Chapter 1

Introduction

1.1 Introduction

Although it is generally perceived that regular exercise is beneficial to the cardiovascular system (Blomqvist and Saltin 1983; Schaible and Scheuer1985), whether exercise has deleterious effects on the heart has in the past and is now again being questioned. In the past this conundrum existed as exercise was and still is recognized as a factor that promotes the development of cardiac hypertrophy (Huston et al 1985; Maron 1986; Shapiro 1984), a change that in pathological states such as hypertension has adverse prognostic implications. Although in the past the concern was that exercise-induced cardiac hypertrophy could have the same adverse effects as pathological hypertrophy, it is presently acknowledged that exercise-induced cardiac hypertrophy does not appear to predict adverse cardiovascular outcomes and may not be associated with the progression to cardiac dysfunction (Atchley et al 2007; Pluim et al 1999b). Hence, in contrast to cardiac hypertrophy which occurs in pathological states (pathological hypertrophy), exercise-induced cardiac hypertrophy is thought to be a compensatory response to the normal demands of activity and as such is called “physiological cardiac hypertrophy”. However, with respect to physiological cardiac hypertrophy, the question that is again foremost in some minds is whether the cardiac geometric change that accompanies regular, sustained medium-to-high intensity exercise has pathophysiological relevance.

As will be discussed, regular, sustained, medium-to-high intensity exercise programs may induce cardiac hypertrophy with a geometric change that may not maintain wall stress during exercise-induced increases in blood pressure and chamber filling.

Indeed, in this form of exercise the cardiac chamber increases in size to accommodate continuously high pre- and after-loads (Abergel et al 2004, Abernethy et al 2003; Colan et al 1987) and this cardiac geometric change is reminiscent of cardiac dilatation in chronic heart failure, where a greater cavity size predicts a worse clinical outcome (Cohn et al 2000). As cardiac chamber dilatation contributes to pump dysfunction in heart failure and subsequent end stage heart failure (Badenhorst et al 2003b, Cohn et al 2000, Cohn et al 1995, Mann et al 1999, Norton et al 2002, Veliotes et al 2005), the obvious question that arises is whether increases in cardiac cavity size in exercise-induced cardiac hypertrophy also promote pump dysfunction? In this regard, presently there is little understanding of the pathophysiological significance of increases in cardiac cavity size in exercise-induced cardiac hypertrophy. Although a reduced pump function has been noted to occur with increased cavity dimensions in endurance athletes (Abergel et al 2004, Abernethy et al 2003, Colan et al 1987, Gilbert et al 1977, Nishimura et al 1980, Pelliccia et al 1999, Rerych et al 1980), whether the dilated chamber promotes pump dysfunction or is the consequence of alternative changes such as a reduced contractile function and heart rate or an increased preload, is unclear.

This dissertation aims to elucidate the pathophysiological relevance of increases in cardiac cavity size in exercise-induced cardiac hypertrophy. As such, the current understanding of the role of pathological versus physiological cardiac hypertrophy will first be reviewed in this chapter. The role of cardiac dilatation in contributing toward heart failure and pump dysfunction will subsequently be discussed. As a major pathophysiological change thought to be responsible for cardiac dilatation in heart failure is excessive sympathetic nervous system activation (Agabiti-Rosei et al 1987; Kelm et al

1996; Schlaich et al 2003), in the present dissertation I compared the impact of exercise-induced cardiac dilatation on pump function to that of cardiac dilatation induced by sympathetic over-activation. Consequently, in the present chapter I will also review the current scientific literature on the role of sympathetic over-activation in heart failure and the potential mechanisms by which neurohumoral activation may lead to cardiac dilatation. Last, I will discuss the evidence to indicate that exercise-induced cardiac hypertrophy is associated with increases in cardiac cavity size and underscore the evidence and arguments both for and against a potential pathophysiological role of exercise-induced cardiac dilatation.

1.2 Pathological versus physiological cardiac hypertrophy.

Cardiac hypertrophy is considered a compensatory response to a chronic pressure or volume load on the heart. In accordance with the law of La Place, where wall tension or stress, is proportional to the product of pressure (P) and radius (r) and inversely proportional to wall thickness (h), an increased wall thickness in cardiac hypertrophy maintains a normal wall stress in the face of either increments in pressure or volume within the cavity. Cardiac hypertrophy maintains wall stress by increasing wall thickness and if the hypertrophic process is concentric, potentially also by reducing internal radius. Based on the principle that ventricular geometry and wall thickness change to maintain systolic stress within normal limits (Grossman et al 1976), cardiac hypertrophy was considered an adaptive reaction to a pressure or volume overload with a more favorable outcome predicted (Gaasch et al 1978, Grossman et al 1976). However, as will be

underscored in subsequent discussion, cardiac hypertrophy can no longer be considered a compensatory change in cardiac pathology. Whether cardiac hypertrophy can be considered a structural adaptation without adverse consequences in subjects who frequently exercise will also be discussed.

1.2.1 Pathological hypertrophy predicts adverse cardiovascular outcomes and cardiac dysfunction independent of blood pressure.

A common form of pathological hypertrophy is that which occurs in response to a high systemic blood pressure (BP) (systemic hypertension). As systemic BP affects the left side of the heart, the hypertrophic process is in the left ventricle. Although systemic BP is the stimulus for the left ventricle enlarging in hypertension, many studies now support the notion that left ventricular hypertrophy is a predictor of cardiovascular risk independent of conventional BP measurements (Casale et al 1986, Drazner et al 2004, Gardin et al 2001, Ghali et al 1998, Koren et al 1991, Levy et al 1990, Levy et al 1994, Verdecchia et al 1996, Verdecchia et al 2001). Even in the absence of arterial hypertension, left ventricular mass is an independent risk factor for cardiovascular events (Gardin et al 2001), coronary heart disease (Koren et al 1991) and all-cause mortality (Koren et al 1991). As the predictive power of left ventricular hypertrophy frequently relates to vascular, rather than cardiac pathology; this raises the question as to whether cardiac hypertrophy really has a pathophysiological role to play in these cardiovascular events. There are nevertheless data to show that cardiac hypertrophy also predicts the development of cardiac dysfunction. Indeed, left ventricular hypertrophy may predict the

development of a decrease in left ventricular ejection fraction (a preload-independent index of pump function) or the development of diastolic dysfunction independent of traditional risk factors including conventional BP (Drazner et al 2004).

Controversy has been generated by data that show that cardiac hypertrophy predicts progressive cardiac dysfunction independent of other factors, such as hypertension or systemic BP. Three possible scenarios could be considered. One possibility is that the current clinical assessments of hypertension and BP are poor indicators of target organ effects of BP, and hence that we need to improve our ability to measure BP effects. In this scenario, BP obviously retains a central pathophysiological role. Second, factors other than BP that induce cardiac hypertrophy may also produce adverse cardiovascular events. In this scenario BP loses a critical role to other potential determinants of both cardiac hypertrophy and cardiovascular events. Obviously these factors need to be identified and targeted therapeutically. Lastly, cardiac hypertrophy alone may be sufficient to promote the development of progressive cardiac dysfunction. In this scenario BP again loses a central role once cardiac hypertrophy has evolved. Under this circumstance, the therapeutic goal would be to regress hypertrophy and not necessarily just to target BP alone. There is indeed evidence to support all three suppositions, evidence that will not be discussed in great detail as it goes beyond the scope of this dissertation. However, in the context of physiological cardiac hypertrophy, what does need to be further considered in some detail are the potential mechanisms by which cardiac hypertrophy alone is sufficient to promote the development of progressive cardiac dysfunction.

1.2.1.1 Mechanisms responsible for the development of progressive dysfunction in cardiac hypertrophy.

The identification of the potential mechanisms by which cardiac hypertrophy in pathological states may promote cardiac dysfunction has been the goal of many studies over the past two-to-three decades. Left ventricular hypertrophy could promote both diastolic and systolic cardiac dysfunction and both functional abnormalities shall be considered in turn.

