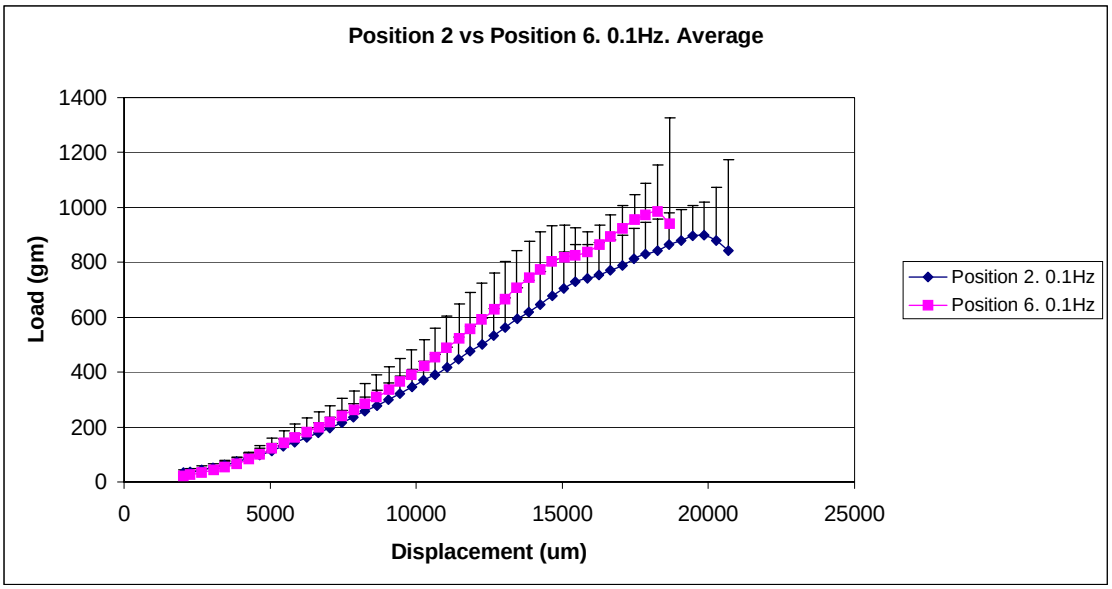


Figure 150 Comparison of strips of ovine descending thoracic aorta from position 2 (amplitude of preconditioning 4000um; frequency of preconditioning 0.1Hz; proximal; transverse) and position 6 (amplitude of preconditioning 4000um; frequency of preconditioning 0.1Hz; distal; transverse).

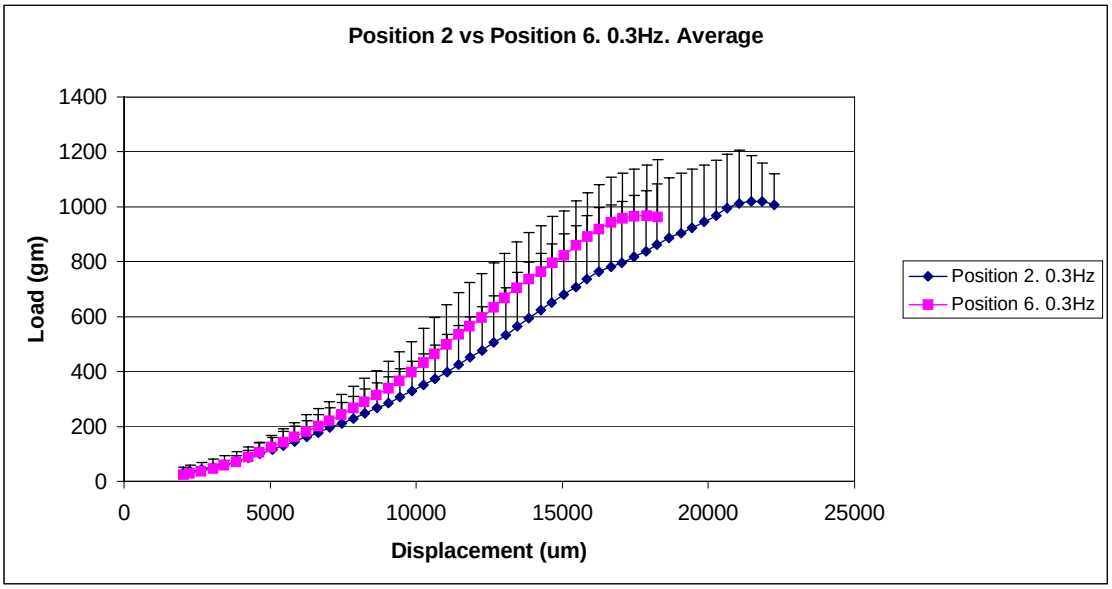


Figure 151 Comparison of strips of ovine descending thoracic aorta from position 2 (amplitude of preconditioning 4000um; frequency of preconditioning 0.3Hz; proximal; transverse) and position 6 (amplitude of preconditioning 4000um; frequency of preconditioning 0.3Hz; distal; transverse).

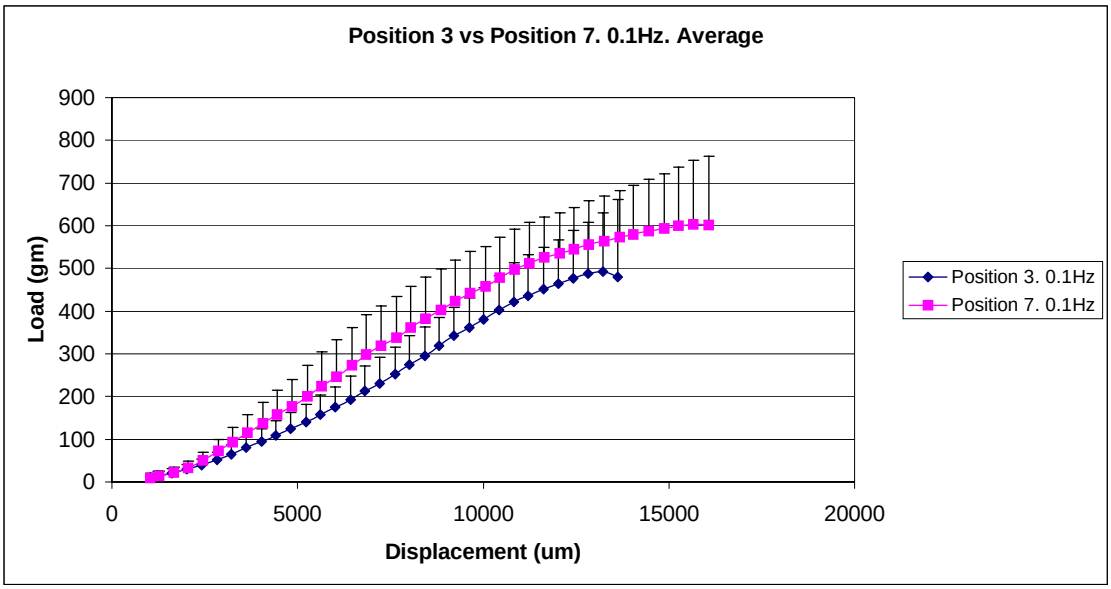


Figure 152 Comparison of strips of ovine descending thoracic aorta from position 3 (amplitude of preconditioning 2000um; frequency of preconditioning 0.1Hz; proximal; longitudinal) and position 7 (amplitude of preconditioning 2000um; frequency of preconditioning 0.1Hz; distal; longitudinal).

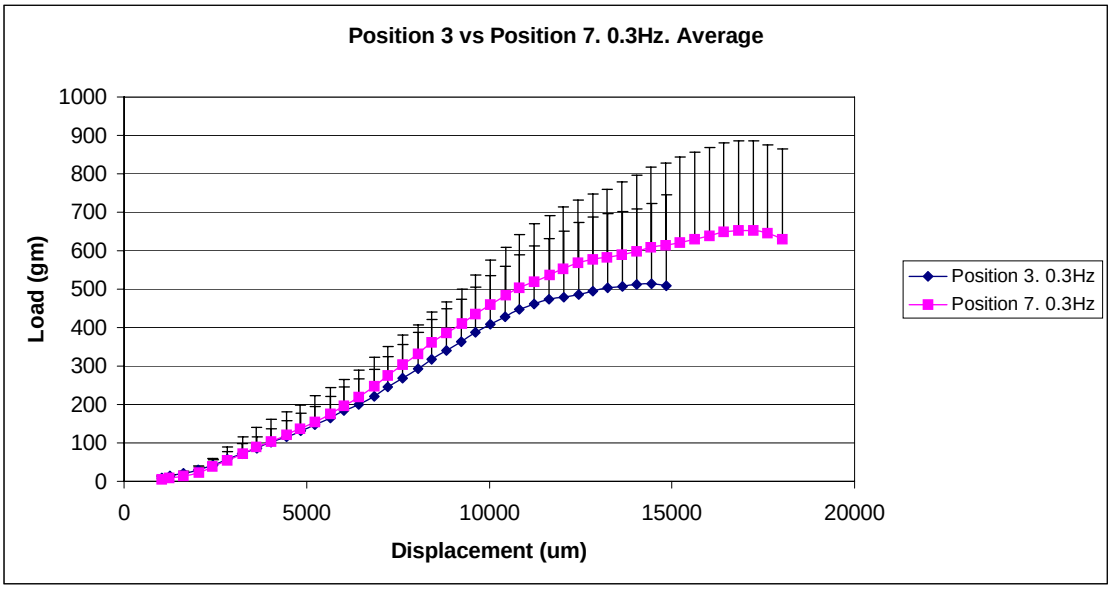


Figure 153 Comparison of strips of ovine descending thoracic aorta from position 3 (amplitude of preconditioning 2000um; frequency of preconditioning 0.3Hz; proximal; longitudinal) and position 7 (amplitude of preconditioning 2000um; frequency of preconditioning 0.3Hz; distal; longitudinal).

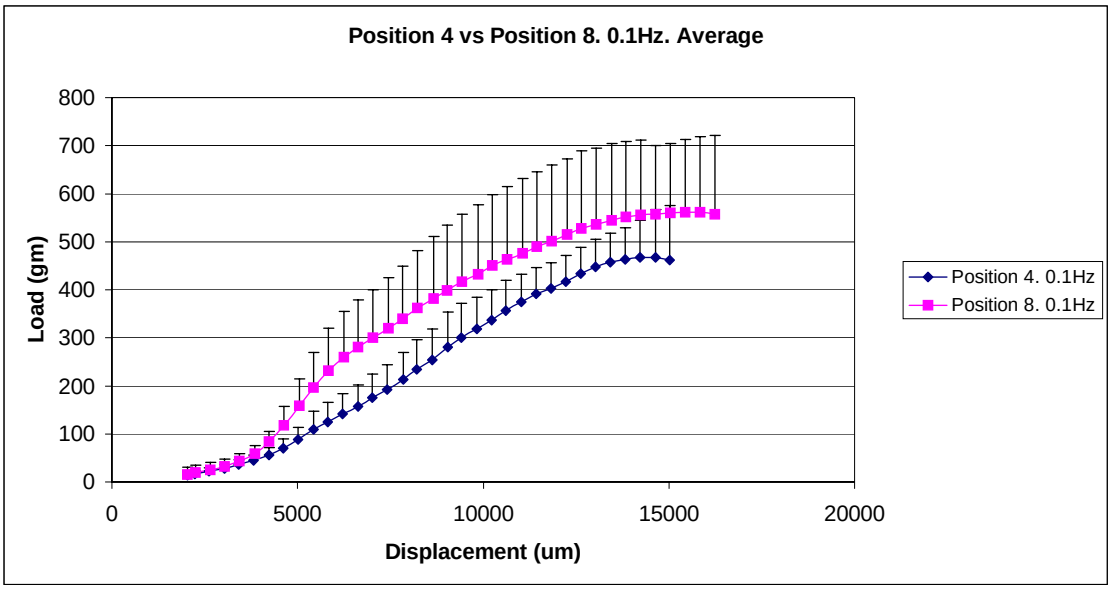


Figure 154 Comparison of strips of ovine descending thoracic aorta from position 4 (amplitude of preconditioning 4000um; frequency of preconditioning 0.1Hz; proximal; longitudinal) and position 8 (amplitude of preconditioning 4000um; frequency of preconditioning 0.1Hz; distal; longitudinal).

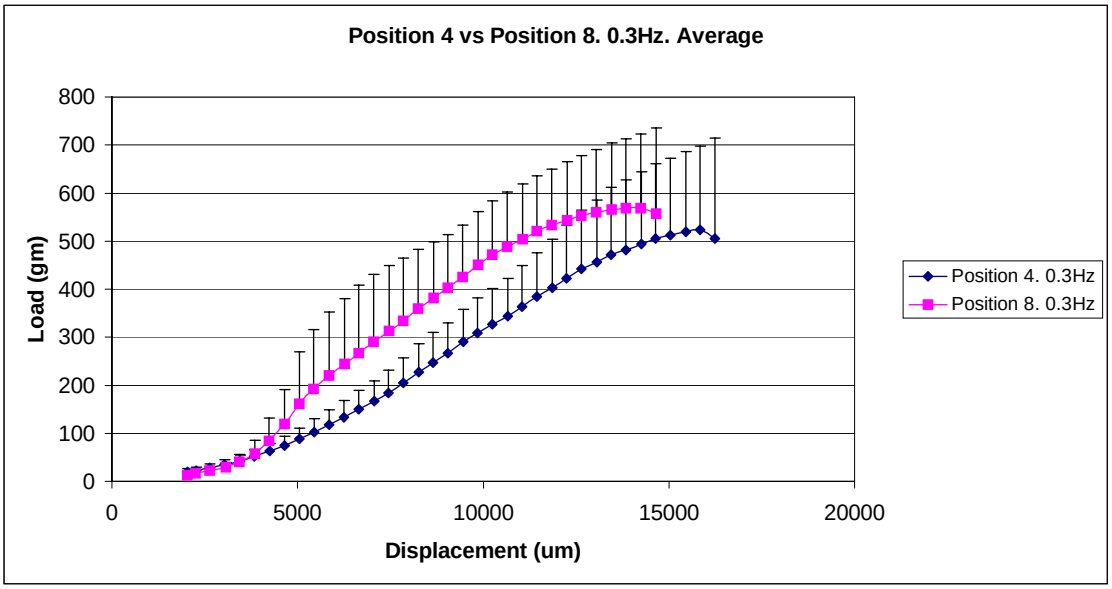


Figure 155 Comparison of strips of ovine descending thoracic aorta from position 4 (amplitude of preconditioning 4000um; frequency of preconditioning 0.3Hz; proximal; longitudinal) and position 8 (amplitude of preconditioning 4000um; frequency of preconditioning 0.3Hz; distal; longitudinal).

8.3.5 Orientation of aortic strip

Failure energy and rupture load were significantly greater in transverse aortic strips than longitudinal aortic strips (groups 1, 2, 5, 6 versus groups 3, 4, 7, and 8). Rupture displacement was significantly greater in transverse aortic strips than longitudinal aortic strips; however significance was reached only in the proximal descending thoracic aorta (groups 1 and 2 versus groups 3 and 4). There were no significant differences in stiffness 1 and stiffness 2 between transverse aortic strips and longitudinal aortic strips.

Position (n=8)	Frequency of preconditioning	Amplitude of preconditioning	Transverse **Stiffness 1 (gm/um)**	Longitudinal **Stiffness 1 (gm/um)**	Significance
1 versus 3	0.1Hz	2000um	0.0271 +/- 0.0062	0.0197 +/- 0.0056	N/S
1 versus 3	0.3Hz	2000um	0.0234 +/- 0.0063	0.0250 +/- 0.0105	N/S
2 versus 4	0.1Hz	4000um	0.0263 +/- 0.0048	0.0161 +/- 0.0044	N/S
2 versus 4	0.3Hz	4000um	0.0285 +/- 0.0079	0.0185 +/- 0.0051	N/S
5 versus 7	0.1Hz	2000um	0.0251 +/- 0.0097	0.0265 +/- 0.0095	N/S
5 versus 7	0.3Hz	2000um	0.0268 +/- 0.0097	0.0237 +/- 0.0129	N/S
6 versus 8	0.1Hz	4000um	0.0274 +/- 0.0058	0.0175 +/- 0.0935	N/S
6 versus 8	0.3Hz	4000um	0.0287 +/- 0.0056	0.0212 +/- 0.0129	N/S

Table 55 Comparison of stiffness 1 for transverse and longitudinal strips from the ovine descending thoracic aorta..