With respect to diastolic dysfunction, this may occur as a consequence of both a decreased early-diastolic relaxation and a reduced late-diastolic compliance (Dreslinski et al 1981, Hanrath et al 1980). Impaired relaxation may occur through decreases in the activity of the sarcoplasmic reticulum Ca^{2+} ATPase pump, a change which accompanies the switch from adult to fetal gene expression during pathological cardiac hypertrophy, a switch that may or may not be attributed to pressure effects alone (Qi et al 1997). With respect to alterations in late (or end) diastolic compliance, these are potentially through increases in concentrations of myocardial collagen of the cross-linked subtype, a change that increases the tensile strength of the myocardium (Norton et al 1997, Badenhorst et al 2003a). The mechanisms of the alterations in myocardial collagen cross-linking are unclear. However, both BP-dependent and independent mechanisms may be responsible for these myocardial collagen changes (Weber et al 1988a, Norton et al 1997, Badenhorst et al 2003a). Lastly, with respect to the mechanisms by which hypertrophy promotes diastolic dysfunction, alterations in both early and late diastolic function may occur simply through a thicker ventricular wall restricting filling. However, the relevance of a

thicker ventricular wall as a determinant of diastolic dysfunction in pressure-overload states has been challenged (Norton et al 1993, Norton et al 1997).

With respect to the mechanisms by which cardiac hypertrophy promotes systolic dysfunction, this could, in-part, occur ultimately as a consequence of diastolic dysfunction. Diastolic dysfunction may increase cardiac filling pressures, augment myocardial transmural pressures during diastole and reduce coronary flow (decrease coronary reserve) (Lorell and Grossman 1987). This, together with an increased myocardial oxygen demand produced by the greater bulk of tissue requiring oxygen (Kannel et al 1970, Ghali et al 1991) could result in pump dysfunction, lethal ventricular arrhythmias (Cosin Aguilar et al 1993, Ghali et al 1991), programmed cell death (apoptosis) (Condorelli et al 1999, Teiger et al 1996) and necrosis (Ferrari et al 1998). Apoptosis and necrosis, which often accompany pathological hypertrophy, could further promote myocardial contractile disturbances. These changes are obviously dependent on the degree of diastolic dysfunction rather than on BP *per se*. More recently, a number of lines of evidence now support the notion that sympathetic over-activation may contribute toward the transition to systolic heart failure in left ventricular hypertrophy, a change that is also BP-independent. This notion is of particular importance with respect to exercise-induced cardiac hypertrophy. After all, exercise conditioning is associated with marked sympathetic over-activation during periods of exercise training. The evidence to suggest that sympathetic over-activation promotes the transition to heart failure in left ventricular hypertrophy is discussed below.

First, increased myocardial noradrenaline concentrations are measured in the coronary sinus in patients with hypertensive hypertrophy prior to the development of

heart failure (Agabiti-Rosei et al 1987; Kelm et al 1996; Schlaich et al 2003). Second, blockade of β-adrenoreceptors prevents the transition from compensated cardiac hypertrophy to heart failure independent of BP effects (Chan et al 2004). Third, in compensated hypertensive hypertrophy excessive adrenergic activation is associated with down-regulation of β-adrenergic receptor-mediated contractile function (Böhm et al 1994a; Böhm et al 1995; Castellano et al 1993; Limas and Limas 1978). Fourth, transgenic animal models with decreased adrenergic activation are protected against the development of cardiac dilatation, pump dysfunction and heart failure when the left ventricle is exposed to a pressure-overload (Esposito et al 2002). Fifth, as demonstrated by our group, compensated left ventricular hypertrophy increases the susceptibility of the heart to chronic β-adrenoreceptor-mediated cardiac dilatation and pump dysfunction (Badenhorst et al 2003b). Thus, it appears that chronic sympathetic over-activation is important in promoting the development of systolic heart failure in pathological hypertrophy. The obvious question that arises from these data is whether habitual exercise, which is a state of sympathetic over-activation during episodes of exercise, promotes similar effects in subjects with exercise-induced cardiac hypertrophy? The answer to this question is unlikely to be straight-forward as it is well recognized that in individuals who are physically conditioned, parasympathetic and not sympathetic tone predominates in-between periods of exercise (Peronnet et al 1981a; Winder et al 1979).

1.2.1.2 Is physiological hypertrophy associated with cardiac dysfunction?

To-date there is little evidence to suggest that physiological hypertrophy

contributes toward excessive cardiovascular events or progressive cardiac dysfunction (Atchley et al 2007; Pluim et al 1999b). Indeed, most studies assessing pump function in either endurance athletes or after physical conditioning programs have failed to show an impaired cardiac systolic function (Table 1.1). Moreover, all studies assessing systolic function in animal models of physical conditioning programs have similarly failed to demonstrate an impaired cardiac systolic function (Table 1.2). However, some older (Colan et al 1987, Gilbert et al 1977, Nishimura et al 1980, Pelliccia et al 1999, Rerych et al 1980) and more recent studies (Abergel et al 2004, Abernethy et al 2003) have provided evidence to suggest that left ventricular ejection fraction (or endocardial fractional shortening), an afterload and heart rate dependent measure of pump function may be reduced in some endurance athletes who undergo medium-to-high intensity endurance exercise training (Table 1.1). These data (Abergel et al 2004, Abernethy et al 2003, Colan et al 1987, Gilbert et al 1977, Nishimura et al 1980, Pelliccia et al 1999, Rerych et al 1980) are obviously of concern, but, as will be discussed, must be interpreted with caution.

1.2.1.3 Potential reasons why exercise-induced cardiac hypertrophy may not be associated with cardiac dysfunction.

There are many reasons to believe that exercise-induced cardiac hypertrophy may of course not be associated with cardiac dysfunction. First, exercise-induced cardiac hypertrophy results in an improved rather than impaired myocardial compliance, a change that enhances ventricular filling and hence improves systolic function (Woodiwiss

Table 1.1. Summary of changes in indices of systolic (pump) function noted in human studies conducted in endurance athletes or after physical conditioning programs.

Study	Type of exercise or sporting activity	Measure of systolic function	Change in systolic function*
1. Abergel et al 2004	Cycling (Tour de France)	EF (echo)	**none, but ↓ in cohort with LVEDD>60mm (↓ HR)**
2. Abernethy et al 2003	Football	EF (echo)	**none, but ↓ (50-59%) in 39%**
3. Arbab-Zadeh et al 2004	Masters athletes	SV, preload recruitable SW (echo and MRI)	↑ SV, preload recruitable SW unchanged
4. Bar-Shlomo et al 1982	Endurance athletes	EF (radionuclide angiography)	none
5. Basavarajaiah et al 2008	Athletes	FS (echo)	none
6. Child et al 1984	Running	FS (echo)	none
7. Colan et al 1987	Running	FS & Vcf (echo)	↓ **FS, but rate corrected Vcf normal**
	Swimming	FS & Vcf (echo)	↑
8. Cox et al 1986	Running & cycling	EF & SV (echo)	↑ (after 7 weeks of training)
9. D'Andrea et al 2002	Swimming & running	EF & SV (echo)	EF none, but ↑ SV (vs. weight-lifting & body-building)
10. DeMaria et al 1978	Endurance (11 weeks training)	FS, SV & Vcf (echo)	↑ (after 11 weeks of training)
11. Dickhuth et al 1987	Marathon runners	FS (echo)	none
12. Douglas et al 1986	Triathletes (swimming, cycling & running)	FS & end-systolic stress (echo)	none
13. Douglas et al 1997	Triathletes (swimming, cycling & running)	EF (echo)	none (values within normal range)
14. duManoir et al 2007	Endurance & strength training	stroke area (echo)	↑ (after 10 weeks of training)
15. Ehsani et al 1978	Swimming (9 weeks training)	EF (echo)	none
16. Fagard et al 1984	Cycling, running	% shortening LVEDD, peak vel. LVIDs (echo)	none

Table 1.1. continued

Study	Type of exercise or sporting activity	Measure of systolic function	Change in systolic function*
16. Gilbert et al 1977	Running	EF (echo)	**↓ EF (range 58-80%), but ↓ HR**
17. Levine et al 1991	Running or Cycling (3 years)	SV (echo)	↑
18. Levy et al 1993	Running & cycling (6 months)	SV (radionuclide ventriculography)	↑
17. Miki et al 1994	Cycling	FS (echo)	none
18. Nishimura et al 1980	Cycling	EF, FS, Vcf (echo)	**EF & FS none, but ↓ Vcf (↓ HR)**
19. Palazzuoli et al 2004	Running	EF, SV &FS (echo)	↑ EF, SV &FS
20. Paulsen et al 1981	Marathon runners	Vcf (echo)	↓ (due to ↓ RPP, contractility not different from controls)
21. Pelliccia et al 1999	Olympic athletes (38 different sports)	EF &FS (echo)	**EF none, but FS ↓ (in cohort with LVEDD>60mm)** (↓ FS not clinically relevant as range 27-43 vs. 24-50% in controls)
22. Pluim et al 1996 & 1998	Cycling	EF (MRI)	none
23. Pluim et al 1999b	Running (meta-analysis)	EF & FS (echo)	none
24. Rerych et al 1980	Swimming (6 months training)	EF & SV (radionuclide ventriculography)	**↓ EF but ↑ SV (after 6 months of training)**
25. Shapiro & Smith 1983	Running (6 weeks training)	FS (echo)	none (after 6weeks of training)
26. Stein et al 1980	Cycling (14 weeks training)	FS (echo)	↑ FS (after 14 weeks of training)
27. Urhausen et al 1996	Rowers	FS (echo)	none
28. Vinereanu et al 2001	Running, weight-lifting	EF (echo)	none
29. Whalley et al 2004	Endurance-trained athletes	FS (echo)	none
30. Wolfe et al 1979	Running (22 weeks training)	EF, Vcf (echo)	none (trend for ↑ after 22 weeks of training)

Studies reporting decreased systolic function are indicated in bold; * change noted in comparison to untrained or sedentary controls unless otherwise indicated; echo, echocardiography; EF, ejection fraction; FS, fractional shortening; LVEDD, left ventricular end-diastolic diameter; LVIDs, left ventricular internal diameter in systole; MRI, magnetic resonance imaging; SV, stroke volume; Vcf, velocity of circumferential shortening; vel., velocity.

Table 1.2. Summary of changes in measures of systolic (pump) function noted in studies conducted in animal models of exercise programs.

Study	Type of exercise	Measure of systolic function	Change in systolic function*
1. Barnard et al 1980	Treadmill running (dogs)	SV, CO, dP/dt (cardiac catheterization)	↑
2. Carew & Covell 1978	Running (greyhounds)	dP/dt, Vcf (micromanometry & sonomicrometry)	none
3. Crews & Aldiger 1967	Swimming (rats)	cardiac muscle tension (isolated cardiac muscle)	↑
4. Eto et al 2000	Voluntary running (rats)	VTI of aortic ejection flow (echo)	↑
5. Fuller & Nutter 1981	Treadmill running (rats)	dP/dt, CO, SV (isolated perfused heart)	none
6. Jin et al 2000	Treadmill running (rats)	SV index, cardiac index (cardiac catheterization, echo)	↑
7. Kammereit et al 1975	Swimming (rats)	dT/dt & peak tension (isolated trabecular muscle)	↑
8. Mole 1978	Swimming (rats)	dT/dt & peak tension (isolated papillary muscle)	↑
9. Pape et al 1986	Running (greyhounds)	dP/dt, SV, cardiac index (LV catheterization)	↑ SV & cardiac index, dP/dt unchanged
10. Ritzer et al 1980	Treadmill running (dogs)	SV, EF (ventriculography)	↑ SV, EF unchanged
11. Schaible & Scheuer 1979	Running (rats) Swimming (rats)	EF, Vcf, SV (isolated perfused heart)	↑ EF & SV, Vcf unchanged ↑ EF, SV & Vcf
12. Schaible & Scheuer 1981	Swimming (rats)	Vcf, dP/dt & EF (isolated perfused heart)	↑
13. Schaible et al 1981	Treadmill running (rats)	SV, EF (isolated perfused working heart)	↑

Table 1.2. continued.

Study	Type of exercise	Measure of systolic function	Change in systolic function
14. Schaible et al 1987	Treadmill running (rats)	EF, FS, Vcf (isolated perfused working heart)	↑ EF & FS (Vcf trend for ↑)
15. Stone 1977	Treadmill running (dogs)	SV, CO, maximum P (cardiac catheterization)	↑
16. Tibbits et al 1981	Treadmill running (rats)	dT/dt, peak tension (isolated papillary muscle)	↑
17. White et al 1987	Treadmill running (pigs)	dP/dt, change in LV wall thickness, SV, EF (sonomicrometry & flow transducer)	↑ SV, but rest no change
18. Woodiwiss &l Norton 1995	Voluntary running (rats)	preload recruitable SW (piezoelectric transducers & flow probe)	↑
19. Woodiwiss et al 1998	Voluntary running (rats)	end-systolic elastance (piezoelectric transducers)	↑

* change noted in comparison to untrained or sedentary controls; CO, cardiac output; dP/dt, maximum rate of pressure development; dT/dt, maximum rate of tension development; echo, echocardiography; EF, ejection fraction; FS, fractional shortening; LV, left ventricle; P, pressure; SV, stroke volume; Vcf, velocity of circumferential shortening; VTI, velocity time integral.

and Norton 1995). A number of factors could contribute toward the inability of exercise-induced cardiac hypertrophy to promote diastolic dysfunction. Unlike pathological hypertrophy, exercise-induced cardiac hypertrophy is not associated with increases in either myocardial collagen concentrations or the degree of cross-linking of myocardial collagen (Thomas et al 1992, Woodiwiss et al 1998). Moreover, myocardial relaxation is maintained in exercise-induced cardiac hypertrophy as the activity of the sarcoplasmic reticulum Ca^{2+} ATPase pump is sustained (Malhotra et al 1981).

There are probably a number of reasons to explain why in contrast to pathological cardiac hypertrophy which often progresses to pump dysfunction, physiological cardiac hypertrophy has generally not been associated with pump dysfunction. First, as indicated above, unlike pathological cardiac hypertrophy, physiological hypertrophy does not lead to diastolic dysfunction. Consequently, cardiac filling pressures are maintained at normal or even low values for a given stroke volume (through an improved compliance-Woodiwiss and Norton 1995) and hence there are unlikely to be limitations on coronary flow produced by increases in transmural pressures during that period of the cardiac cycle when most coronary flow occurs, namely diastole. Moreover, physiological hypertrophy has not been shown to be accompanied by cardiomyocyte apoptosis (Jin et al 2000), necrosis (Maron et al 1993), or down-regulation of β-adrenergic-induced contractile responses (Stones et al 2008). Nevertheless, the relevance of much of these data needs to be questioned as the intensity or duration of the exercise programmes and the degree of physiological hypertrophy may simply have been insufficient to produce pathological changes. More intense exercise programs indeed appear to promote pump dysfunction in

association with marked degrees of cardiac cavity enlargement (Abergel et al 2004, Abernethy et al 2003, Pelliccia et al 1999; see section 5.0, table 1.3).