Position (n=8)	Frequency of preconditioning	Amplitude of preconditioning	Transverse **Stiffness 2 (gm/um)**	Longitudinal **Stiffness 2 (gm/um)**	Significance
1 versus 3	0.1Hz	2000um	0.0723 +/- 0.0080	0.0581 +/- 0.0130	N/S
1 versus 3	0.3Hz	2000um	0.0688 +/- 0.0222	0.0639 +/- 0.0193	N/S
2 versus 4	0.1Hz	4000um	0.0728 +/- 0.0233	0.0567 +/- 0.0128	N/S
2 versus 4	0.3Hz	4000um	0.0681 +/- 0.0237	0.0561 +/- 0.0166	N/S
5 versus 7	0.1Hz	2000um	0.0823 +/- 0.0115	0.0674 +/- 0.0118	N/S
5 versus 7	0.3Hz	2000um	0.0863 +/- 0.0266	0.0738 +/- 0.0299	N/S
6 versus 8	0.1Hz	4000um	0.0924 +/- 0.0169	0.0935 +/- 0.0420	N/S
6 versus 8	0.3Hz	4000um	0.0894 +/- 0.0150	0.1076 +/- 0.0497	N/S

Table 56 Comparison of stiffness 2 for transverse and longitudinal strips from the ovine descending thoracic aorta.

Position (n=8)	Frequency of preconditioning	Amplitude of preconditioning	Transverse **Failure energy (gm.um)**	Longitudinal **Failure energy (gm.um)**	Significance
1 versus 3	0.1Hz	2000um	1.24×10^7 +/- 3.93×10^6	4.96×10^6 +/- 3.54×10^6	$P < 0.05$
1 versus 3	0.3Hz	2000um	1.01×10^7 +/- 3.88×10^6	4.56×10^6 +/- 2.85×10^6	N/S
2 versus 4	0.1Hz	4000um	1.69×10^7 +/- 6.65×10^6	3.36×10^6 +/- 9.82×10^5	$P < 0.001$
2 versus 4	0.3Hz	4000um	1.23×10^7 +/- 2.44×10^6	4.84×10^6 +/- 3.61×10^6	$P < 0.05$
5 versus 7	0.1Hz	2000um	1.13×10^7 +/- 6.05×10^6	6.10×10^6 +/- 5.03×10^6	N/S
5 versus 7	0.3Hz	2000um	1.01×10^7 +/- 3.07×10^6	5.56×10^6 +/- 1.72×10^6	N/S
6 versus 8	0.1Hz	4000um	1.19×10^7 +/- $4.56x\ 10^6$	4.39×10^6 +/- 9.26×10^5	$P < 0.05$
6 versus 8	0.3Hz	4000um	9.80×10^6 +/- 2.72×10^6	4.94×10^6 +/- 3.20×10^6	N/S

Table 57 Comparison of failure energy for transverse and longitudinal strips from the ovine descending thoracic aorta.

Position (n=8)	Frequency of preconditioning	Amplitude of preconditioning	Transverse **Peak load (gm)**	Longitudinal **Peak load (gm)**	Significance
1 versus 3	0.1Hz	2000um	1155.45 +/- 184.22	581.45 +/- 188.40	P < 0.001
1 versus 3	0.3Hz	2000um	1030.38 +/- 297.99	595.82 +/- 213.23	P = 0.005
2 versus 4	0.1Hz	4000um	1245.66 +/- 240.92	487.85 +/- 82.97	P < 0.001
2 versus 4	0.3Hz	4000um	1117.02 +/- 100.02	586.79 +/- 289.51	P < 0.001
5 versus 7	0.1Hz	2000um	1095.19 +/- 227.45	648.87 +/- 248.67	P < 0.005
5 versus 7	0.3Hz	2000um	1110.86 +/- 236.01	677.61 +/- 205.25	P < 0.01
6 versus 8	0.1Hz	4000um	1173.88 +/- 167.59	572.97 +/- 141.42	P < 0.001
6 versus 8	0.3Hz	4000um	1080.03 +/- 189.74	590.43 +/- 165.01	P = 0.001

Table 58 Comparison of peak load for transverse and longitudinal strips from the ovine descending thoracic aorta.

Position (n=8)	Frequency of preconditioning	Amplitude of preconditioning	Transverse **Peak displacement (um)**	Longitudinal **Peak displacement (um)**	Significance
1 versus 3	0.1Hz	2000um	22670.85 +/- 4335.55	15148.58 +/- 5156.45	P < 0.05
1 versus 3	0.3Hz	2000um	21124.43 +/- 4100.14	14198.03 +/- 4009.02	N/S
2 versus 4	0.1Hz	4000um	25958.10 +/- 6208.62	13413.83 +/- 2290.00	P < 0.001
2 versus 4	0.3Hz	4000um	22700.93 +/- 3015.74	14968.50 +/- 4373.83	P < 0.05
5 versus 7	0.1Hz	2000um	20712.38 +/- 5681.32	18462.38 +/- 2480.32	N/S
5 versus 7	0.3Hz	2000um	19653.09 +/- 3313.76	15112.95 +/- 4581.69	N/S
6 versus 8	0.1Hz	4000um	20016.68 +/- 4927.60	15442.05 +/- 1729.06	N/S
6 versus 8	0.3Hz	4000um	18462.38 +/- 2480.32	13268.93 +/- 2193.56	N/S

Table 59 Comparison of peak displacement for transverse and longitudinal strips from the ovine descending thoracic aorta.

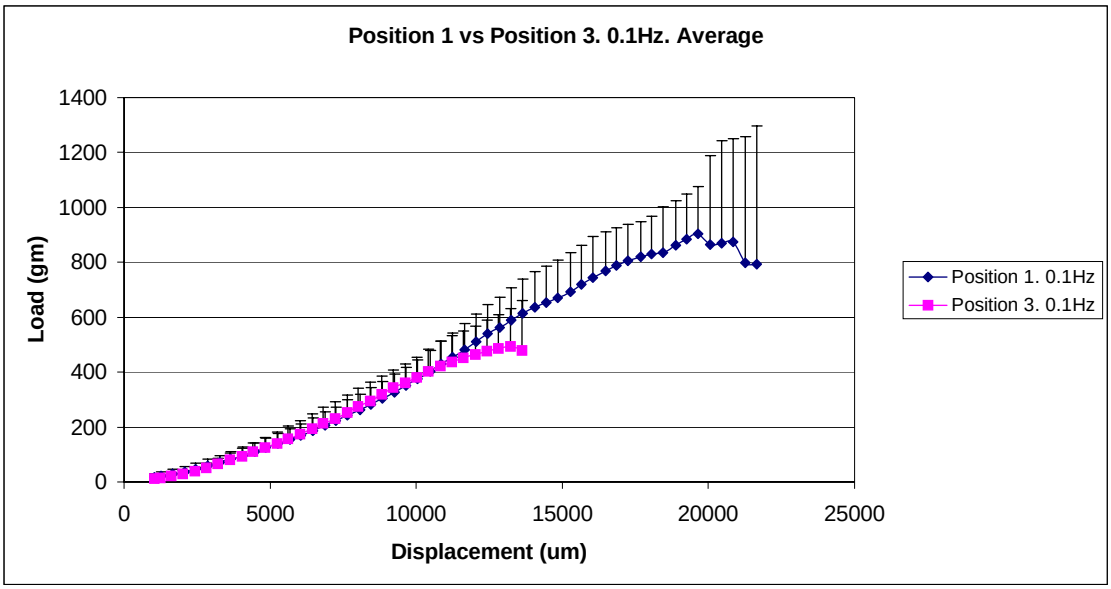


Figure 156 Comparison of strips of ovine descending thoracic aorta from position 1 (amplitude of preconditioning 2000um; frequency of preconditioning 0.1Hz; proximal; transverse) and position 3 (amplitude of preconditioning 2000um; frequency of preconditioning 0.1Hz; proximal; longitudinal).

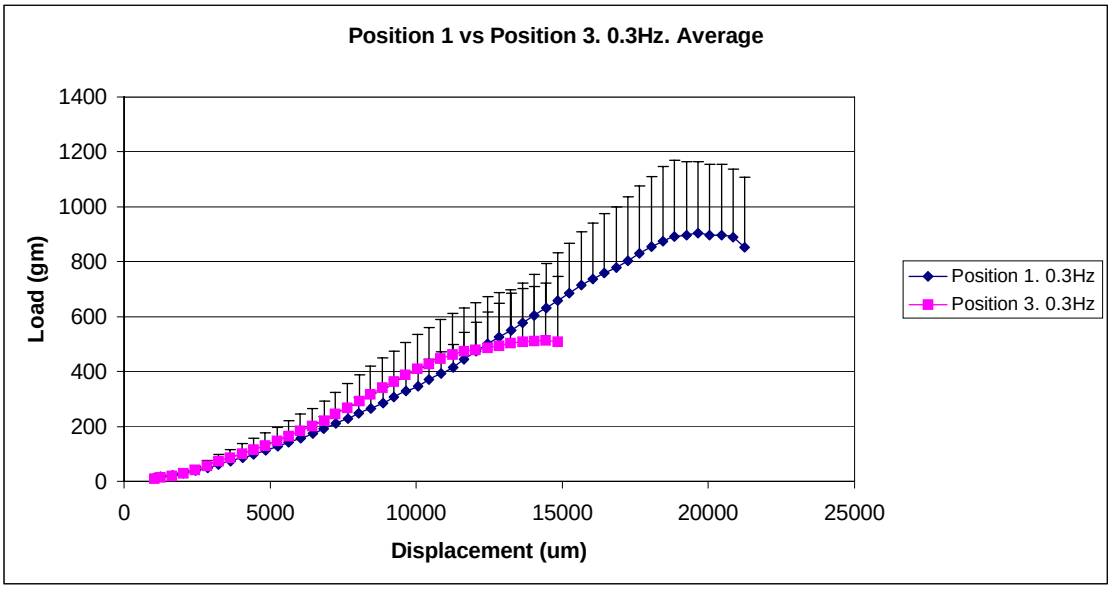


Figure 157 Comparison of strips of ovine descending thoracic aorta from position 1 (amplitude of preconditioning 2000um; frequency of preconditioning 0.3Hz; proximal; transverse) and position 3 (amplitude of preconditioning 2000um; frequency of preconditioning 0.3Hz; proximal; longitudinal).

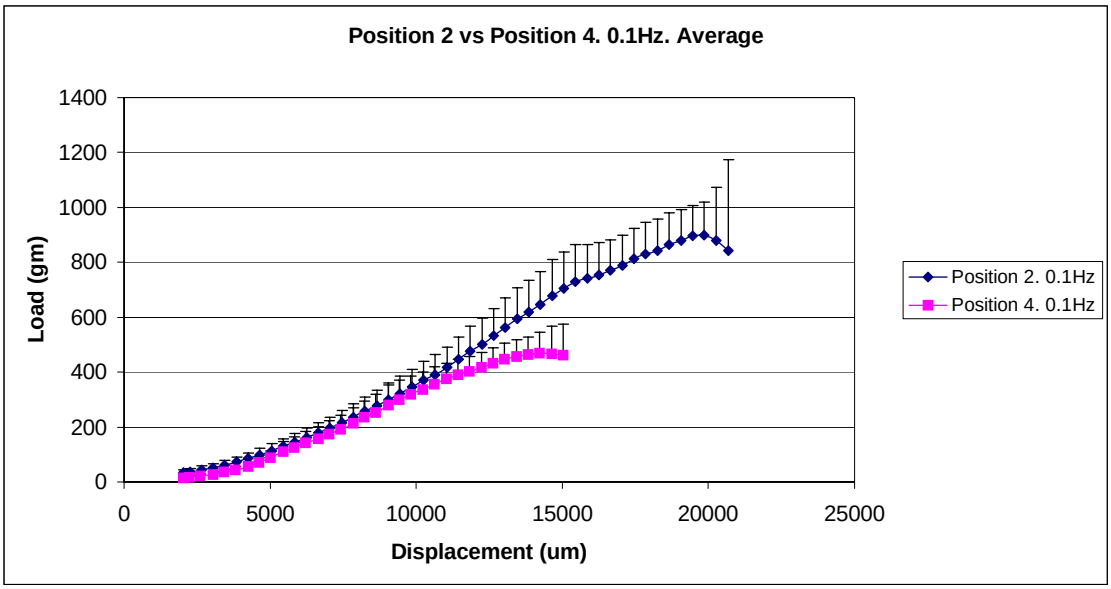


Figure 158 Comparison of strips of ovine descending thoracic aorta from position 2 (amplitude of preconditioning 4000um; frequency of preconditioning 0.1Hz; proximal; transverse) and position 4 (amplitude of preconditioning 4000um; frequency of preconditioning 0.1Hz; proximal; longitudinal).

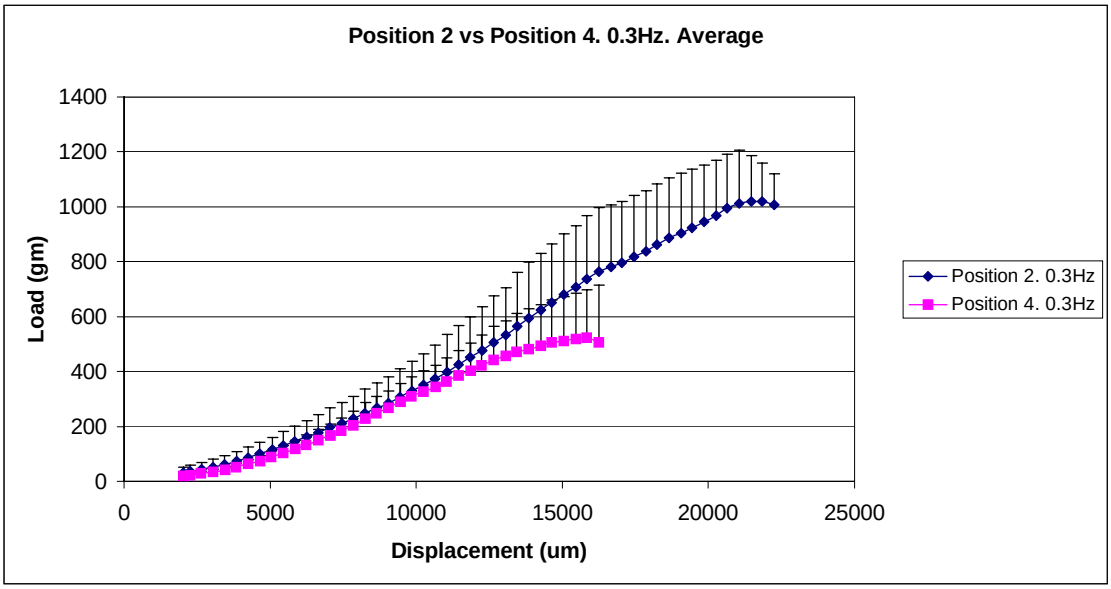


Figure 159 Comparison of strips of ovine descending thoracic aorta from position 2 (amplitude of preconditioning 4000um; frequency of preconditioning 0.3Hz; proximal; transverse) and position 4 (amplitude of preconditioning 4000um; frequency of preconditioning 0.3Hz; proximal; longitudinal).

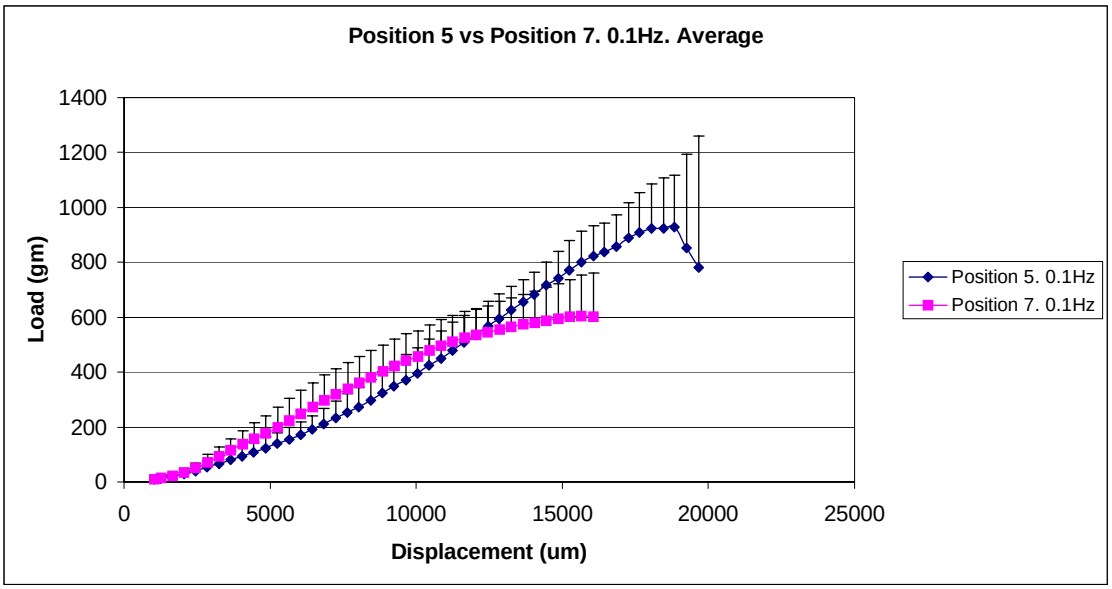


Figure 160 Comparison of strips of ovine descending thoracic aorta from position 5 (amplitude of preconditioning 2000um; frequency of preconditioning 0.1Hz; proximal; transverse) and position 7 (amplitude of preconditioning 2000um; frequency of preconditioning 0.1Hz; proximal; longitudinal).