1.2.1.4 Is advanced cardiac enlargement produced by exercise, a pathological condition?

As indicated above (see Table 1.1), most studies evaluating exercise effects on cardiac function have been relatively short-term (a few weeks) and the degree of cardiac hypertrophy and dilatation produced has generally not been that remarkable (see sections 2.2.1 and 5.0, and table 1.3). In contrast, the transition to heart failure in pressure-overload states may take years to emerge and is generally associated with advanced cardiac hypertrophy and marked cardiac dilatation (Tsotetsi et al 2001, Norton et al 2002). The question therefore arises as to whether more prolonged periods of exercise, more advanced hypertrophy, or hypertrophy with associated cardiac dilatation promotes pump dysfunction? This is particularly important as our group have recently demonstrated an increased myocardial norepinephrine release from the myocardium of rats with exercise-induced cardiac hypertrophy (Woodiwiss et al, personal communications), a change which in pathological states promotes the transition to cardiac dilatation and subsequent pump dysfunction (Badenhorst et al 2003b, Gibbs et al 2004, Osadchii et al 2007, Veliotes et al 2005). Moreover, there is presently evidence to suggest that sustained, medium-to-high intensity exercise training induces marked cardiac dilatation (LVEDD>60mm) (Abergel et al 2004, Abernethy et al 2003, Douglas et al 1997, Pelliccia et al 1999), a change which our group have recently observed as being a

major pathophysiological mechanism responsible for pump dysfunction following chronic sympathetic activation (Badenhorst et al 2003b, Osadchii et al 2007, Veliotes et al 2005). Indeed, marked cardiac dilatation associated with sustained, medium-to-high intensity exercise is also associated with pump dysfunction (Abergel et al 2004, Abernethy et al 2003, Pelliccia et al 1999).

Importantly, a relationship between cardiac dilatation and pump dysfunction does uniformly not imply that cardiac dilatation is the cause of pump dysfunction. Contractile changes will reduce pump function and simultaneously increase cardiac cavity dimensions (more blood is left in the heart). Thus, the obvious question that arises is whether subjects with marked exercise-induced cardiac hypertrophy with pathological levels of cardiac dilatation (Abergel et al 2004, Abernethy et al 2003, Pelliccia et al 1999) have pump dysfunction from cardiac dilatation or is the cardiac dilatation secondary to a reduced contractile function following an attenuated sympathetic tone? In other words, is the cardiac dilatation following sustained, medium-to-high intensity exercise a cause or a consequence of pump dysfunction (Abergel et al 2004, Abernethy et al 2003, Pelliccia et al 1999)?

1.3 Cardiac dilatation: definition and physiological or pathophysiological relevance

In cardiac pathology, three general mechanisms explain pump dysfunction. These are an increased ventricular afterload, decreases in the intrinsic contractile properties of the myocardium, and cardiac dilatation. The functional changes that accompany pump

failure are best explained by the Frank-Starling relation. Figure 1.1 illustrates the normal Frank-Starling relationship and the changes that occur in association with either an enhanced pump function or a decreased pump function. Movement of the ventricular function curve to the left of normal occurs when either intrinsic myocardial contractility increases (e.g. increased circulating catecholamines as may occur with exercise); afterload decreases (such as following vasodilatation); or the relationship between wall thickness and internal radius increases (such as with concentric cardiac hypertrophy), changes that enhance pump function. In contrast, as is the case in most forms of heart failure due to systolic functional abnormalities, displacement to the right and downward from the normal occurs when either ventricular contractility is depressed, afterload is increased or the heart dilates. Although the impact of changes in intrinsic myocardial contractility and the resistance to flow are relatively easy concepts to grasp, cardiac dilatation is sometimes a conceptually difficult issue. In this regard the important questions to ask and answer are what is cardiac dilatation, and how does it produce deleterious effects on pump function?

1.3.1 Cardiac chamber dilatation and pump dysfunction

Cardiac chamber dilatation refers to an increase in chamber cavity volumes or dimensions as a consequence of right shifts in diastolic pressure-volume relations (Figure 1.2). Cardiac dilatation is not simply an increase in cavity volume alone, as this may result from an enhanced blood volume or venous return without necessarily being accompanied by a right shift in the diastolic pressure-volume relation. Moreover, cardiac

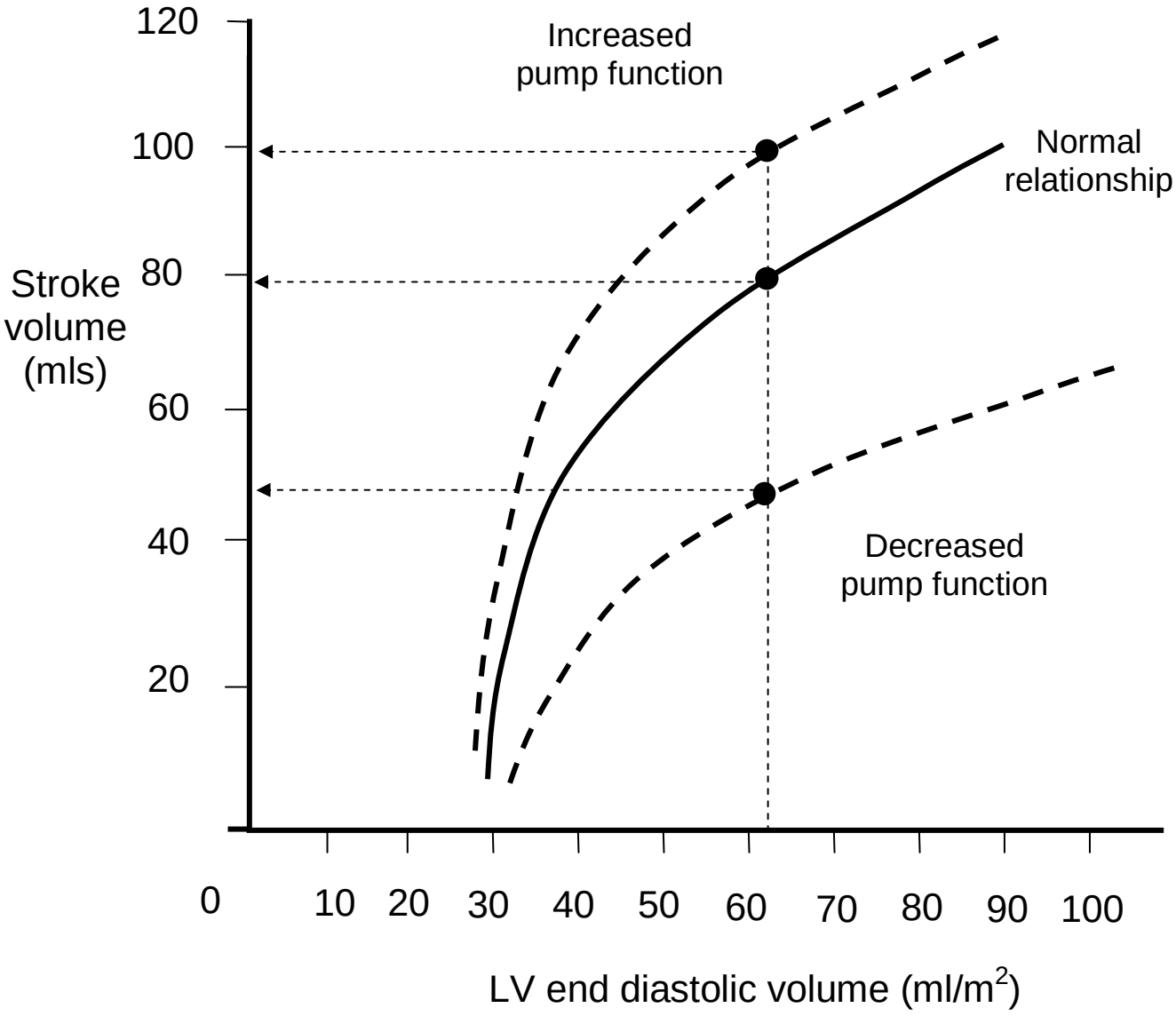

Figure 1.1. The normal relationship between left ventricular end diastolic volume and stroke volume (straight line) and the change in the relationship when pump function either improves (left sided dashed line) or declines (pump failure)(right sided dashed line). The impacts of changes in pump function for a given filling volume, on stroke volume are illustrated by the dashed arrows.