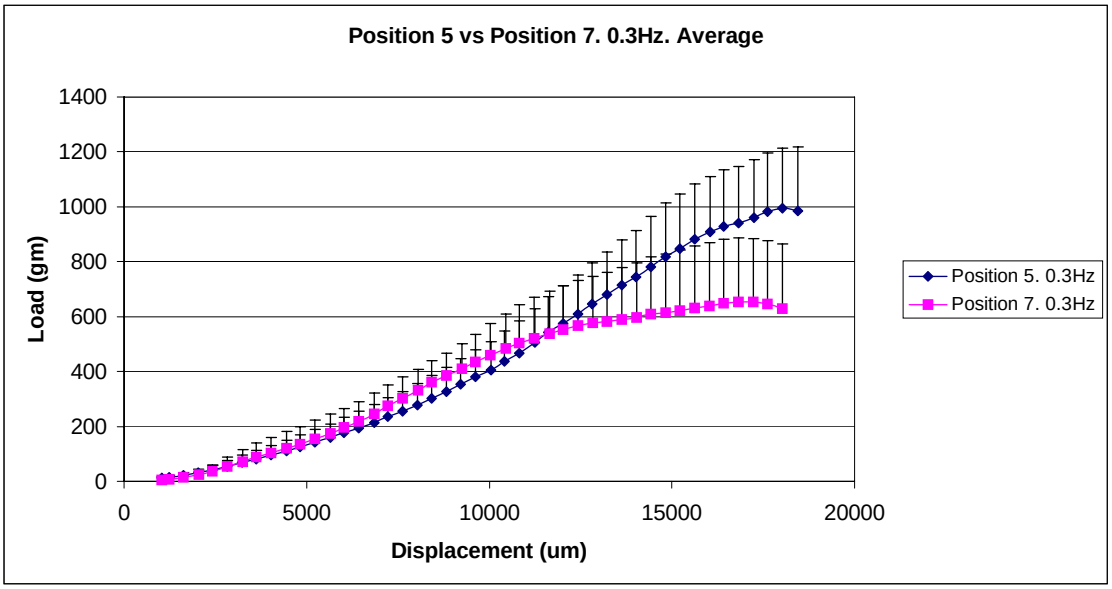


Figure 161 Comparison of strips of ovine descending thoracic aorta from position 5 (amplitude of preconditioning 2000um; frequency of preconditioning 0.3Hz; proximal; transverse) and position 7 (amplitude of preconditioning 2000um; frequency of preconditioning 0.3Hz; proximal; longitudinal).

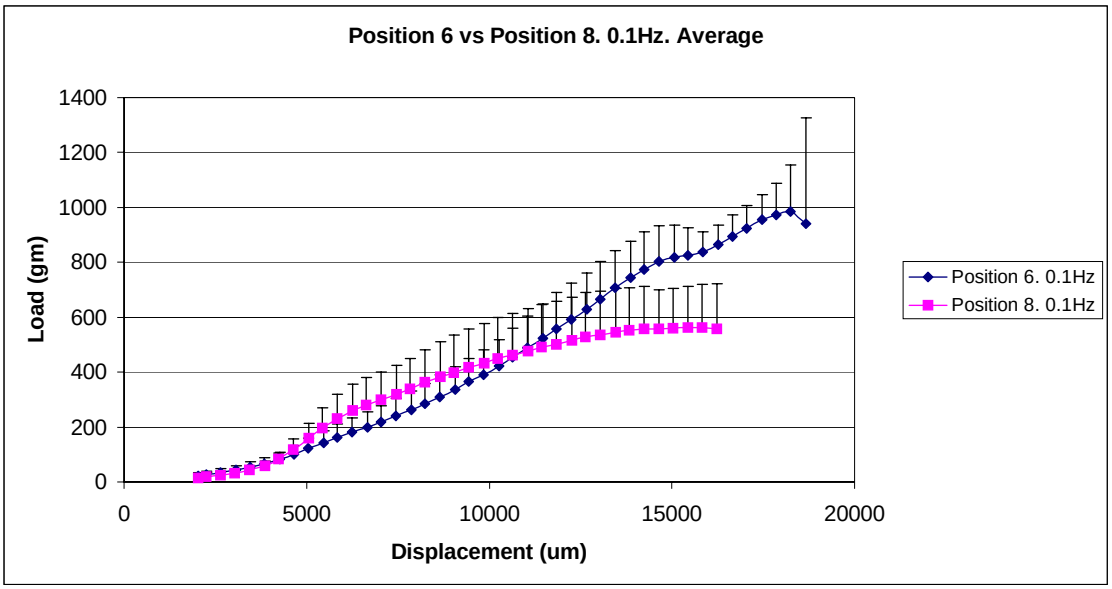


Figure 162 Comparison of strips of ovine descending thoracic aorta from position 6 (amplitude of preconditioning 4000um; frequency of preconditioning 0.1Hz; proximal; transverse) and position 8 (amplitude of preconditioning 4000um; frequency of preconditioning 0.1Hz; proximal; longitudinal).

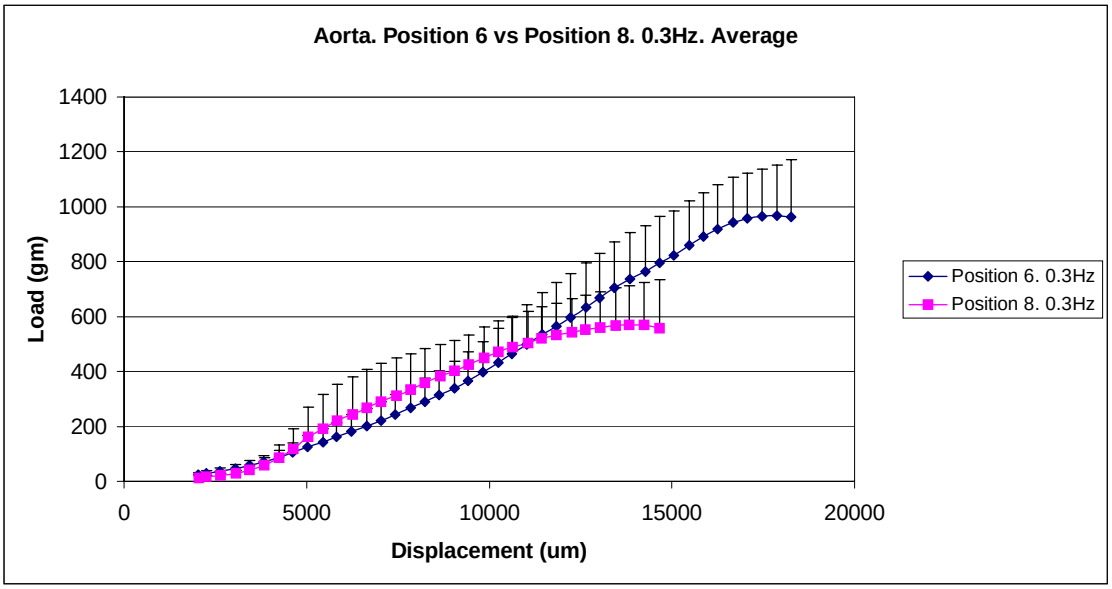


Figure 163 Comparison of strips of ovine descending thoracic aorta from position 6 (amplitude of preconditioning 4000um; frequency of preconditioning 0.3Hz; proximal; transverse) and position 8 (amplitude of preconditioning 4000um; frequency of preconditioning 0.3Hz; proximal; longitudinal).

8.3.6 Elastic wrap

There were no significant differences in stiffness 1 and stiffness 2 in the transverse and longitudinal orientations for the 12% wrap material. Stiffness 1 and stiffness 2 were significantly greater in the transverse orientation than the longitudinal orientation for the 4% material.

Material (N = 4)	Parameter	Transverse	Longitudinal	Significance
12%	Stiffness 1	0.0290 +/- 0.0006	0.0266 +/- 0.0006	N/S
12%	Stiffness 2	0.0087 +/- 0.0010	0.0088 +/- 0.0012	N/S
4%	Stiffness 1	0.0959 +/- 0.0111	0.0697 +/- 0.0064	$P < 0.001$
4%	Stiffness 2	0.0317 +/- 0.0065	0.0208 +/- 0.0013	$P < 0.005$

Figure 164 Comparison of stiffness 1and stiffness 2 of transverse and longitudinal strips of elastic wrap material.

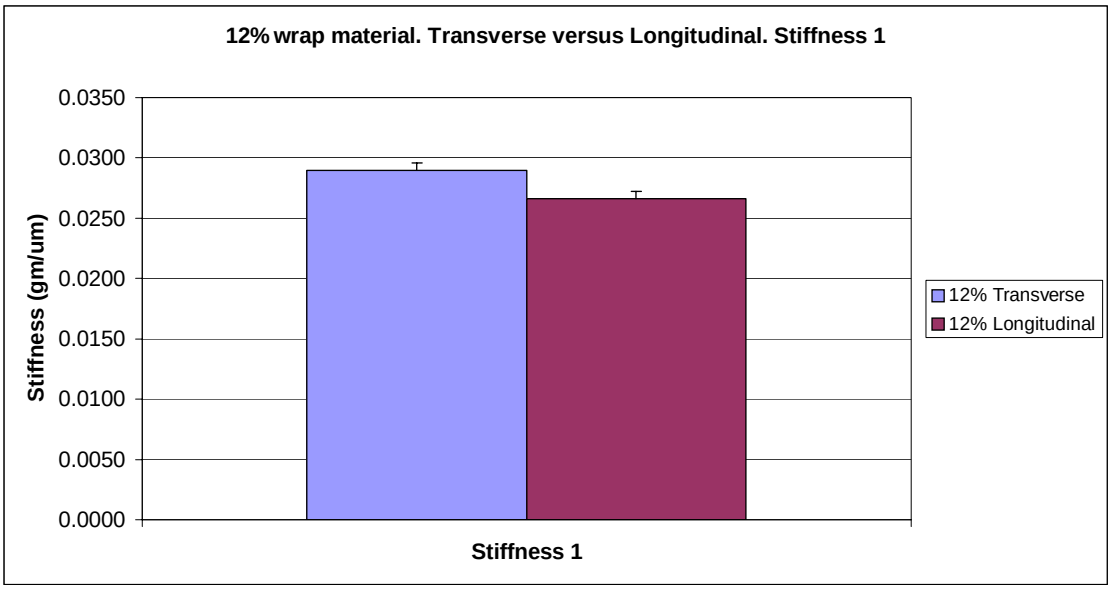


Figure 165 Comparison of stiffness 1 of transverse and longitudinal strips of the 12% wrap material.

Figure 166 Comparison of stiffness 1 of transverse and longitudinal strips of the 4% wrap material.

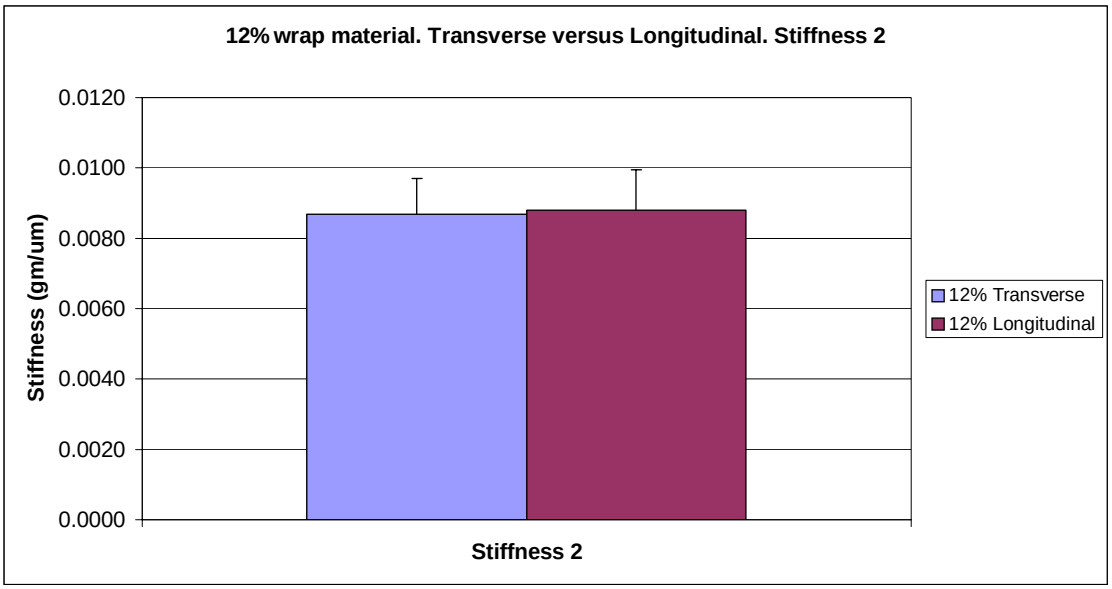


Figure 167 Comparison of stiffness 2 of transverse and longitudinal strips of the 12% wrap material.

Figure 168 Comparison of stiffness 2 of transverse and longitudinal strips of the 4% wrap material.

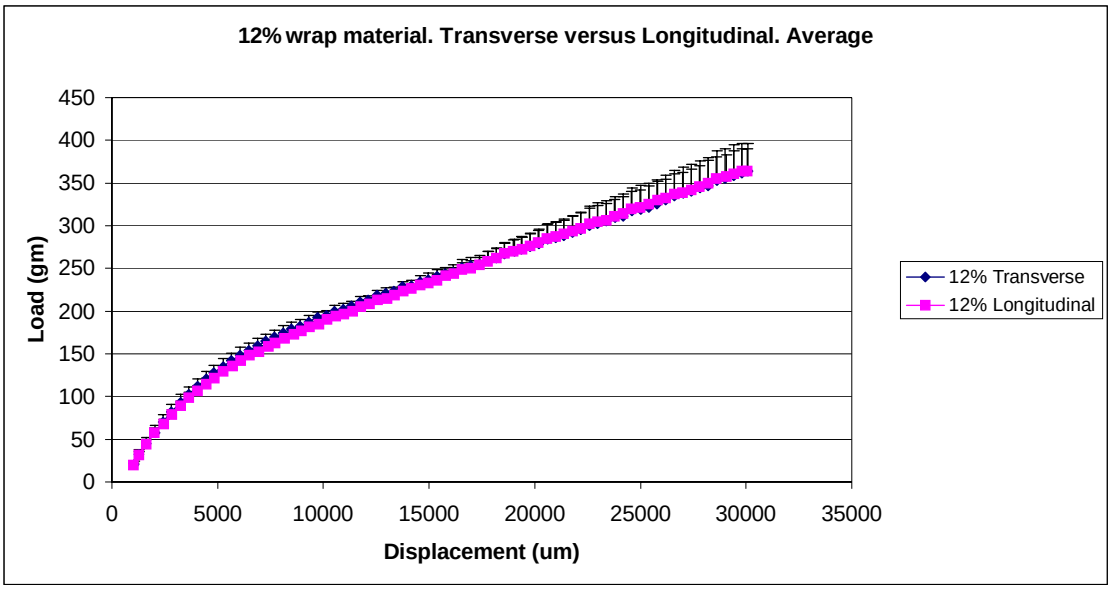


Figure 169 Comparison of transverse and longitudinal strips of the 12% wrap material**.**

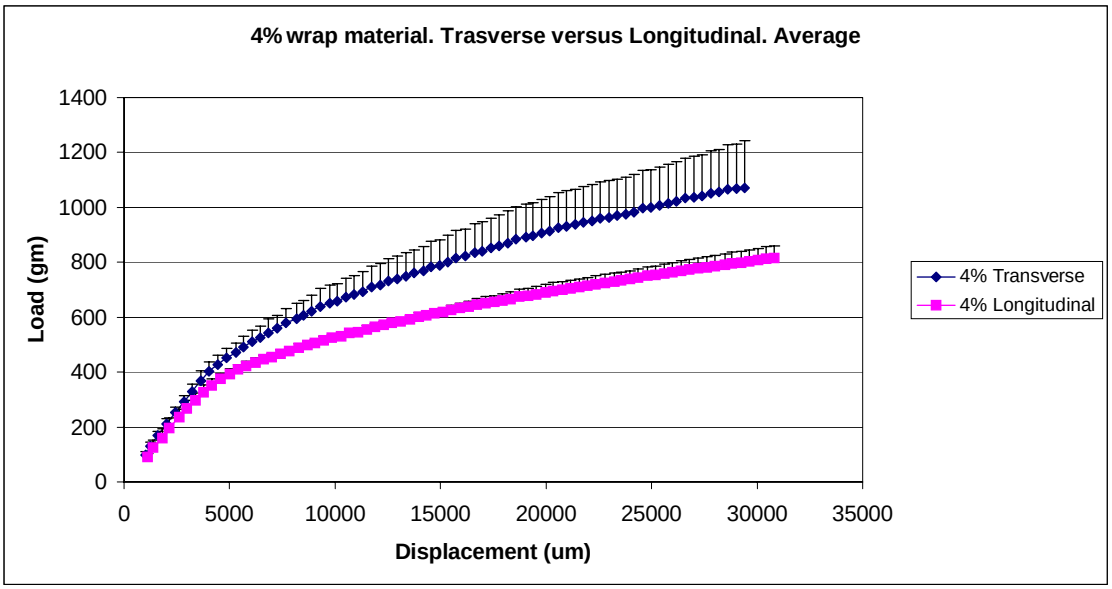


Figure 170 Comparison of transverse and longitudinal strips of the 4% wrap material**.**

The 4% material was significantly stiffer than the 12% material. Stiffness 1 of the 4% material was 3.3 times greater than stiffness 1 of the 12% material in the transverse orientation. Stiffness 2 of the 4% material was 3.6 times greater than stiffness 2 of the 12% material in the transverse orientation.