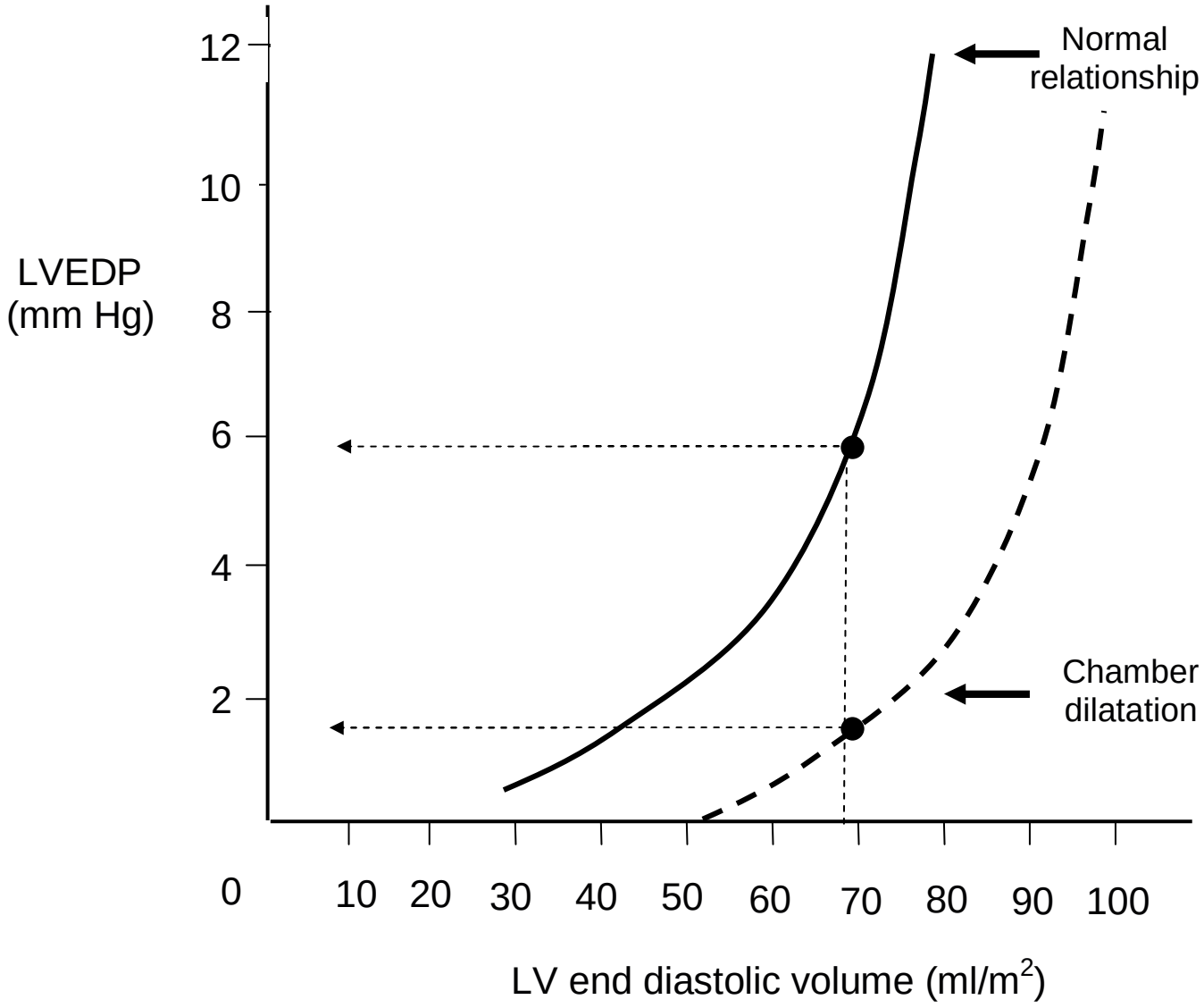

Figure 1.2. Left ventricular end diastolic pressure (LVEDP)-volume relationship showing a normal relationship (straight line), and the change in the relationship in the presence of cardiac chamber dilatation (dashed line). The effect of a cardiac dilatation on diastolic pressure for a given filling volume is illustrated by the arrows.

dilatation is not a right shift in diastolic pressure-volume relations produced by alterations in the slope of this relationship. Changes in the slope of the cardiac diastolic pressure-volume relationship occur as a consequence of alterations in chamber compliance, a modification that usually follows variations in myocardial material properties (Gilbert and Glantz 1989). In contrast, cardiac chamber dilatation is the consequence of an increased volume intercept of the diastolic pressure-volume relationship (Gibbs et al 2004).

For many years cardiac chamber dilatation was perceived as a compensatory change in heart failure (Ertl et al 1991). This relative misconception was based on the following argument. In heart failure, fluid accumulation and a reduced cardiac contractility increase ventricular filling volumes (Patterson and Adams 1996). Although pump dysfunction is reduced, increased ventricular filling volumes may maintain a normal ejection volume (stroke volume) through the Frank-Starling effect. The obvious negative impact of increased filling volumes is however an increased filling pressure which may increase pulmonary capillary hydrostatic pressures and produce pulmonary congestion. To allow the heart to accommodate greater filling volumes at normal filling pressures a rightward shift in the diastolic pressure-volume relation occurs, where a greater filling volume occurs at much lower filling pressure, thus reducing the chances of pulmonary congestion (Figure 1.2). However, a more recent view of cardiac dilatation is that it is causally related to pump dysfunction and heart failure. Indeed, cardiac dilatation is a precursor of pump dysfunction and clinical heart failure (Gaudron et al 1993; Pfeffer et al 1992; Vasan et al 1997). The intriguing question then is how does cardiac dilatation produce pump dysfunction?

1.3.2 Mechanisms of the impact of cardiac dilatation on pump function

La Place's law as applied to the heart could in-part explain the impact of cardiac dilatation on pump function. Indeed, chamber dilatation is associated with an increased cavity volume and hence radius, and a reduced wall thickness, effects that will, according to La Place's law, increase wall tension or stress. As wall stress determines myocardial oxygen consumption, a dilated ventricle may increase the myocardial oxygen demand-to-supply ratio. A demand-to-supply mismatch may subsequently decrease cardiac contraction. However, when systolic function is measured using a stress (or load)-independent measure of pump function (end systolic elastance) in an animal model of congestive cardiac failure and pump dysfunction associated with massive cardiac dilatation (Norton et al 2002), pump function was noted to be reduced without parallel changes in myocardial contractility. These data would suggest that a mechanism unrelated to a stress or load-induced effect contributes to pump dysfunction in cardiac dilatation. One potential explanation is that inappropriate force transduction occurs in dilated ventricles during myocyte contraction which in-turn leads to pump dysfunction. Alternatively, a dilated chamber could simply be remodelled so that larger chamber volumes are required to produce cardiomyocyte stretch and hence recruit the Frank-Starling effect.

Although an enhanced release of catecholamines during episodes of exercise increase cardiac pump function, an important question is what does repetitive sympathetic activation during exercise training programs do to the heart? In this regard, there is now substantial evidence to support a role for chronic sympathetic activation in

both cardiac pathology and in normal hearts as a major determinant of progressive pump dysfunction, largely through an impact on cardiac dilatation. The evidence to support a role for chronic sympathetic activation in promoting progressive pump dysfunction will therefore be discussed, with particular reference to sympathetic effects on cardiac dilatation.

1.4 Deleterious effects of chronic sympathetic activation on the heart.

The evidence in favour of over-activation of the sympathetic nervous system contributing toward pump dysfunction is as follows. Plasma noradrenaline concentrations are increased in patients with systolic heart failure and predict the severity of heart failure (symptoms based on the New York Heart Association classification) and pump dysfunction in heart failure (Anand et al 2003; Cohn et al 1984, Francis et al 1993, Kluger et al 1982, Sigurdsson et al 1994, Swedberg et al 1990). Myocardial noradrenaline levels are enhanced in patients with chronic heart failure and pump dysfunction (Esler et al 1997). In randomized-controlled clinical trials, blockade of β-adrenergic receptors improves pump function and subsequently decreases morbidity and mortality in patients with mild-to-moderate and severe systolic heart failure (CIBIS-II 1999, Flather et al 2005, Gerson et al 2002, MERIT-HF 1999, Packer et al 1996, Packer et al 2001, Poole-Wilson et al 2003, Toyama et al 2003, Waagstein et al 1993, Waagstein et al 2003). At a pre-clinical level, a fifteen-fold increase in β_1-adrenoreceptor expression in transgenic mice results in pump failure (Molenaar and Parsonage 2005) and chronic β-adrenergic receptor activation alone for prolonged periods produces marked pump dysfunction (Woodiwiss et al 2001). Despite the overwhelming evidence indicating that chronic β-

adrenoreceptor activation reduces pump function, there is presently substantial debate as to whether these effects are mediated by decreases in intrinsic myocardial contractility or cardiac chamber dilatation or both. In the following discussion I will therefore highlight the main arguments for and against a principle role of cardiac dilatation in mediating sympathetic-induced pump dysfunction.

1.4.1 Are the adverse effects of chronic sympathetic activation on pump function due to reductions in contractility or effects of cardiac dilatation?

A reduction in intrinsic myocardial contractility may occur if there is a loss of a substantial number of myocytes or if the function of viable myocytes is reduced. Chronic β-adrenoreceptor activation could promote progressive decreases in cardiac contraction by targeting both of these mechanisms. Indeed, chronic β-adrenoreceptor activation leads to a reduced β-adrenoreceptor-agonist-stimulated muscle contraction (Böhm et al 1988; Bristow et al 1982; Bristow et al 1986; Brodde et al 1986; Brodde et al 1989; Brodde 1991; Schotten et al 2000; Steinfath et al 1991; Tevaearai and Koch 2004); a defect in cardiomyocyte sarcoplasmic reticulum calcium release (Marx et al 2001); and both cardiomyocyte necrosis (Mann et al 1992; Sabbah 1999) and apoptosis (Sabbah 1999; Singh et al 2001).

Reductions in myocardial contractility subsequent to chronic β-adrenoreceptor activation could lead to cardiac dilatation, a change that would promote further pump dysfunction. Indeed, transgenic animal models with decreased adrenergic activation are protected against the development of dilatation when exposed to pressure-overloads (Esposito et al 2002). Moreover, blockade of β-adrenoreceptors prevents the transition

from cardiac hypertrophy to a dilated ventricle in hypertension (Chan et al 2004), a genetically modified fifteen-fold increase in β_1-adrenoreceptor expression results in cardiac dilatation (Molenaar and Parsonage 2005); and chronic β-adrenergic receptor activation for prolonged periods produces marked cardiac dilatation (Woodiwiss et al 2001). Measures of neurohumoral activation are closely associated with cardiac dimensions in patients with heart failure (Davila et al 2000; Patten et al 1998). Further, treatment of patients with β-adrenoreceptor blockers results in decreases in cardiac dimensions (Doughty et al 1997; Lechat et al 1997; Sharpe and Doughty 1998). However, another view of the relationship between chronic β-adrenoreceptor activation and cardiac dilatation is that the impact of β-adrenoreceptor activation or β-adrenoreceptor blockade on cardiac dimensions may not be secondary to changes in cardiac contractility and subsequent alterations in cardiac preloads, but rather through a direct effect of β-adrenoreceptor activation on cardiac dimensions. Indeed, as will be described, our group have recently provided evidence to suggest that this may be the mechanism by which chronic β-adrenoreceptor activation promotes pump dysfunction.

Our group have shown that chronic β-adrenoreceptor activation promotes the development of cardiac dilatation and pump dysfunction without producing concomitant changes in intrinsic myocardial contractility and subsequent alterations in cardiac preloads (Badenhorst et al 2003b, Veliotes et al 2005, Osadchii et al 2007). In these studies (Badenhorst et al 2003b, Veliotes et al 2005, Osadchii et al 2007) load-independent measures of intrinsic myocardial contractility (the slope of the left ventricular developed stress-strain relationship) and load-dependent measures of intrinsic myocardial function (left ventricular midwall fractional shortening) were unchanged,

despite a marked decrease in chamber systolic function (decreased slope of the left ventricular pressure-volume relationship as well as a decrease in left ventricular ejection fraction) following chronic β-adrenoreceptor activation (Badenhorst et al 2003b, Veliotes et al 2005, Osadchii et al 2007). The reduced chamber systolic function could only be attributed to an increase in left ventricular cavity dimensions and a right shift in the left ventricular diastolic pressure-volume relationship (left ventricular dilatation) (Badenhorst Aet al 2003b, Veliotes et al 2005, Osadchii et al 2007).

The obvious question that arises from these studies performed by our group (Badenhorst et al 2003b, Veliotes et al 2005) is how intrinsic myocardial contractility remains unchanged following chronic β-adrenoreceptor activation, when there is substantial evidence to indicate that chronic β-adrenoreceptor activation promotes downregulation of β-adrenoreceptor-mediated contractile responses and apoptosis and necrosis (see above discussion)? Indeed, although the dose of the β-adrenoreceptor agonist used by us on a daily basis to promote cardiac dilatation and pump dysfunction does not induce necrosis (Badenhorst et al 2003b), this dose used over prolonged periods is able to attenuate β-adrenoreceptor-mediated contractile responses and to induce apoptosis (Osdachii et al 2005, Osadchii et al 2007). The answer to this conundrum has been provided by us in recent studies. We have been able to show that attenuated β-adrenoreceptor-mediated contractile responses either translate into reduced norepinephrine-induced contractile responses at supraphysiological norepinephrine concentrations (Osadchii et al 2005), or that intrinsic myocardial contractility is sustained through enhanced myocardial α-adrenoreceptor mediated contractile responses and an increased presynaptic myocardial norepinephrine release (Osadchii et al 2007).

Our group have provided substantial evidence to indicate that chronic β-adrenoreceptor activation promotes cardiac dilatation through direct mechanisms, rather than effects secondary to decreases in intrinsic myocardial contractility. Hence, an important question that arises is through what mechanisms does chronic β-adrenoreceptor activation promotes cardiac dilatation?

1.4.2 Potential cellular mechanisms of the impact of chronic β-adrenoreceptor activation on cardiac cavity dimensions.

The cellular mechanisms by which chronic β-adrenoreceptor activation could produce cardiac dilatation, independent of effects on myocardial contractility, include increases in cardiomyocyte cell lengthening, or side-to-side slippage of cardiomyocytes. Although it is well recognized that chronic β-adrenoreceptor activation promotes cardiac hypertrophy (Woodiwiss et al 2001, Badenhorst et al 2003b, Veliotes et al 2005, Osadchii et al 2005, Osadchii et al 2007), presently there are no published studies that have explored whether chronic β-adrenoreceptor activation mediates this effect through cardiomyocyte cell lengthening. However, unpublished data from our laboratory (Correia et al, personal communications), indicate that the transition from compensated hypertrophy to cardiac dilatation mediated by chronic β-adrenoreceptor activation cannot be attributed to increases in cardiomyocyte length-to-width ratios.