Stiffness 1 of the 4% material was 2.6 times greater than stiffness 1 of the 12% material in the longitudinal orientation. Stiffness 2 of the 4% material was 2.4 times greater than stiffness 2 of the 12% material in the longitudinal orientation.

Orientation	Stiffness	12% material	4% material	Significance
Transverse	Stiffness 1	0.0290 +/- 0.0006	0.0959 +/- 0.0111	$P < 0.001$
Transverse	Stiffness 2	0.0087 +/- 0.0010	0.0317 +/- 0.0065	$P < 0.001$
Longitudinal	Stiffness 1	0.0266 +/- 0.0006	0.0697 +/- 0.0064	$P < 0.001$
Longitudinal	Stiffness 2	0.0088 +/- 0.0012	0.0208 +/- 0.0013	$P< 0.005$

Figure 171 Comparison of stiffness 1and stiffness 2 between the 12% and 4% wrap materials.

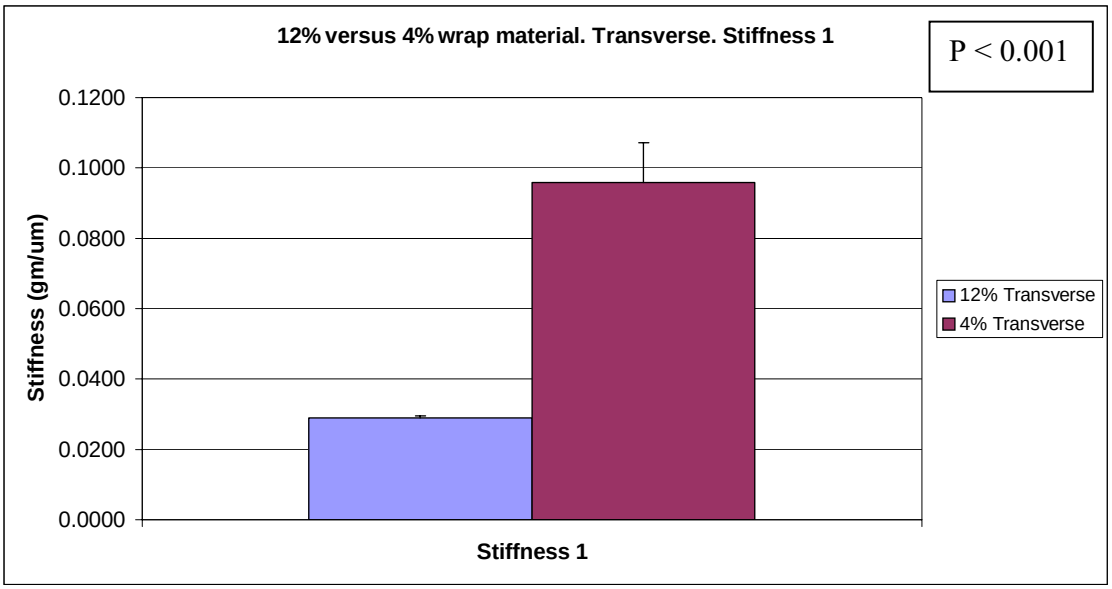


Figure 172 Comparison of stiffness 1 between transverse strips of the 12% and 4% wrap materials.

Figure 173 Comparison of stiffness 1 between longitudinal strips of the 12% and 4% wrap materials.

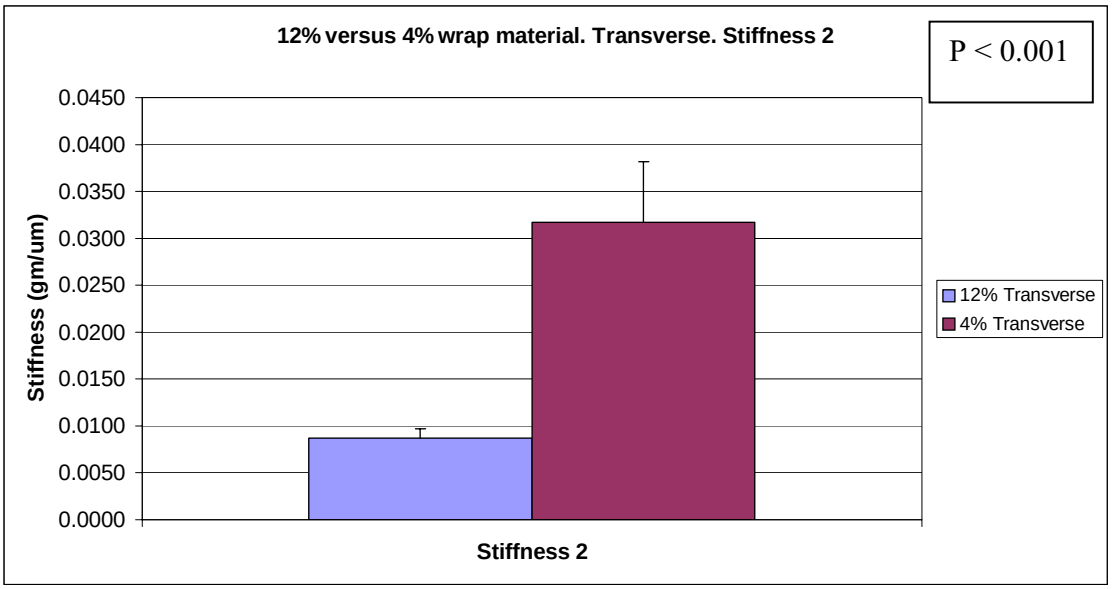


Figure 174 Comparison of stiffness 2 between transverse strips of the 12% and 4% wrap materials.

Figure 175 Comparison of stiffness 2 between longitudinal strips of the 12% and 4% wrap materials.

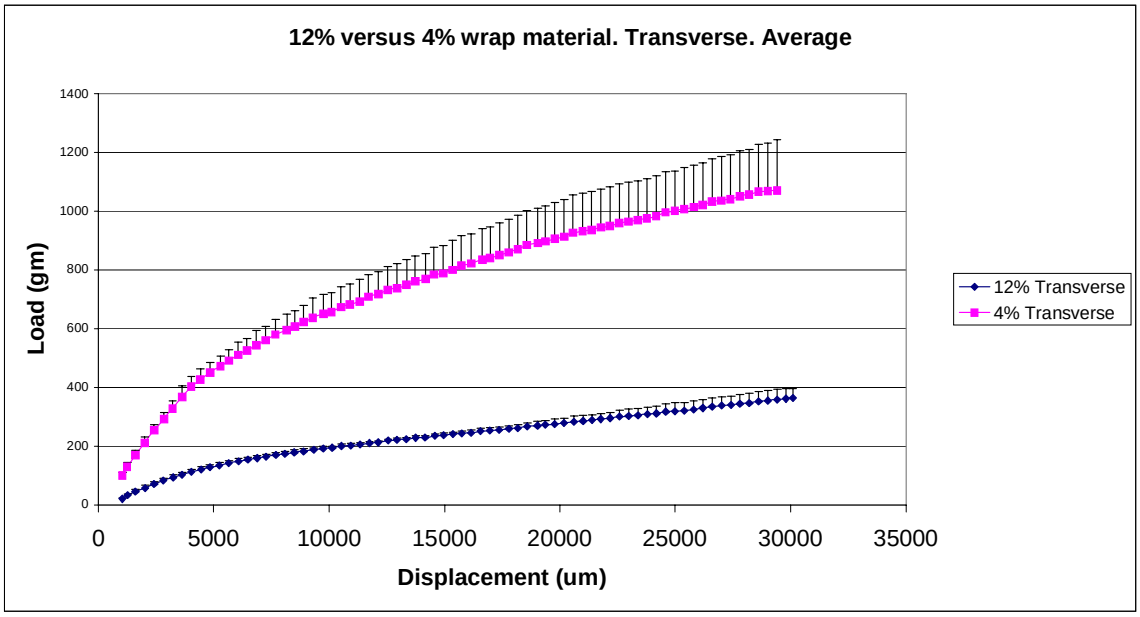


Figure 176 Comparison of transverse strips of the 12% and 4% wrap materials.

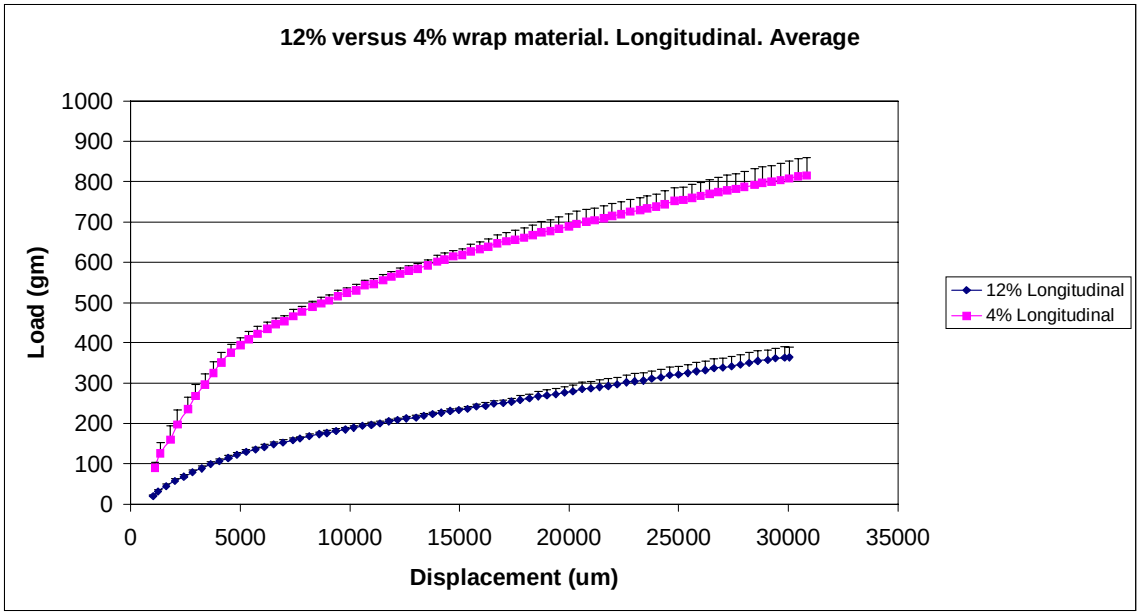


Figure 177 Comparison of longitudinal strips of the 12% and 4% wrap materials.

8.3.7 Comparison of the elastic wrap and aorta

Stiffness 1 of transverse strips of the 12% material approximates stiffness 1 of transverse strips of the proximal descending aorta. Stiffness 2 of transverse strips of the 4% wrap approximates stiffness 1 of transverse strips of proximal descending thoracic aorta.

Material (Transverse strip)	Stiffness 1 (gm/um)	Stiffness 2 (gm/um)
Aorta. Position 1. 0.1Hz	0.0271 +/- 0.0062	0.0723 +/- 0.0080
Aorta. Position 1. 0.3Hz	0.0234 +/- 0.0063	0.0688 +/- 0.0222
12% wrap material	0.0290 +/- 0.0006	0.0087 +/- 0.0010
4% wrap material	0.0959 +/- 0.0111	0.0317 +/- 0.0065

Figure 178 Comparison of stiffness 1 and stiffness 2 of transverse strips of the proximal descending thoracic aorta and the 12% and 4% wrap materials.

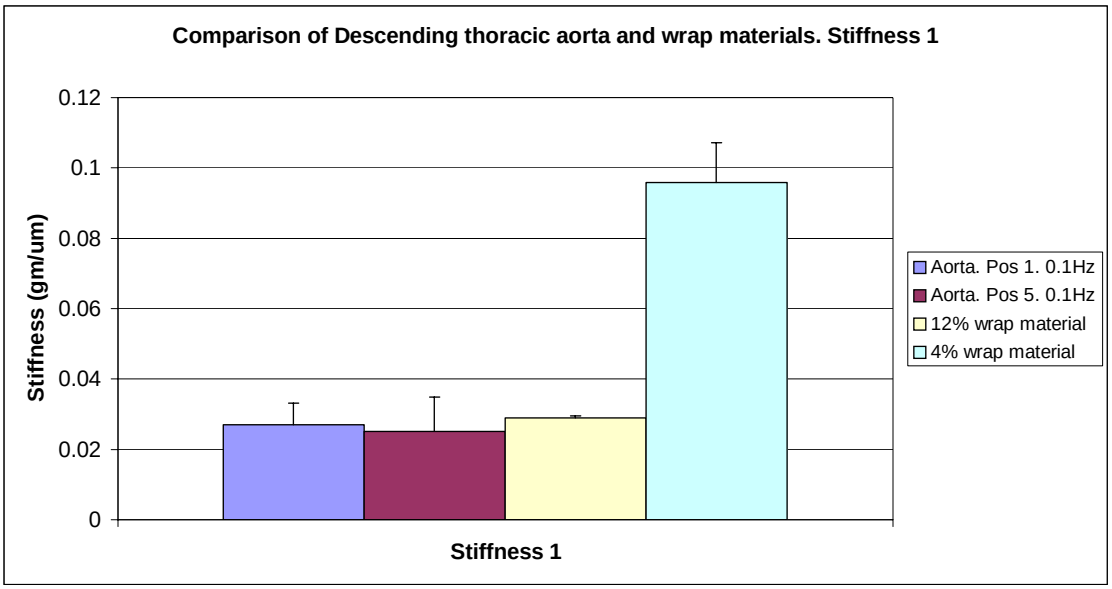


Figure 179 Comparison of stiffness 1 of transverse strips of the proximal descending thoracic aorta and the 12% and 4% wrap materials.

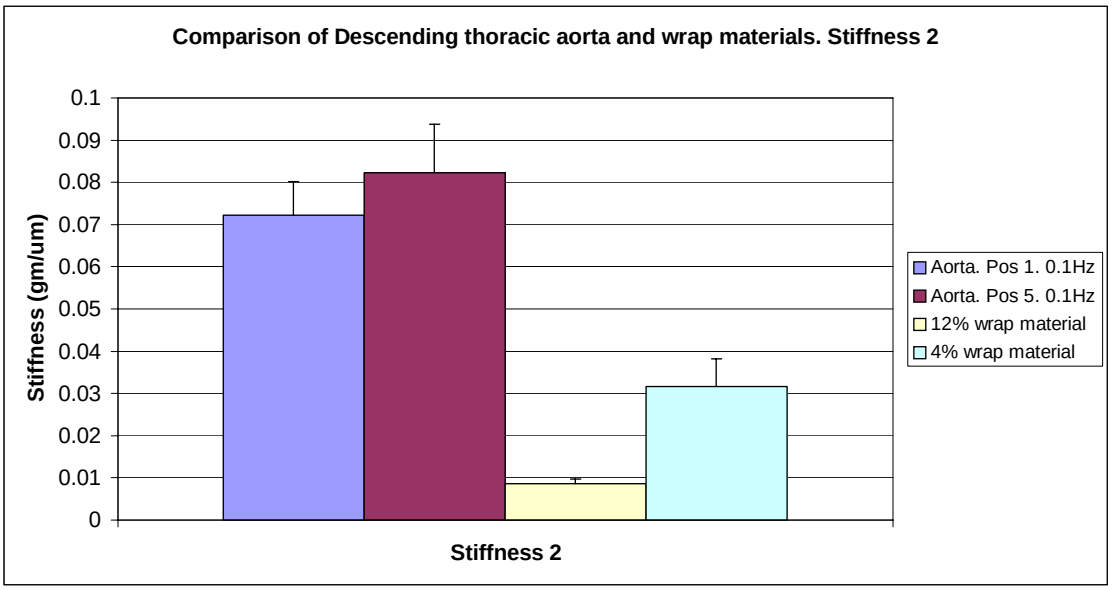


Figure 180 Comparison of stiffness 2 of transverse strips of the proximal descending thoracic aorta and the 12% and 4% wrap materials.