With respect to side-to-side slippage of cardiomyocytes, there are two potential interstitial changes that may account for β-adrenoreceptor-induced cardiac dilatation, independent of effects on intrinsic myocardial contractility. First, stimulation of cultured

cardiomyocytes by β-adrenoreceptor agonists, activates matrix metalloproteinases (MMPs) (Menon et al 2005). MMP activation could in-turn reduce cardiomyocyte attachments through degradation of intercellular collagen struts, and hence promote cardiomyocyte side-to-side slippage. Second, in association with cardiac dilatation, chronic β-adrenoreceptor activation promotes the synthesis of myocardial collagen of preferentially the non-cross-linked phenotype (Badenhorst et al 2003b, Veliotes et al 2005). As this collagen is susceptible to MMP degradation (Woodiwiss et al 2001), its preferential accumulation may also result in excessive breaks and tears in intercellular collagen struts and thus side-to-side slippage of cardiomyocytes.

Apoptotic changes may also account for β-adrenoreceptor-induced cardiac dilatation, independent of effects on intrinsic myocardial contractility. Indeed, as indicated in the above discussion, via β-adrenoreceptors, adrenergic stimulation of cell cultures promotes increases in cell death by activation of apoptotic signaling pathways (Singh et al 2001). Moreover, our group have recently demonstrated that the doses of the β-adrenoreceptor agonist used by us on a daily basis to promote cardiac dilatation and pump dysfunction (Woodiwiss et al 2001) are associated with substantial cardiomyocyte apoptotic effects (Osadchii et al 2007). However, we have also recently observed that β-adrenoreceptor-mediated cardiac dilatation can be prevented by aldosterone receptor blockade (Veliotes et al 2005) without a similar beneficial effect of aldosterone receptor blockade on β-adrenoreceptor agonist-induced apoptosis (Mielke et al, personal communications). Based on this evidence, the role of apoptosis should be questioned.

1.5 Cardiac dilatation subsequent to chronic exercise

From the above discussion it should be apparent that cardiac dilatation in pathological cardiac hypertrophy does have consequences to pump function, and that this effect appears to be mediated in-part by chronic β-adrenoreceptor activation. As regular exercise is accompanied by sympathetic activation, it is important to consider whether cardiac dilatation occurs with physiological cardiac hypertrophy, whether these changes are as extensive as pathological dilatation and whether this has functional consequences? There is extensive evidence to indicate that increases in cardiac dimensions do indeed occur with endurance training. Indeed, most studies in endurance athletes or after physical conditioning programs have shown an increase in left ventricular internal dimensions (Table 1.3). Moreover, some studies have reported increases in left ventricular internal dimensions which reach pathological proportions (LVEDD>60mm) (Abergel et al 2004, Abernethy et al 2003, Basavarajaiah et al 2008, Douglas et al 1997, Pelliccia et al 1999). The proportion of athletes with left ventricular internal dimensions within the pathological range, is reported to be as high as 51% (Abergel et al 2004), although other studies have reported much lower proportions (6%, Abernethy et al 2003; 7%, Douglas et al 1997). However, as the measurements of left ventricular internal dimensions in athletes have not been corrected for the impact of preload, heart rate and contractility, these data need to be interpreted with caution. Increases in preload and decreases in heart rate, which occur with training, could account for the increases observed in left ventricular internal dimensions. Similarly, in animal models of physical

conditioning, some studies have shown increases in left ventricular internal dimensions whereas others have reported no change (Table 1.4). Indeed, in those studies in which measurements have been made at the same heart rate (a paced rate), no differences between physical conditioned and sedentary animals have been reported (Ritzer et al 1980).

As discussed cardiac dilatation is not simply an increase in cavity volume alone, as this may result from an enhanced preload (blood volume or venous return) or a decreased heart rate. A load and rate independent measure of cardiac dilatation is a right shift in the LV diastolic pressure-volume relation; whereby cavity volume is increased for a given filling pressure without altering the slope of the relation. A right shift in the diastolic pressure-volume which is accompanied by a decrease in the slope of the relation occurs when the compliance of the ventricle is enhanced. Those few studies which have assessed changes in left ventricular dimensions from LV diastolic pressure-volume relations, have reported right shifts in the LV diastolic pressure-volume relations in endurance trained athletes (Levine et al 1991), following endurance training in healthy subjects (Arbab-Zadeh et al 2004), and following voluntary exercise in rats (Woodiwiss and Norton 1995, Woodiwiss et al 1998). Although, these changes in the LV diastolic pressure-volume relation appear to be through an improved myocardial compliance (Arbab-Zadeh et al 2004, Levine et al 1991, Woodiwiss and Norton 1995, Woodiwiss et al 1998), the presence of cardiac dilatation cannot be ruled out.

Do pathological levels of cardiac dimensions mediated by endurance exercise translate into pump dysfunction? The majority of studies do not support the notion that increases in cardiac cavity dimensions are associated with pump dysfunction

Table 1.3. Summary of human studies assessing cardiac cavity dimensions in endurance athletes or subsequent to physical conditioning programs.

Study	Type of exercise or sporting activity	Change in internal dimensions or diastolic pressure-volume relation	Associated pump dysfunction
1. Abergel et al 2004	Cycling (Tour de France)	↑ **LVEDD (51% >60mm)**	**YES, ↓ EF & FS (EF<60% in ½ of those with ↑ LVEDD)**
2. Abernethy et al 2003	Football	↑ **LVEDD (6% >60mm)**	**YES, EF normal except ↓ (50-59%) in 39%**
3. Arbab-Zadeh et al 2004	Masters athletes	↑ LVEDV & right shift in LVEDP-LVEDV relation† (echo and MRI)	NO, ↑ SV, preload recruitable SW unchanged
4. Basavarajaiah et al 2008	Athletes	↑ **LVEDD (range 44-64mm)**	NO, FS normal
5. Child et al 1984	Running	↑ LVEDD/BSA	NO, FS normal
6. Colan et al 1987	Running	↑ LVEDD (mean 52.0±1.0mm)	**YES, ↓ FS, but rate corrected Vcf normal**
	Swimming	↑ LVEDD (mean 54.0±1.5mm)	NO, ↑ FS & rate corrected Vcf
7. Cox et al 1986	Running & cycling	↑ LVEDD (mean 51.3±1.9mm) & ↑ LVEDV	NO, ↑ SV & EF
8. D'Andrea et al 2002	Swimming & running vs. weight-lifting & body-building	↑ LVEDD (mean 55.4±4.7mm)	NO, EF not different & ↑ SV
9. DeMaria et al 1978	Endurance (11 weeks training)	↑ LVEDD (range 40-60mm)	NO, ↑ FS, SV & Vcf (after 11 weeks training)
10. Dickhuth et al 1987	Marathon runners	↑ LVEDD (mean 56.6±2.8mm)	NO, FS normal
11. Douglas et al 1986	Triathletes (swimming, cycling & running)	LVEDD unchanged	NO, FS normal
12. Douglas et al 1997	Triathletes (swimming, cycling & running)	↑ **LVEDD (range 40-65mm) (7% >60mm)**	NO, mean EF normal
13. duManoir et al 2007	Endurance & strength training	↑ LVED cavity area	NO, ↑ stroke area
14. Ehsani et al 1978	Swimming (9 weeks training)	↑ LVEDD (mean 52.0±1.7mm)	NO, EF unchanged
15. Fagard et al 1984	Running Cycling	↑ LVEDD (mean 52.5±1.0mm) ↑ LVEDD (mean 55.2±1.0mm)	NO, % shortening LVEDD & % peak vel. LVIDs normal
16. Gilbert et al 1977	Running	↑ LVEDV/BSA, normal LVEDD	**YES, ↓ EF (range 58-80%), but ↓ HR**