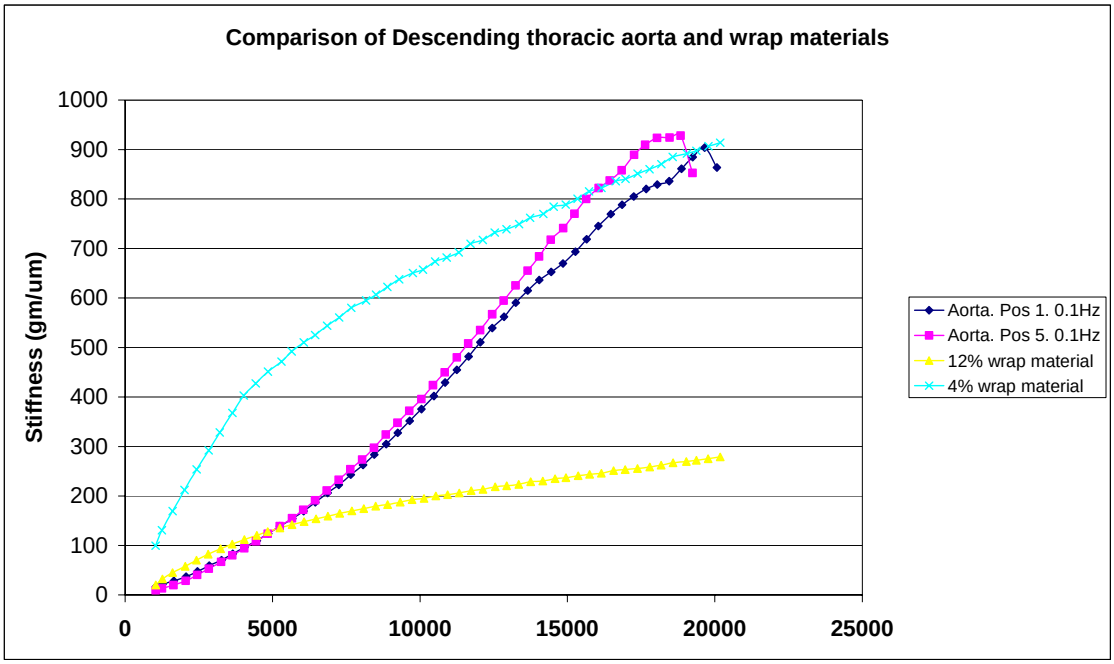


Figure 181 Comparison of transverse strips of the proximal descending thoracic aorta and the 12% and 4% stiffness materials.

8.4 Discussion

8.4.1 Function of the aorta

The thoracic aorta functions as the trunk of the arterial tree that distributed blood from the left ventricle to the organs and tissues of the body (Gray 1858; Gabella 1995). The thoracic aorta also has an elastic function in that it converts the intermittent pulsatile output of the left ventricle to the smoother pattern seen in the peripheral circulation (Berne and Levy 1977; Milnor 1989; Boudoulas and Wooley 1996; Li 2000; Li 2004; Nichols and O'Rourke 2005). Elastic expansion of the thoracic aorta during ventricular ejection limits the rise in systolic pressure and afterload. Elastic recoil of the aortic wall during ventricular relaxation maintains diastolic pressure and forward blood flow (including coronary blood flow).

8.4.2 Elastic properties of the aorta

The mechanical properties of the aortic wall are central to this pulse smoothing function. The aortic wall exhibits non-linear elasticity with increasing stiffness at increasing strain (Roy 1880; Bergel 1961a). The non-linear elasticity of the aortic wall results from the geometric arrangement of collagen and elastic in the tunica media. Wolinsky and Glagov (1964) described the architecture of the tunica media as an orderly array of lamellar units consisting of smooth muscle, elastin and collagen. At physiologic pressures elastic lamellae are arranged as a series of concentric rings with uniform thickness and radial spacing. Within the inter-lamellar spaces are smooth muscle cells and collagen fibres orientated helically. The lamellar unit model of the arterial wall was modified by Clark and Glagov (1985). They showed that elastic tissue between concentric

layers of smooth muscle consists of two layers of elastin fibres, each associated with adjacent muscle layers. This system of "musculo-elastic fascicles" allows for uniform distribution of tensile stress across the arterial wall (Dobrin 1983; Dobrin 1999).

There is a strain dependant transfer of load from elastin fibres to collagen fibres with increasing stress (Burton 1954; Roach and Burton 1957; Wolinsky and Glagov 1964; Wolinsky and Glagov 1967). Elastin is a highly extensible structural protein with an elastic modulus comparable to that of rubber (Aaron and Gosline 1980), whereas collagen is relatively inextensible with an elastic modulus that is much greater than that of elastin (Burton 1954; Fung 1981; Armentano, Levenson et al. 1991; Barra, Armentano et al. 1993; Armentano, Barra et al. 1995). This strain dependant transfer of load provides the elastic pulse smoothing function of the aortic wall, as well as providing structural stability and prevention of rupture at high distending pressures.

8.4.3 Uniaxial tensile testing

Uniaxial tensile testing is a simple method for the measurement of the mechanical properties of arterial strips or rings. A uniaxial load is applied to the material while the load and resulting specimen elongation (displacement) are measured to generate a load-displacement curve (Park and Lakes 1992). A stress-strain curve can be generated by converting load into stress, and displacement into strain (Park and Lakes 1992).

The load-displacement (or stress-strain) curve of the arterial wall is characteristically biphasic with the initial proportion determined predominantly by the stiffness of elastin fibres, increasing recruitment of collagen fibres with increasing load, and the second portion determined primarily by the stiffness of collagen fibres (Armentano, Levenson et al. 1991; Armentano, Barra et al. 1995). A number of investigations have used

static and dynamic uniaxial tensile tests to describe the mechanical properties of arteries (Roy 1880; Cohen, Litwin et al. 1972; Pynadath and Mukherjee 1977; Hayashi 1982; Mohan and Melvin 1982; Cox 1983; Dunn and Silver 1983; Yin, Spurgeon et al. 1983; Bashey, Cox et al. 1989; Matsuda, Nosaka et al. 1989; Adham, Gournier et al. 1996; Angouras, Sokolis et al. 2000).

There are a number of possible sources of errors in data from arterial strips and rings relating to specimen preparation. Strips need to be immersed and tested in a solution that simulates the physiologic environment, as strips exposed to air lose moisture resulting in altered material properties. Arteries are under longitudinal tension in-vivo and will retract when cut (Learoyd and Taylor 1966; McDonald 1974). The free edges of the specimen produce "edge effects" that may produce minor alterations to mechanical testing data (Nichols and O'Rourke 1998). Despite these limitations, the use of strips and rings for uniaxial tensile testing is beneficial in that these tests are simple and provide valuable data about the mechanical properties of the arterial wall and vascular prostheses. These tests however, do not provide information about the mechanical properties of the intact vessel (McDonald 1974; Cox 1983).

8.4.3 Mechanical properties of the ovine descending thoracic aorta

The sheep model has been widely used for cardiovascular research (see section 3.4.1), however, the uniaxial tensile properties of the ovine descending thoracic aorta have not been well characterised. Characterisation of the in-vitro mechanical properties of the ovine descending aorta have previously been characterised using pressure-diameter testing (Wells, Langille et al. 1998a; Wells, Langille et al. 1999).

In this study, uniaxial tensile testing of strips was used to measure the uniaxial tensile properties of the ovine descending thoracic aorta (as well as the elastic wrap material). The non-linear behaviour of the aortic wall with uniaxial tensile testing was confirmed, and baseline values of stiffness, rupture load and displacement, and failure energy were determined.

8.4.4 Alteration in elastic properties with increasing distance from the heart

There is a decrease in elastin content and increase in collagen content in the aorta with increasing distance from the heart (Harkness, Harkness et al. 1957; Apter 1966; Fischer and Llaurado 1966). These alterations in elastin and collagen content produce an increase in aortic stiffness with increasing distance from the heart (Bergel 1961a; Learoyd and Taylor 1966; Nichols and McDonald 1972; Latham, Westerhof et al. 1985). In this study, the increase in aortic stiffness with increasing distance from the heart was confirmed. The increase in aortic stiffness was evident in both the transverse and longitudinal orientation.

8.4.5 Longitudinal elastic properties of the aorta

The aorta is tethered in vivo by perivascular connective tissue as well as arterial branches such as the intercostal arteries (Patel and Fry 1966; McDonald 1974). As a result of this tethering, longitudinal expansion of the aorta with each cardiac pulsation is significantly less that the circumferential expansion in-vivo (Patel and Fry 1964; Patel and Fry 1966). Excision of segments of the aorta produces retraction of these segments because of disruption of this tethering (Bergel 1961a; Learoyd and Taylor 1966).

The aortic (and arterial) wall is known to be anisotropic (Patel, Janicki et al. 1969; Vaishnav, Young et al. 1972; Dobrin 1986). In this study, there was no significant difference in stiffness between transverse and longitudinal strips; however there were differences in rupture load and failure energy. The ovine descending thoracic was therefore found to be anisotropic. Similar values of stiffness in the transverse and longitudinal direction alone are not sufficient to describe the ovine descending thoracic aorta as isotropic (Zhou and Fung 1997).

The rupture load and failure energy were significantly less in longitudinal strips which is in keeping with physiologic principles. The aorta is protected from longitudinal stresses and rupture by tethering from perivascular connective tissue and arterial branches, as well as by the tensile strength of the tunica media. In contrast, protection from circumferential stresses is predominantly provided by the tensile strength of the tunica media.

8.4.6 Preconditioning

A period of preconditioning is required to stabilise the stress-strain response of the thoracic aorta so that repeatable results are achieved (Fung 1981). Aortic tissue may be preconditioned using dynamic sinusoidal displacements of differing amplitude and frequency. A number of preconditioning protocols have been used in the literature; however there is no standardised protocol in routine use. The effect of different preconditioning protocols on the stress-strain response has not been previously described.

In this study, two different preconditioning protocols that were within the capability of the testing machine were evaluated. There was no obvious effect of altering the

frequency or amplitude of the dynamic sinusoidal displacements used for preconditioning on the load-displacement curves of the ovine descending thoracic aorta.

8.4.7 Elastic wrap material

Uniaxial tensile testing has been used to characterise the mechanical properties of vascular prostheses and biomaterials (Quaglini, Villa et al. 2002). The effect of alterations in geometry, design, material properties, and the effect of chronic implantation of artificial materials used for clinical purposes is easily and rapidly assessed using uniaxial tensile testing.

In this study, the uniaxial tensile properties of the elastic wrap material were characterised. The elastic wrap material exhibited a biphasic load-displacement curve; however, the material was stiffer at low strains and became less stiff at higher strains i.e. a 'reverse' biphasic load-displacement curve. This may result (at least partially) from thinning of the material as it is stretched; as a reduction in thickness will produce a reduction in Young's modulus (see Section 2.5.5). The 4% material was stiffer than the 12% material.

8.5 Conclusions

In conclusion, the ovine descending thoracic aorta exhibited non-linear elastic behaviour and anisotropy. The circumferential and longitudinal stiffness were, however, similar, and increased with increasing distance from the heart. The use of different preconditioning protocols did not alter the load-displacement curves generated produced, and both may be used for further experimental testing. The elastic wrap material showed a biphasic load-displacement curve, that was the opposite of the aorta i.e. high stiffness at

low displacements, and low stiffness at higher displacements. This ‘reverse’ biphasic response of the elastic wrap material has implications for the design of future wrap materials.

CHAPTER 9: DISCUSSION

9.1 HEART FAILURE

9.1.1 The clinical problem

The clinical problem of heart failure is a health crisis currently facing Western industrialised nations (Braunwald 1997). The number of heart failure patients in these countries is substantial (e.g. 5 million patients in the United States) and is expected to rise with aging of the population and increased survival of patients with cardiovascular disease (Kelly 1997; NHF/CSANZ 2002; Chobanian, Bakris et al. 2003; AHA 2005). Heart failure is the only cardiovascular disorder that is increasing in incidence and prevalence (AIHW 2004; AHA 2005). Heart failure is predominantly a disease of the elderly and is a leading cause of admission and readmission in patients aged 65 years or older (Gooding and Jette 1985; Massie and Shah 1997; Rich and Nease 1999; Jessup and Brozena 2003). The economic burden of treating heart failure is considerable (AHA 2005).

9.1.2 Aetiology of heart failure in the elderly

The generation of the arterial pulse has a mechanical basis- ventricular contraction, and the interaction between the left ventricle and systemic arterial system is mechanical in nature and can be altered by a change in the haemodynamic properties of the cardiovascular system (O'Rourke, Kelly et al. 1992; Nichols and O'Rourke 2005).

The development of heart failure in the elderly has a haemodynamic basis (Westerhof and O'Rourke 1995; Nichols and O'Rourke 2005). Aging is accompanied by stiffening and dilatation of the aorta that is most pronounced in its proximal more elastic

portions (Avolio, Chen et al. 1983; Avolio, Deng et al. 1985; Virmani, Avolio et al. 1991). The aorta progressively stiffens and dilates through life as a result of repetitive cyclic stress that damages inert elastin fibres (Nichols and O'Rourke 2005). With aging the aortic wall shows fracture and degeneration of elastin fibres with an increase in collagen fibre content (Schlatmann and Becker 1977; Lakatta, Mitchell et al. 1987; Virmani, Avolio et al. 1991; Lakatta, Gerstenblith et al. 1997; Nichols and O'Rourke 1998). As a result the there is a progressive increase in the stiffness and pulse wave velocity of the large elastic arteries with aging (Nakashima and Tanikawa 1971; Gozna, Marble et al. 1974; Merillon, Motte et al. 1978; Langewouters 1982; Avolio, Chen et al. 1983; Avolio, Deng et al. 1985; Lanne, Sonesson et al. 1992; Sonesson, Hansen et al. 1993; van der Heijden-Spek, Staessen et al. 2000; Hundley, Kitzman et al. 2001). This process is accompanied by progressive dilatation of the aorta (Gould 1960; Learoyd and Taylor 1966; Nakashima and Tanikawa 1971; Gerstenblith, Frederiksen et al. 1977; Nichols, O'Rourke et al. 1985; Towfiq, Weir et al. 1986; Kawasaki, Sasayama et al. 1987; Virmani, Avolio et al. 1991; Lanne, Sonesson et al. 1992; Pedersen, Aslaksen et al. 1993; Sonesson, Hansen et al. 1993; Lanne, Hansen et al. 1994; Pearson, Guo et al. 1994; Sonesson, Lanne et al. 1994; Vasan, Larson et al. 1995a; Nichols and O'Rourke 1998; Lakatta and Boluyt 2000; Lakatta and Levy 2003a).

Aortic stiffening and dilatation produces the increase in systolic and pulse pressure (isolated systolic hypertension), the decrease in diastolic pressure, and the increase in cardiac load that is seen with aging (Kannel, Gordon et al. 1971; Kannel, Dawber et al. 1980; Kannel, Wolf et al. 1981; Merillon, Motte et al. 1982b; Nichols, O'Rourke et al. 1985; Nichols, Nicolini et al. 1992; Burt, Whelton et al. 1995; Westerhof and O'Rourke 1995; Franklin, Gustin et al. 1997; Chae, Pfeffer et al. 1999; Hundley, Kitzman et al. 2001; Nichols and O'Rourke 2005).

Aortic stiffening and dilatation is the fundamental cause of heart failure in the elderly (Nichols, O'Rourke et al. 1985; O'Rourke, Avolio et al. 1986; Westerhof and O'Rourke 1995; Nichols and O'Rourke 2005). Increased systolic and pulse pressure increase cardiac load and myocardial oxygen consumption, produce left ventricular hypertrophy and diastolic dysfunction, and accelerates coronary artery disease (Merillon, Motte et al. 1982a; Merillon, Motte et al. 1982b; Nichols, O'Rourke et al. 1985; O'Rourke, Avolio et al. 1986; Girerd, Laurent et al. 1991; Nichols, Nicolini et al. 1992; Westerhof and O'Rourke 1995; Nichols and O'Rourke 1998; Chae, Pfeffer et al. 1999; Hundley, Kitzman et al. 2001; Morita, Asou et al. 2002; Kawaguchi, Hay et al. 2003; Safar and Smulyan 2004). Acceleration of coronary artery disease, and reduced coronary blood flow produce myocardial ischaemia, acute myocardial infarction, and ischaemic cardiomyopathy, and therefore systolic dysfunction (Watanabe, Ohtsuka et al. 1993; Kass, Saeki et al. 1996; Franklin, Khan et al. 1999; Nishijima, Nakayama et al. 2001; Safar and Smulyan 2004; Weber, Auer et al. 2004).

There is also a strong association between indices of large artery stiffness and the development of microvascular disease in the brain and kidney that produces cerebrovascular accident, dementia, and renal failure (O'Rourke and Safar 2005).

9.1.3 Treatment of heart failure

The treatment of heart failure has a haemodynamic basis in that the most effective treatment of heart failure is the reduction in mechanical load (Katz 1998; Nichols and O'Rourke 2005). In systolic heart failure the heart acts as a pressure source with an exquisite dependence on afterload for ejection (Westerhof and O'Rourke 1995). Small changes in afterload produce large inverse changes in ejection and cardiac output. A

reduction in afterload also improves diastolic function (Leite-Moreira, Correia-Pinto et al. 1999).

The reduction of mechanical load in heart failure has been achieved pharmacologically as well as through the use of mechanical devices and surgical procedures. Diverse treatments ranging from ACE inhibitors to ventricular assist devices show that the reduction of mechanical load is the most effective treatment (and prevention) of heart failure and results in clinical improvement, improved survival and regression of pathologic changes in ventricular structure (CONSENSUS 1987; Cohn, Johnson et al. 1991; SOLVD 1991; Konstam, Rousseau et al. 1992; SOLVD 1992; Konstam, Kronenberg et al. 1993; El-Banayosy, Korfer et al. 1999; Farrar 2000; Deng, Loebe et al. 2001; El-Banayosy, Korfer et al. 2001; Rose, Gelijns et al. 2001; Arnold, Yusuf et al. 2003; Dembitsky, Tector et al. 2004; Morgan, John et al. 2004).

9.1.4 Problems with pharmacologic agents for the treatment of heart failure

Pharmacologic agents that produce vasodilation and reduction of the reflected wave act to reduce central aortic pressure and therefore cardiac load (Yaginuma, Avolio et al. 1986; Kelly, Gibbs et al. 1990; Chen, Ting et al. 1995; Ting, Chen et al. 1995; Jiang, O'Rourke et al. 2002; London, Asmar et al. 2004; Hirata, Vlachopoulos et al. 2005; Nichols and O'Rourke 2005; Pauca, Kon et al. 2005). Agents such as ACE inhibitors, ARBs, beta blockers, and vasodilators have been effective in reducing mortality and increasing functional status in heart failure patients but have reached their therapeutic limit (CONSENSUS 1987; Cohn, Johnson et al. 1991; SOLVD 1991; SOLVD 1992; Packer, Bristow et al. 1996; Pitt, Segal et al. 1997; CIBIS-II 1999; MERIT-HF 1999; Pitt, Poole-

Wilson et al. 2000; Cohn, Tognoni et al. 2001; Packer, Coats et al. 2001; Levy, Kenchaiah et al. 2002; Granger, McMurray et al. 2003; Roger, Weston et al. 2004; Bristow, Linas et al. 2005). Despite the improvements in survival produced by these agents, the prognosis for patients with heart failure remains poor and newer pharmacologic agents have failed to further improve outcomes (Levy, Kenchaiah et al. 2002; Roger, Weston et al. 2004; Bristow, Linas et al. 2005). A major limitation of current pharmacologic agents is that they do not treat the fundamental cause of heart failure in the elderly- aortic dilatation and stiffness (Safar and London 2000; Van Bortel, Struijker-Boudier et al. 2001; Bristow, Linas et al. 2005; Nichols and O'Rourke 2005; Zieman, Melenovsky et al. 2005).

Newer pharmacologic agents are currently being developed to inhibit collagen cross linking in the aortic wall to reduce aortic stiffening (Wolffenbuttel, Boulanger et al. 1998; Aronson 2003; Susic, Varagic et al. 2004). The effectiveness of such agents as well as the side effects they may produce has not yet been adequately determined to allow wide use in human subjects.

9.1.5 Problems with conventional surgical procedures for the treatment of heart failure

Conventional surgical treatments such as coronary artery bypass grafting, geometric mitral reconstruction, and geometric ventricular remodelling have been successful in improving functional class, ventricular function and geometry, and survival in heart failure patients but can only be used in the presence of coronary artery disease (coronary artery bypass grafting) or when heart failure is advanced (geometric mitral reconstruction or geometric ventricular remodelling) (Coles, Del Campo et al. 1981; ECSS 1982; CASS 1983; Elefteriades, Tolis et al. 1993; Elefteriades, Morales et al. 1997; Bolling, Pagani et al.

1998; Chen, Adams et al. 1998; Bishay, McCarthy et al. 2000; Topkara, Cheema et al. 2005).. These procedures aim to improve coronary blood flow (coronary artery bypass grafting) or reduce mechanical load (geometric mitral reconstruction, and geometric ventricular remodelling), but fail to treat aortic stiffening and dilatation.

Heart transplantation is an effective treatment of end-stage heart failure but is severely limited by the availability of donor hearts and is not available as a treatment option in the elderly (Steinman, Becker et al. 2001; AHA 2005).

9.1.6 Problems with current mechanical devices for the treatment of heart failure

A number of mechanical devices that act by unloading the left ventricle have been developed for the treatment of heart failure and have been shown to arrest or cause regression of ventricular remodelling in the long term (Burkhoff, Holmes et al. 2000; Heerdt, Holmes et al. 2000; Barbone, Holmes et al. 2001; Madigan, Barbone et al. 2001).

Mechanical devices that are currently used or are being developed for the treatment of heart failure have a number of significant limitations:

1. There is no currently available mechanical device for the treatment of heart failure that treats the underlying cause of heart failure in the elderly- aortic dilatation and stiffness.
2. Mechanical devices are only effective in established heart failure and may not be used to prevent the development of heart failure.
3. Generally, mechanical devices are invasive and involve a major surgical procedure for implantation e.g. ventricular assist devices, aortomyoplasty, cardiomyoplasty, and para-aortic counterpulsation devices (Neilson and Chiu 1986; Trainini, Barisani

et al. 1999; Trainini, Cabrera Fischer et al. 2002; Cohn and Edmunds 2003; Cabrera Fischer, de Forteza et al. 2004). This is especially the case with mechanical assist devices that require median sternotomy (or left thoracotomy in the case of the Jarvik 2000); anastomosis to at least the left ventricle and aorta; and often creation of an abdominal or subcutaneous pocket (Cohn and Edmunds 2003).

4. The combination of an extensive procedure, large amount of prosthetic material, blood-device interface, as well as extracorporeal components results in a high rate of serious infection for ventricular assist devices (El-Banayosy, Korfer et al. 1999; Deng, Loebe et al. 2001; El-Banayosy, Korfer et al. 2001; Robbins, Kown et al. 2001; Dembitsky, Tector et al. 2004; Morgan, John et al. 2004; Copeland, Smith et al. 2004b).
5. Many devices e.g. ventricular assist devices and IABP involve a blood-device interface with a high incidence of thromboembolic complications (Kantrowitz, Wasfie et al. 1986; Deng, Loebe et al. 2001; El-Banayosy, Korfer et al. 2001; Robbins, Kown et al. 2001; Baskett, Ghali et al. 2002; Copeland, Smith et al. 2004b).
6. Most devices are active devices and consist of complex components that may fatigue, rupture, or fail e.g. IABP, para-aortic counterpulsation devices, ventricular assist devices, aortomyoplasty, and cardiomyoplasty (Kantrowitz, Wasfie et al. 1986; Neilson and Chiu 1986; Trainini, Barisani et al. 1999; Deng, Loebe et al. 2001; El-Banayosy, Korfer et al. 2001; Robbins, Kown et al. 2001; Baskett, Ghali et al. 2002; Trainini, Cabrera Fischer et al. 2002; Cabrera Fischer, de Forteza et al. 2004; Dembitsky, Tector et al. 2004; Morgan, John et al. 2004; Copeland, Smith et al. 2004b)

7. The cost and availability of many devices limits their use in many patients e.g. ventricular assist devices.
8. Some mechanical devices e.g. HeartMate LVAS and CardioWest TAH cannot be used in small sized patients (Dembitsky, Tector et al. 2004).

9.1.7 Importance of developing new treatments of heart failure in the elderly

Despite the improvements in the treatment of heart failure resulting from the use of pharmacologic agents, surgical procedures, and mechanical devices, the prognosis in heart failure patients remains poor (Levy, Kenchaiah et al. 2002; Roger, Weston et al. 2004). In the Framingham study, 1-year and 5-year mortality rates are 28% and 59%, respectively in males (Levy, Kenchaiah et al. 2002). In the Olmsted County study, 1-year mortality and 5-year mortality are 21% and 50%, respectively in males (Roger, Weston et al. 2004). This poor outlook may result from the fact that current treatments of heart failure do not treat the fundamental and root cause of heart failure in the elderly- aortic stiffening and dilatation.

The increasing incidence and prevalence of heart failure, as well as increasing number of hospitalizations and deaths resulting from heart failure has made heart failure a major health issue in western nations (Braunwald 1997; NHF/CSANZ 2002; AIHW 2004; AHA 2005). The economic burden of burden of treating heart failure patients in the United States alone has been estimated at 30 billion dollars annually (AHA 2005). There is an impetus to develop new pharmacologic agents, and surgical procedures and devices for the treatment of heart failure. At present there is no effective treatment for the fundamental cause of heart failure in the elderly- aortic dilatation and stiffness.

9.2 THE AORTIC WRAP

In this thesis, the proof of concept of a simple surgical treatment of stiffening and dilatation of the ascending aorta is described. An elastic wrap is applied to the external surface of the aged ascending aorta, to reduce the diameter of the aorta towards values seen in youth where ventricular-vascular interaction is optimal. The wrap is an elastic material whose elastic properties simulate those of the young ascending aorta. The hypothesis is that by reducing the diameter of the native vessel, the elastic wrap will bear the load of pulsatile pressure and flow. The wrap will thereby restore elasticity (reduce stiffness) of the wrapped aorta by unloading the aortic wall.

9.2.1 Haemodynamic effects of the aortic wrap procedure

Application of an elastic wrap to the ascending aorta of elderly humans with a reduction in diameter is expected to unload the aortic wall with the load being borne by the elastic wrap and a subsequent reduction in the stiffness of the ascending aorta towards that seen in young human subjects. A reduction of the stiffness of the ascending aorta in elderly humans is expected to arrest or reverse the adverse haemodynamic effects produced by age-related aortic stiffening and dilation (Nichols, O'Rourke et al. 1985; Nichols, O'Rourke et al. 1986; O'Rourke, Avolio et al. 1986; Lakatta, Mitchell et al. 1987; Kelly, Tunin et al. 1992; Watanabe, Ohtsuka et al. 1993; Ohtsuka, Kakihana et al. 1994; Westerhof and O'Rourke 1995; Franklin, Gustin et al. 1997; Lakatta and Boluyt 2000; Hundley, Kitzman et al. 2001; Morita, Asou et al. 2002; Lakatta and Levy 2003a; Lakatta and Levy 2003b; O'Rourke and Nichols 2005). A reduction in ascending aortic stiffness is expected to reduce central aortic systolic and pulse pressure, and increase diastolic pressure. A reduction in systolic pressure and pulse pressure is expected to reduce afterload and myocardial oxygen

demand i.e. to unload the heart and improve ventricular-vascular interaction. An increase in diastolic pressure coupled with a decrease in systolic pressure is expected to increase coronary perfusion.

9.2.2 Clinical effects of the aortic wrap procedure

There is currently no effective treatment of aortic dilatation and stiffness (Safar and London 2000; Van Bortel, Struijker-Boudier et al. 2001; Bristow, Linas et al. 2005; Nichols and O'Rourke 2005; Zieman, Melenovsky et al. 2005). A reduction in age-related ascending aortic stiffness and dilatation is expected to have the following clinical effects:

1. To reduce the increase in ascending aortic systolic and pulse pressure with aging and therefore improve isolated systolic hypertension.
2. To increase ascending aortic diastolic pressure and improve myocardial perfusion.
3. Retard or reverse the progression of the effects of arterial stiffening on the heart and therefore prevent the development of heart failure.
4. To reduce afterload and so improve ventricular ejection and ventricular vascular interaction, improve ventricular mechanics and geometry, and improve functional status and mortality of heart failure patients.
5. To arrest or induce regression of microvascular changes in the kidney and brain produced by large artery stiffening.

9.2.3 Experimental findings

The study design in this thesis has been in keeping with the principles of animal experimentation. These broad principles are the refinement of investigative techniques to reduce the impact on animals, and ultimately the replacement of animals with other

methods. This has been achieved through the use of an in-vitro model and a mathematical model, and limitation of the numbers of animals used in the non-survival and chronic animal studies.

The two materials tested in this thesis were two silicon polymers that simulate the elasticity of the young human aorta and pulmonary artery in-vivo. The two materials come in pre-fabricated cylindrical lengths and are used for the testing of artificial valves (aortic and pulmonary) in an in-vitro circuit where they are exposed to pulsatile pressure and flow. The 4% stiffness material cylinder simulates the pulsation of the young human ascending aorta, and its diameter increases by 4% with each pulsation that simulates physiologic pressure and flow. Similarly, the 12% stiffness material simulates the pulsation of the native young pulmonary artery. Each cylindrical length was opened longitudinally to facilitate placement of the wrap around the aorta or vascular conduit and secured using a clamp.

In chapter 3, "the effect of application of an elastic wrap on the ovine thoracic aorta", the elastic wrap was placed around the sheep proximal descending thoracic aorta in-vivo. Application of both wrap materials increased the stiffness of the wrapped vessel, however application of the stiffer 4% material increased stiffness more than application of the less stiff 12% material. Previous studies have showed that application of a non-elastic material (e.g. Dacron) around the normal aorta increases aortic stiffness (Tropea, Schwarzacher et al. 2000). In this study the increase in stiffness resulting from application of an elastic wrap was not as great as the increase in aortic stiffness that has been reported in the literature following application of a non-elastic wrap (Tropea, Schwarzacher et al. 2000). Furthermore, the final vessel stiffness was dependent on the stiffness of the elastic

wrap suggesting that the stiffness of the elastic wrap plays a major role in determining the stiffness of the wrapped vessel.

In chapter 4 “the effect of application of an elastic wrap in an ovine model of aortic dilatation and stiffness” an animal model of aortic dilatation and stiffness was described. An oversized stiff Dacron aortic prosthesis was anastomosed as an interposition graft in the region of the sheep proximal descending thoracic aorta to simulate a stiffened and dilated vessel subjected to physiologic pulsatile pressure and flow. Application of an elastic wrap onto the Dacron graft that reduced the diameter of the graft, reduced the stiffness of the graft. The stiffness of the wrapped conduit was in the range of the stiffness of the wrapped aortas in chapter 3. These findings suggest that application of an elastic wrap to a stiffened and dilated vessel or conduit that reduces its diameter towards normal will reduce the stiffness of the vessel. The stiffness of the material plays a major role in determining the stiffness of the wrapped vessel or conduit and may act by unloading the wrapped vessel or conduit and by bearing the load of pulsatile pressure and flow.

In chapter 5, “the effects of application of an elastic wrap in an in-vitro model of the aged human ascending aorta”, an in-vitro pressure model of the human ascending aorta was described. Human ascending aorta from elderly subjects was placed in an in-vitro pressure circuit and subjected to pulsatile pressure. Application of an elastic wrap to the human ascending aorta in-vitro reduced its stiffness and decreased maximum and pulse pressure, and increased minimum pressure. The greatest reduction in stiffness and alteration in pressure was produced by the material that simulated the elastic properties of the young human aorta (4% material) when applied to reduce diameter towards that seen in youth (30% diameter reduction). These findings show that the stiffness of the aged human ascending aorta can be reduced by application of an elastic wrap, and that this may reduce

systolic and pulse pressure, and increase diastolic pressure in-vivo. The optimal result may be seen when a material that simulates the young ascending aorta is applied to reduce diameter towards the value seen in youth i.e. when there is restoration of aortic elasticity and diameter.

In chapter 6, “the effect of the aortic wrap procedure on pulse pressure using a multibranched model of the human arterial model” a mathematical model was used to assess the effect of a reduction in ascending aortic pressure on ascending aortic pulse pressure. A reduction in the stiffness and diameter of the ascending aorta reduced pulse pressure. A reduction in aortic stiffness of 95% (as predicted in chapter 5 using the 4% wrap material at 70% diameter) produced a reduction in pulse pressure of 23%. These findings suggest that wrapping the ascending aorta alone is sufficient to reduce ascending aortic pulse pressure by levels that are expected to produce significant improvement in ventricular-vascular interaction and clinical outcome.

9.2.4 Experimental summary

The animal and human in-vitro models have shown that application of the elastic wrap to a stiffened vessel or conduit that reduces the diameter of the vessel or conduit will reduce the stiffness of the vessel or conduit. The stiffness of the wrap material plays a major role in determining the stiffness of the wrapped vessel, and the material may act by unloading the vessel wall so that the load of pulsatile flow and pressure is borne predominantly by the wrap material.

The in-vitro human model and computer model have shown that a reduction in ascending aortic stiffness in patients with aortic stiffening and dilatation is expected to reduce systolic and pulse pressure and to increase diastolic pressure. These effects are

expected to decrease left ventricular load, improve ventricular-vascular interaction, and increase coronary blood flow.

The computer model has shown that wrapping the ascending aorta is sufficient to produce these beneficial haemodynamic changes and that wrapping of the arch and descending thoracic aorta is not required. The ascending aorta is easily accessed through a median sternotomy or minimal access surgery, and is easily mobilised from surrounding structures to facilitate wrap placement (Cohn and Edmunds 2003; Kouchoukos, Blackstone et al. 2003).

The 4% wrap material produced the greatest reduction in stiffness and pulse pressure when diameter was reduced by 30% in the human in-vitro and computer model. The 4% material simulates the elasticity of the young human aorta under physiologic pressure and flow. The human thoracic aorta dilates by 40% or more between ages 20 and 80 years, although this is highly variable (Nichols, O'Rourke et al. 1985; Pearson, Guo et al. 1994; Hager, Kaemmerer et al. 2002). These findings suggest that the optimal wrap is one that simulates the mechanical properties of the human ascending aorta in youth that is applied to reduce ascending aortic diameter to that seen in youth. It is expected that reduction of diameter will at some point become obstructive and act to increase cardiac load, as in aortic coarctation (O'Rourke and Cartmill 1971; Declusin, Boerboom et al. 1987).

In summary, application of an elastic wrap to a stiffened and dilated vessel that reduces the diameter of the vessel will reduce the stiffness of the vessel. The elastic wrap may act by unloading the native vessel wall and taking the load of pulsatile pressure and flow. When the elastic wrap is applied to the aged ascending aorta (that is stiffened and dilated), there is a reduction in systolic and pulse pressure, and increase in diastolic

pressure. Application of an elastic wrap to the ascending aorta in elderly human subjects may be an effective mechanical treatment of aortic dilatation and stiffness and its detrimental sequelae such as isolated systolic hypertension, left ventricular hypertrophy, and ultimately heart failure.

9.2.5 Benefits of the aortic wrap procedure

The wrap has a number of benefits when compared to currently available mechanical (and pharmacologic) treatments of heart failure in the elderly:

1. The aortic wrap procedure targets the pathologic process that is the underlying cause of heart failure in the elderly.
2. The aortic wrap procedure can be used at any stage of heart failure to prevent progression to a more advanced stage (Hunt, Abraham et al. 2005). The procedure may be used to treat isolated systolic hypertension and coronary insufficiency as a primary treatment or adjunct thereby preventing the development of heart failure. Application of the wrap in patients with asymptomatic left ventricular hypertrophy and aortic stiffening may prevent progression to heart failure.
3. The device is non blood contacting and therefore should have a lower incidence of thromboembolic and infective complications than blood contacting devices.
4. The wrap procedure relies on a passive process (elasticity of the wrap material) rather than an active process and therefore should be less prone to mechanical failure than active devices.
5. The aortic wrap procedure improves ventricular-vascular interaction by restoring ascending aortic elasticity.

6. The wrap may be applied concomitantly during cardiac surgery or by minimal access surgery as a primary procedure. Application through minimally invasive surgery limits the surgical insult and may allow the procedure to be performed as a primary stand-alone procedure, or prior to further intervention to optimise haemodynamics.

9.2.6 Other wrap procedures in current use or development

Reduction aortoplasty

At present, stiffened inelastic materials (e.g. Dacron) are used to wrap the ascending aorta, in cases of aneurysmal disease of the ascending aorta as an alternative to replacement of the ascending aorta and/or aortic root (reduction aortoplasty) (Robicsek 1982; Bauer, Pasic et al. 2002; Arsan, Akgun et al. 2004; Robicsek, Cook et al. 2004). Reduction aortoplasty is used in cases where the aorta is not sufficiently dilated to warrant replacement and/or when the patient is not suitable for replacement (i.e. is medically unfit or has a contraindication to replacement).

Good long term results have been reported, however the procedure may rarely be complicated by dislocation of the wrap, erosion of the aortic wall, false aneurysm formation, and rupture of the aortic wall (Bauer, Grauhan et al. 2003; Robicsek, Cook et al. 2004). There effects of the procedure on the underlying disease process, the histology and geometry of the aorta, and on ventricular-vascular interaction have not been well studied.

Application of a stiffened wrap to the ascending aorta is haemodynamically detrimental in that it is expected to stiffen the ascending aorta and increase systolic pressure, pulse pressure, and to decrease diastolic pressure (Bauernschmitt, Schulz et al.

1999; Tropea, Schwarzacher et al. 2000; Ioannou, Stergiopulos et al. 2003). Application of an elastic wrap to the thinned and dilated ascending aorta may be more useful for the prevention of aortic rupture (reduction aortoplasty).

Aortomyoplasty

Wraps of latissimus dorsi are placed around the aorta to augment diastolic pressure and coronary blood flow through regular synchronous muscular contraction (aortomyoplasty) (Neilson and Chiu 1986; Chachques, Grandjean et al. 1990; Pattison, Cumming et al. 1991; Cabrera Fischer, Christen et al. 1999; Trainini, Barisani et al. 1999; Trainini, Cabrera Fischer et al. 2002). Despite initial promise this treatment modality has been abandoned by the developing company (Medtronic).

Aortomyoplasty is inherently more complex than the aortic wrap procedure and relies on an active process rather than passive process. There are a number of complications relating to harvest of the muscle (infection, haemorrhage, necrosis), reliance on a mechanical device for contraction (i.e. device failure), as well as damage to the thoracic organs and contents. Furthermore, this device does not correct the underlying cause of heart failure in the elderly- aortic stiffening and dilatation. All of these factors; reliance on an active process, failure to correct the underlying cause, and the extent of the procedure and associated complications all make aortomyoplasty much less attractive than the aortic wrap procedure.

Para-aortic counterpulsation

Para-aortic counterpulsation devices are currently being developed for the treatment of heart failure (Cabrera Fischer, de Forteza et al. 2004). Para-aortic counterpulsation

devices have been developed to avoid the blood-device interface that is present in intra-aortic balloon counterpulsation to avoid the thromboembolic complications resulting from intra-aortic balloon counterpulsation and to increase the duration of implantation.

Generally, para-aortic counterpulsation devices consist of placement of a gas filled cuff around the aorta. Deflation of the cuff during systole reduces systolic pressure and reduces afterload. Inflation during diastole increases diastolic blood pressure and increases coronary blood flow. The haemodynamic effects of these devices are similar to these achieved by intra-aortic balloon counterpulsation.

These devices differ from the aortic wrap procedure in a number of ways:

1. These complex devices inherently rely on an active process for inflation and deflation and are therefore more likely to malfunction or fail mechanically e.g. due to rupture of the cuff or failure of the control mechanism.
2. They are more invasive and require implantation of the inflation device and controller as well as connectors to the para-aortic cuff. There is expected to be a higher incidence of complications relating to the more extensive dissection and implantation of prosthetic material e.g. infection and hematoma.
3. They do not treat the underlying cause of heart failure in the elderly- ascending aortic dilatation and stiffness. They cannot be used to treat aortic dilatation and stiffness or its sequelae i.e. ISH, impaired VVI, and LVH.
4. They are beneficial in only established heart failure and cannot be used to prevent heart failure.

9.2.7 Artificial and biological aortic grafts

Prosthetic thoracic aortic grafts in current clinical use are made of stiff inelastic materials and replacement of variable segments of the thoracic aorta with these grafts has been shown to adversely affect ventricular-vascular interaction (Kim, Hinkamp et al. 1995; Bauernschmitt, Schulz et al. 1999). Current preservation techniques of biologic aortic grafts from animals e.g. glutaraldehyde result in cross-linking of collagen and stiffening of the graft (Baue, Geha et al. 1996; Zhou, Quintero et al. 1997). Aortic grafts harvested from human donors (homografts) are preserved using cryopreservation techniques that do not significantly stiffen the graft and represent the only clinically available compliant aortic grafts (Gournier, Adham et al. 1993; Baue, Geha et al. 1996). Homografts are however available in specialised centres and only in limited numbers (Baue, Geha et al. 1996). Compliant arterial prosthesis as well as endovascular stents are currently being developed (Shum-Tim, Stock et al. 1999; Hiromichi Sonoda 2002; Hiromichi Sonoda 2003; Seifalian, Salacinski et al. 2003).

Theoretical alternatives to elastic wrapping to reduce aortic stiffness and dilatation include replacement of the ascending aorta with a compliant vascular prosthesis or placement of a compliant endovascular stent.

Replacement of the ascending aorta with a compliant vascular prosthesis is a major surgical undertaking that has an unacceptably high morbidity and mortality in the elderly and in patients with end-stage heart failure (Baue, Geha et al. 1996; Cohn and Edmunds 2003; Kouchoukos, Blackstone et al. 2003). There is a limited availability of compliant biological aortic prostheses (homografts) (Baue, Geha et al. 1996). It is therefore not a

suitable surgical treatment of ascending aortic stiffness and dilatation or heart failure in the elderly.

Endovascular grafts have been used to treat lesions of the abdominal aorta, arch of aorta, and descending thoracic aorta, but not of the ascending aorta (Kouchoukos, Blackstone et al. 2003; Faries 2004; Morrissey 2004). Placement of a compliant endovascular stent in the ascending aorta to improve ventricular-vascular interaction is limited by the potential thromboembolic complications, motion of the device with cardiac pulsation, persistent endovascular leak as well as damage to the coronary artery ostia and aortic valve.

9.3 THE SURGICAL PROCEDURE

9.3.1 Clinical indications for the aortic wrap procedure

Initially the procedure may be limited to elderly patients with aortic dilatation and stiffness and end-stage heart failure that are undergoing another surgical procedure for the treatment of heart failure e.g. coronary artery bypass surgery and/or geometric mitral reconstruction.

Future indications for the wrap procedure in elderly patients with aortic dilatation and stiffness may be:

1. The treatment of symptomatic heart failure as a primary treatment or as an adjunct to pharmacologic agents, myocardial revascularization, valve repair or reconstruction, and other mechanical treatments of heart failure.
2. Prevention of heart failure in patients with isolated systolic hypertension.

3. Prevention of the development of heart failure symptoms in asymptomatic heart failure patients with aortic dilatation and stiffening.
4. Treatment of isolated systolic hypertension as a primary treatment or as an adjunct to pharmacologic agents.
5. Treatment of myocardial ischaemia as a primary treatment (in patients unsuitable for revascularisation) or as an adjunct to CABG and coronary artery angioplasty and stenting.
6. Treatment of microvascular disease of the brain and kidney that is secondary to large artery stiffening and increased pulse pressure.

The aortic wrap procedure is technically very easy to perform and may be carried out through a median sternotomy or by minimally invasive surgery to gain access to the ascending aorta. The material may come in prefabricated diameters and stiffness that are used based on stiffness and diameter data collected preoperatively and intraoperatively.

9.3.2 The aortic wrap as a preventative strategy

The recent shift in the view of heart failure as a progressive disorder is particularly relevant to the problem of aortic stiffening and dilatation in that it is the underlying cause of development of heart failure in the elderly (Hunt, Abraham et al. 2005; Nichols and O'Rourke 2005). Treatment of this condition before the appearance of left ventricular dysfunction or symptoms may therefore reduce the incidence and morbidity and mortality of heart failure in the elderly.

The clinical implications of stiffening and dilatation of the large elastic arteries may be viewed as a continuum that extends from isolated systolic hypertension, increased left ventricular load and hypertrophy, and ultimately cardiac failure (Westerhof and O'Rourke

1995). The treatment of aortic stiffening and dilatation may arrest the progression of the disease at its current stage. The reduction of ascending aortic stiffness and pulse pressure may arrest or prevent the development of microvascular disease of the brain and kidney (O'Rourke and Safar 2005).

9.3.3 Surgical technique

Application of an elastic wrap to the ascending aorta alone is expected to confer haemodynamic benefit. This is highly advantageous as the ascending aorta is easily accessible through a median sternotomy or minimal access approach (Baue, Geha et al. 1996; Cohn and Edmunds 2003; Kouchoukos, Blackstone et al. 2003). Median sternotomy is the most commonly used incision in cardiac surgery and provides excellent access to the ascending aorta to facilitate placement of the elastic wrap concomitantly with other procedures. The ascending aorta is also easily accessible via a number of minimal access surgical approaches such as the MID-CAB approach, superior hemisternotomy, or thoracoscopy.

Avoidance of more extensive wrapping of the arch and descending thoracic aorta is highly desirable. The arch of the aorta is difficult to access surgically, has a number of large branches, and is intimately adherent to critical nerves such as the phrenic nerve, vagus nerve, and left recurrent laryngeal nerve (Baue, Geha et al. 1996; Cohn and Edmunds 2003; Kouchoukos, Blackstone et al. 2003). Because of these factors application of elastic wraps to the arch is technically very challenging and fraught with danger.

The descending thoracic aorta is easily accessed through a left thoracotomy or through thoracoscopy (Baue, Geha et al. 1996; Cohn and Edmunds 2003; Kouchoukos, Blackstone et al. 2003). The descending thoracic aorta, however, is covered by the pleural

surface, is closely related to the oesophagus, and has multiple intercostals branches (damage to which may result in haemorrhage or spinal ischaemia and paralysis). Application of elastic wraps to the descending thoracic aorta is similarly fraught with peril.

The ascending aorta has a gentle curvature and is easily mobilised from the pulmonary artery to which it is adherent to provide a suitable length of vessel for wrap application (Baue, Geha et al. 1996; Cohn and Edmunds 2003; Kouchoukos, Blackstone et al. 2003). Unlike the majority of cardiothoracic procedures that are technically challenging and require a high level of surgical skill (and stress), application of an elastic wrap to the ascending aorta is a relatively simple procedure that may be successfully carried out by surgeons with relatively basic skills. This is equally applicable to open surgery (through median sternotomy) or minimal access surgery.

9.3.4 Advantages of the aortic wrap procedure

Minimally invasive surgery

The aortic wrap procedure may be carried out as a minimally invasive procedure and is expected to have a low morbidity and mortality.

The surgical insult resulting from the aortic wrap procedure may be minimised using a minimal access incision. The aortic wrap procedure does not require aorto-caval cannulation, cardiopulmonary bypass, or cardiotomy for placement unlike ventricular assist devices and total artificial hearts.

Conjoint procedure

The procedure may be done in conjunction with other conventional surgical treatments of heart failure or as a primary stand-alone procedure for the treatment or prevention of heart failure.

Non-blood contacting

The aortic wrap procedure is a non blood-contacting device and therefore should have a significantly lower rate of thrombo-embolic complications than blood-contacting devices.

Simple

The aortic wrap is a simple device and is less likely to suffer from mechanical failure than active devices used for the treatment of heart failure.

9.3.5 Possible problems of the aortic wrap procedure

Problems relating to the aortic wrap procedure may include:

1. Device failure and fatigue. With chronic implantation (10 weeks) the elastic material and clamp showed no macroscopic deterioration, fatigue, or slippage, and uniaxial tensile testing of the explanted material showed no alteration in stiffness.
2. Dislodgment/rupture of atheromatous plaques with embolisation of plaque material. Severe atherosclerosis may be a contraindication as may be lead pipe or porcelain aorta (the heavily calcified aorta).
3. Aneurysmal dilatation: There was no evidence of aneurysm formation in the 2 animals implanted with the elastic wrap at 2 months

4. Proximal anastomosis for coronary artery bypass grafts: The material may come prefabricated with holes to facilitate proximal anastomosis.

9.3.6 Contraindications

Contraindications to wrapping the ascending aorta are likely to be the porcelain aorta and the heavily atheromatous aorta. Porcelain aorta describes the pathological state were the ascending aorta is completely rigid and stiff secondary to calcification and resembles a solid pipe that precludes manipulation or surgical intervention (Cohn and Edmunds 2003). The porcelain aorta is uncommonly encountered intraoperatively.

Atherosclerosis of the ascending aorta is a separate disease from age related stiffening and dilatation of the thoracic aorta (or arteriosclerosis), although the two may co-exist (Nichols and O'Rourke 2005). In some cases atherosclerotic disease may be widespread or consist of soft plaque or fungating plaque where manipulation of the aorta will result in embolisation of the material producing adverse outcome such as cerebrovascular accident (Cohn and Edmunds 2003; Little 2004). Severe atherosclerotic disease that precludes aortic manipulation e.g. cannulation for cardiopulmonary bypass and proximal anastomosis, is also uncommonly encountered intraoperatively, and may be detected using epiaortic ultrasound intra-operatively (Cohn and Edmunds 2003; Little 2004).

9.4 LIMITATIONS OF THIS THESIS

The acute haemodynamic effects of elastic wrap placement on the stiffened and dilated ascending aorta in an animal model were not assessed. Only a localised model of

aortic dilatation and stiffness was used where alterations in descending thoracic aortic or Dacron graft stiffness were measured.

Investigation of the acute effects of application of the aortic wrap on the ascending aorta in a generalised model of aortic dilatation and stiffness is technically very challenging, and similar information can be provided by in-vitro and computer models. There are no animal models of aortic stiffness and dilatation that adequately model ascending aortic stiffness and dilatation (O'Rourke 1967b; Morita, Kuboyama et al. 1991; Kelly, Tunin et al. 1992; Watanabe, Ohtsuka et al. 1993; Mekkaoui, Rolland et al. 2003). An accurate model of generalised thoracic aortic dilatation and stiffness requires replacement of the aorta from the aortic root to the diaphragm with an anatomically accurate and oversized Dacron (or other stiff conduit). The animal models described by Morita et al. (Morita, Kuboyama et al. 1991) and Kelly et al. (Kelly, Tunin et al. 1992) use a prosthetic tube as an extra-anatomic bypass to simulate aortic dilatation and stiffness. The proximal anastomosis in both these models was situated beyond the ascending aorta. The model cannot therefore be an accurate model for determining the effect that wrapping the ascending aorta will have on arterial haemodynamics and ventricular-vascular interaction as the native ascending aorta is left intact.

Replacement of the ascending aorta, arch of aorta, and descending aorta with an oversized Dacron conduit is a technically very challenging procedure with a high incidence of morbidity and mortality in humans in even specialised units (Baue, Geha et al. 1996; Cohn and Edmunds 2003; Kouchoukos, Blackstone et al. 2003). Replacement of the entire thoracic aorta in an animal with a Dacron graft requires the use of cardiopulmonary bypass, cardioplegic arrest, and deep hypothermic circulatory arrest (Baue, Geha et al. 1996; Cohn and Edmunds 2003; Kouchoukos, Blackstone et al. 2003). Technical problems relate to the:

1. anastomosis between the aortic root and oversized Dacron graft,
2. alterations in myocardial function relating to cardiopulmonary bypass, cardioplegic arrest, and hypothermia
3. high incidence of bleeding requiring transfusion of blood and coagulation products
4. high incidence of complications such as respiratory dysfunction, cerebrovascular accident, spinal chord ischaemia, and renal failure

All of the above may impact on haemodynamic function and ventricular-vascular interaction as well impact on the survival of the animal to the point where meaningful data may not be collected. The effect of wrapping the ascending aorta on arterial haemodynamics and ventricular-vascular interaction was therefore assessed using a human in-vitro model and computer model.

The wrap material and clamp were only implanted in two animals. More extensive biocompatibility and fatigue data from animal implantation will be required prior to implantation in humans.

Finally, in-vivo haemodynamic data from acute human studies will be required prior to longer term implantation in humans. Prior to acceptance for routine clinical use in human subjects the aortic wrap procedure will need to undergo appropriate clinical trials. Phase 1 will assess the application safety of the device (e.g. fatigue of the wrap material and clamp mechanism) and surgical procedure (e.g. median sternotomy versus thoracotomy). Phase 2 will determine the appropriate target group and phase 3 will assess the efficacy in the appropriate target group.

Limitations relating to the wrap material and clamp mechanism include the lack of biocompatibility data and long-term fatigue testing. In this thesis, a silicon polymer was used as the elastic wrap material, however this may not be the optimal material. The

optimal material may in fact be a biologic material (i.e. human or animal aorta) or two phase artificial material that simulates the mechanical properties of the aorta.

Human aortas are currently preserved using cryopreservation; a process that does not alter the mechanical properties of the aortic wall (Adham, Gournier et al. 1996; Baue, Geha et al. 1996). Human aortas are in limited supply (as are donor hearts for transplantation) and will not be sufficient to treat the expected patient population that would benefit from this treatment. Current techniques of preserving animal aortas e.g. glutaraldehyde fixation, significantly increase their stiffness rendering them useless as an aortic wrap (Gournier, Adham et al. 1993; Baue, Geha et al. 1996). Implantation of cryopreserved human or animal aortas as wrap may result in infarction and loss of mechanical properties of these materials due to a lack of blood supply (Stefanadis, Vlachopoulos et al. 1995; Angouras, Sokolis et al. 2000).

A two phase artificial material that simulates the stress-strain curve of the ascending aorta of young human subjects is not currently available but represents a future area for study. Tissue engineered compliant arterial grafts are currently in development (Shum-Tim, Stock et al. 1999; Hiromichi Sonoda 2002; Hiromichi Sonoda 2003; Seifalian, Salacinski et al. 2003).

9.5 AREAS FOR FUTURE INVESTIGATION

Areas for future investigation include the following:

1. Optimisation of the wrap material, design, and geometry.
2. Optimisation of the clamping or fixation mechanism
3. Further biocompatibility and fatigue testing of the wrap material and clamp or fixation device.

4. The design of new instruments to facilitate minimal access placement of the device.
5. Further investigation of the effects of the device on the thoracic aorta in an animal model (long term implantation).
6. Acute human studies involving placement of the device on the ascending aorta of humans undergoing cardiothoracic procedures through a median sternotomy.
7. Chronic human studies.

CHAPTER 10: CONCLUSIONS

Application of an elastic wrap to a stiffened and dilated vessel, that reduces the diameter of the vessel, will reduce the stiffness of the vessel. The elastic wrap may act by unloading the native vessel wall and taking the load of pulsatile pressure and flow. The elastic wrap reduced the stiffness of the aged human aorta in the in-vitro model (Chapter 5) as well as the stiffness of a non-elastic vascular graft (Dacron) in the animal model (Chapter 4).

When the elastic wrap is applied to the aged ascending aorta (that is stiffened and dilated), a reduction in ascending aortic systolic and pulse pressure, and increase in diastolic pressure is expected. The reduction in ascending aortic stiffness reduced systolic pressure and pulse pressure, and increased diastolic pressure in the in-vitro (Chapter 5) and mathematical models (Chapter 6).

A reduction in systolic and pulse pressure is expected to reduce left ventricular and myocardial oxygen demand and improve cardiac efficiency. These changes are expected to arrest or reverse myocardial remodelling and improve cardiac function in elderly patients with heart failure. An increase in diastolic pressure is expected to increase coronary blood flow and myocardial oxygen supply. A reduction in ascending aortic stiffness and pulse pressure may also arrest (or induce regression) of microvascular changes in the brain and kidney.

Potential adverse effects of the aortic wrap procedure include stiffening of the underlying vessel with loss of the unloading effect of the aortic wrap on the aortic wall. Other potential adverse effects include fatigue and failure of either the material or clamp

mechanism, or dislocation of the wrap material. Finally the wrap may induce aneurysmal changes in the underlying aorta.

Application of an elastic wrap to the ascending aorta in elderly human subjects may be an effective surgical treatment of aortic dilatation and stiffness and its detrimental sequelae such as isolated systolic hypertension, left ventricular hypertrophy, heart failure, as well as microvascular disease of the kidney and brain. Possible clinical indications may include the treatment of heart failure (by reduction of mechanical load and improved coronary blood flow) and isolated systolic hypertension. The procedure may be a useful adjunct to the medical and surgical treatment of myocardial ischaemia (by reduction of ventricular load, regression of myocardial hypertrophy, and improved coronary blood flow). Elastic wrap application to the thinned and dilated ascending aorta may be useful for the prevention of aortic rupture (reduction aortoplasty), as well as the treatment of microvascular disease of the kidney and brain.

In conclusion, application of an elastic wrap to a stiffened and dilated vessel, that reduces the diameter of the vessel, will reduce the stiffness of the vessel. Application of the elastic wrap to the aged human ascending aorta in-vivo is expected to reduce systolic and pulse pressure, and increase diastolic pressure with a reduction in cardiac load and improvement in coronary perfusion. The aortic wrap procedure may be an effective surgical procedure for the treatment of heart failure as well as isolated systolic hypertension.

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APPENDIX 1: ANIMAL MODEL- PREOPERATIVE CARE, ANAESTHESIA, AND POSTOPERATIVE CARE

All animal work in this study was reviewed by and agreed to by the UNSW Animal Ethics Committee. Mature crossbred Merino ovine wethers were used in the animal studies.

A1 Preoperative care / preparation

Neutered adult male sheep were used in this study. The animals were purchased from a commercial farm where adequate husbandry was provided to ensure both disease control and adequate nutrition.

Upon receipt at the Biological Resources Centre (University of New South Wales) sheep unit, the animals underwent drenching and vaccination. Animals were examined to screen for infection and congenital abnormalities.

Each animal was assigned an identification number physically adhered to the animal (ear tag) by BRC personnel. This number was used for identification of the animal throughout the study.

The sheep were housed for 4 weeks before undergoing any surgical procedures, and were provided with food daily and water ad libitum. Animals that showed any evidence of respiratory or other illness were excluded from the study. Documentation regarding indoctrination, housing, transport, surgery, and management for the duration of the study was maintained as part of the animals study record.

The sheep were transported in to the Clinical Sciences Building, Prince Henry Hospital, 3-5 days prior to surgery. This was a short trip within the same facility lasting

only 5 –10 minutes. The impact of trucking the sheep was minimised by the use of specially designed trailers or air-conditioned trucks (BRC equipment). At all times the sheep were under the care and control of UNSW staff that were experienced in the transport of sheep, and in the immediate care required by sheep after trucking.

The animals were maintained on a normal diet until the night before surgery. They were then fasted overnight although water was not withheld.

A2 Animal Preparation / Anaesthesia

A2.1 Anaesthesia

Anaesthesia was induced and maintained as described below in all animal studies. Anaesthesia was induced by intravenous injection of a barbiturate (Pentobarbitone sodium; 30mg/kg). A cuffed endotracheal tube was inserted and anaesthesia maintained using halothane (2-3%) and 100% oxygen. Lung ventilation was achieved using a positive pressure respirator.

A long acting opioid (Buprenorphine 0.01mg/kg) was injected subcutaneously for analgesia. The two survival animals also received an anti-inflammatory and analgesic agent (Carprofen 4mg/kg), as well as prophylactic antibiotics (Keflin 1gm IV) at induction.

Intravenous maintenance fluids (Hartmann's solution) were administered throughout the surgery. The electrocardiogram was continuously monitored throughout all experiments.

Body temperature was kept constant using a heating mattress. A rectal temperature probe was placed and secured to record core body temperature.

A2.2 Preparation

The sheep was placed in the right lateral recumbency and the left chest was clipped, and the animal transported to the operating room. The sheep was positioned in a stable full lateral position with the side to be operated on (left side) uppermost. The animal was firmly fixed into position with the use of foam sponges placed at the right and left flanks, and by tying down both hind limbs as well as the right forelimb. The skin was prepared for aseptic surgery by scrubbing with povidone-iodine solution and draped with sterile surgical drapes.

A2.3 Monitoring

The equipment used for anaesthesia included an anaesthetic machine, which allowed fine control of the delivery of anaesthetic gases and the supply of 100% oxygen. This allowed fine control of the depth of anaesthesia.

Anaesthetised animals were monitored throughout the surgical procedure. The following physiologic parameters were monitored and recorded every 15 minutes during all surgical procedures:

1. Heart rate and arterial oxygen saturation using a pulse oximeter.
2. Respiratory rate, depth of respiration and, end tidal carbon dioxide.
3. Capillary refill, eye reflex, jaw reflex, and mucous membrane colour.
4. Aortic blood pressure, the aortic pressure waveform, and heart rate using a Miller catheter (Model SPC-771; Millar Instruments, Houston, TX) inserted into the femoral artery and advanced into the proximal descending thoracic aorta.

A3 Recovery / monitoring

The animals in the chronic survival study (see chapter 7) were recovered and monitored until sacrifice at 10 weeks as set out below.

A3.1 Recovery

The animal was weaned from the ventilator as soon as there was spontaneous respiration with adequate tidal volumes, and stable haemodynamics. When the animal was able to breathe spontaneously, mechanical ventilation was discontinued and the animal allowed breathe through the endotracheal tube for as long as the tube was tolerated. The endotracheal tube was then removed. Oxygen was supplemented through the endotracheal tube prior to its removal.

The animal was transferred from the operating table to a transport cage. When the animal was sufficiently awake and ventilating adequately, the animal was transferred from the operating theatre to the animal holding area of the Clinical Sciences Building.

Monitoring occurred for the first 6 postoperative hours to ensure the animals were breathing freely, pain free, haemodynamically stable, and able to stand. Observations were made of the animal's general demeanor looking for signs of pain or respiratory distress.

The rate and depth of respiration were assessed hourly. The left and right lung fields were auscultated hourly. Heart rate was measured hourly by auscultation. Core body temperature was measured four hours postoperatively using a rectal probe.

Acute phase (Days 1- 7)

<u>The animal was assessed daily</u>

Observations were made of the animal's general demeanor looking for signs of pain, respiratory distress, or general distress. Oxygen saturation, heart rate, blood pressure and temperature were measured. The rate and depth of respiration was assessed. Pain assessment was performed and included monitoring for teeth grinding, salivation, ease of movement, and weight bearing. Note was made of the animals appetite and drinking, urination and defecation, interest in surroundings, and mobility.

The surgical incision was inspected for signs of infection, inflammation and general integrity. Examination of the thorax included percussion and auscultation of the lung fields for signs of collapse, pleural effusion or pneumothorax.

Cage side observations

Offsite observations were performed for 1 week postoperatively. Animals were observed during feeding and during long-term housing by animal care staff for behavioural changes. They were monitored for appetite, thirst, urination, defecation, demeanor, interest in surroundings, and ambulation.

Clinical observations

Clinical observations were performed and recorded daily for one week. During clinical observations, evidence of a clinical effect was noted, with observations including, but not limited to, changes in: the skin and hair, eyes and mucous membranes, respiratory system, circulatory system, central nervous system, motor activity, behaviour pattern; occurrence of tremors, convulsions, salivation, diarrhoea, or lethargy.

A veterinarian was available if required during this period for consultation to ensure the best possible care and recovery of the animals.

Chronic monitoring

After the first week the animals were monitored on a weekly basis until reoperation and sacrifice at 10 weeks. The animal was transported to the BRC sheep-holding unit for chronic monitoring and housing.

Monitoring was recorded weekly after the acute phase. Note was made of their general demeanor, appetite, drinking, urination, defecation, breathing weight change, interest in surroundings, mobility and signs of pain and distress.

The surgical site was inspected for signs of infection or inflammation. The thorax was examined by auscultation and percussion.

During clinical observations, evidence of a clinical effect was noted, with observations including, but not limited to changes in: the skin and hair, eyes and mucous membranes, respiratory system, circulatory system, central nervous system, motor activity, behaviour pattern, occurrence of tremors, convulsions, salivation, diarrhoea, or lethargy.

Preoperative care / preparation (Summary)

1. Order animal
2. Receipt: BRC sheep unit
3. Indoctrination: drenching and vaccination
4. Initial housing prior to surgery
    a. Duration: 4 weeks
    b. Location
        i. BRC- Preoperatively
        ii. Clinical Sciences Building, sheep holding room, peri operatively
    c. Cage dimensions: 2.3 x 2.0 metres or 1.1 x 2.0 metres
    d. Stocking
        i. 2.3 x 2.0 – 2 animals per cage
        ii. 1.1x 2.0 – 1 animal per cage
    e. Feeding and Watering: Animals were fed once a day and had continuous access to water.
5. Transport to Clinical Sciences Building, Prince Henry Hospital
    a. 3-5 days prior to surgery
    b. Duration: 5 –10 minutes
    c. The impact of trucking the sheep was minimised by the use of specially designed trailers or air-conditioned trucks (BRC equipment).
    d. At all times the sheep were under the care and control of UNSW staff who are experienced in the transport of sheep, and in the immediate care required by sheep after trucking.

6. Fasted overnight, water not withheld.

Postoperative recovery timeline

At the end of the first 24 hours the animal was expected to:

1. Be able to weight bear and mobilise comfortably
2. Be able to breathe freely and to maintain adequate oxygenation of the blood on room air
3. Be able to eat and drink

By the end of the first week postoperatively it was expected that the animal would have fully recovered from the operation:

1. There would be in minimal <u>if any</u> pain from the procedure
2. The animal would be able to bear weight and mobilise comfortably
3. The wound would have healed
4. Any changes in the left pleural space and left lung would have resolved e.g. atelectasis, fluid collection
5. The animal would be able to breathe freely and oxygenate the blood on room air/atmospheric oxygen concentration
6. The animal would be able to eat, drink, and graze.