Table 1.3. continued

Study	Type of exercise or sporting activity	Change in internal dimensions or diastolic pressure-volume relation	Associated pump dysfunction
17. Levine et al 1991	Running or Cycling (3 years)	↑ LVEDV & right shift in LVEDP-LVEDV relation† (echo)	NO, ↑ SV
18. Levy et al 1993	Running & cycling (6 months)	↑ LVEDV & ↑ LV filling rate (radionuclide ventriculography)	NO, ↑ SV
19. Miki et al 1994	Cycling	↑ LVEDD (mean 54.0±3.7mm)	NO, FS normal
20. Nishimura et al 1980	Cycling	↑ LVEDD (mean 54.5±2.8mm)	**YES, ↓ Vcf (but ↓ HR & EF & FS normal)**
21. Palazzuoli et al 2004	Running	normal LVEDD, ↑ LVEDV/BSA	NO, ↑ EF, SV &FS
22. Paulsen et al 1981	Marathon runners	↑ LVEDD (mean 56.0±4.0mm)	**YES, ↓ Vcf (but ↓ RPP, contractility not different from controls)**
23. Pelliccia et al 1999	Olympic athletes (38 different sports)	**↑ LVEDD (14% >60mm)**	**YES, FS ↓ but EF normal (in cohort with LVEDD>60mm)** (↓ FS: 27-43 vs 24-50% in controls)
24. Pluim et al 1996 & 1998	Cycling	↑ LVEDV/BSA	NO, EF normal
25. Pluim et al 1999b	Running (meta-analysis)	↑ LVEDD (range 52.8-54.6mm)	NO, EF & FS normal
26. Rerych et al 1980	Swimming (6 months training)	↑ LVEDV	**YES, ↓ EF but ↑ SV & ↓ HR**
27. Shapiro & Smith 1983	Running (6 weeks training)	LVEDD unchanged	NO, FS unchanged
28. Stein et al 1980	Cycling (14 weeks training)	↑ LVEDD (mean 50.0±1.1mm)	NO, ↑ FS
29. Urhausen et al 1996	Rowers	↑ LVEDD (>55mm, 69% M & 23% F)	NO, FS normal
30. Vinereanu et al 2001	Running, weight-lifting	↑ LVEDD (mean 55.0±1.0mm)	NO, EF normal
31. Whalley et al 2004	Endurance-trained athletes	↑ LVEDD (mean 55.6±0.6mm)	NO, FS normal
32. Wolfe et al 1979	Running (22 weeks training)	LVEDD unchanged	NO, trend for ↑ EF, Vcf

Studies reporting marked dilatation (LVEDD>60mm), and studies reporting pump dysfunction are indicated in bold.

† right shift in LVEDP-LVEDV relation indicates ↑ LVEDV for given LV filling pressure; BSA, body surface area; EF, ejection fraction; F, female; FS, fractional shortening; HR, heart rate; LVEDD, left ventricular end-diastolic diameter; LVEDV, left ventricular end diastolic volume; LVIDs, left ventricular internal diameter in systole; M, male; MRI, magnetic resonance imaging; RPP, rate-pressure product; SV, stroke volume; Vcf, velocity of circumferential shortening; vel., velocity.

Table 1.4. Summary of studies assessing cardiac cavity dimensions in animal models of exercise programs.

Study	Type of exercise	Change in internal dimensions or diastolic pressure-volume relations	Associated pump dysfunction
1. Barnard et al 1980	Treadmill running (dogs)	↑ LV wall thickness (cardiac catheterization)	NO, ↑ SV, CO & dP/dt
2. Carew & Covell 1978	Running (greyhounds)	↑ **LVEDD** (sonomicrometry)	NO, dP/dt &Vcf unchanged
3. Crews & Aldiger 1967	Swimming (rats)	↑ heart weight	NO, ↑ cardiac muscle tension
4. Eto et al 2000	Voluntary running (rats)	↑ **LVEDD** (echo)	NO, ↑ VTI of aortic ejection flow
5. Fuller & Nutter 1981	Treadmill running (rats)	heart weight unchanged	NO, dP/dt, CO & SV unchanged
6. Jin et al 2000	Treadmill running (rats)	LVEDD unchanged (echo)	NO, ↑ SV index, cardiac index
7. Kammereit et al 1975	Swimming (rats)	8% ↑ heart weight	NO, ↑ dT/dt & peak tension
8. Mole 1978	Swimming (rats)	15% ↑ heart weight	NO, ↑ dT/dt & peak tension
9. Pape et al 1986	Running (greyhounds)	LVEDD unchanged (LV catheterization)	NO, ↑ SV & cardiac index, dP/dt unchanged
10. Ritzer et al 1980	Treadmill running (dogs)	↑ **LVEDV** (normal when paced) (ventriculography)	NO, ↑ SV, EF unchanged
11. Schaible & Scheuer 1979	Running (rats) Swimming (rats)	LVEDV unchanged (isolated perfused heart)	NO, ↑ EF & SV, Vcf unchanged NO, ↑ EF, SV & Vcf
12. Schaible & Scheuer 1981	Swimming (rats)	↑ heart weight (isolated perfused working heart)	NO, ↑ Vcf, dP/dt & EF
13. Schaible et al 1981	Treadmill running (rats)	LVEDV unchanged (isolated perfused working heart)	NO, ↑ SV, EF

Table 1.4. continued.

Study	Type of exercise	Change in internal dimensions or diastolic pressure-volume relations	Associated pump dysfunction
14. Schaible et al 1987	Treadmill running (rats)	↑ **LVEDV** (isolated perfused working heart)	NO, ↑ EF & FS (Vcf trend for ↑)
15. Stone 1977	Treadmill running (dogs)	no dimensions	NO, ↑ SV, CO, maximum P
16. Tibbits et al 1981	Treadmill running (rats)	LV weight unchanged	NO, ↑ dT/dt, peak tension
17. White et al 1987	Treadmill running (pigs)	↑ **LVEDD & LVEDV** (sonomicrometry & flow transducer)	NO, ↑ SV, but dP/dt, change in LV wall thickness, & EF unchanged
18. Woodiwiss et al 1995	Voluntary running (rats)	right shift in LVEDP-LVEDV relation† (piezoelectric transducers & flow probe)	NO, ↑ preload recruitable SW
19. Woodiwiss et al 1998	Voluntary running (rats)	right shift in LVEDP-LVEDV relation† (piezoelectric transducers)	NO, ↑ end-systolic elastance

Studies reporting enlarged ventricular internal dimensions are indicated in bold. * change noted in comparison to untrained or sedentary controls; † right shift in LVEDP-LVEDV relation indicates ↑ LVEDV for given LV filling pressure; CO, cardiac output; dP/dt, maximum rate of pressure development; dT/dt, maximum rate of tension development; echo, echocardiography; EF, ejection fraction; FS, fractional shortening; LV, left ventricle; P, pressure; SV, stroke volume; SW, stroke work; Vcf, velocity of circumferential shortening; VTI, velocity time integral.

(Tables 1.3 and 1.4). However, some studies have provided evidence to indicate that pump dysfunction noted after endurance training (Abergel et al 2004, Abernethy et al 2003, Colan et al 1987, Pelliccia et al 1999) could occur through increases in cardiac chamber dimensions (chamber dilatation). However, there are many arguments to support the notion that reductions in pump function in endurance athletes with increases in cardiac cavity dimensions are through non-pathological decreases in myocardial contractility, rather than because of a dilated chamber. These arguments are as follows. First, endurance training is associated with decreases in sympathetic activity (Janssen et al 1993, Pluim et al 1999a), and hence when cardiac function is measured at rest, a reduced contractile function may be evident. Of course this would only occur if basal (resting) contractile function was dependent on sympathetic drive. This is indeed the case as β-adrenoreceptor blockers produce profound effects on basal contractile function (Osadchii et al 2007). Second, despite a reduced ejection fraction (pump function) noted at rest in 39% of footballers, ejection fraction appropriately increases with exercise when sympathetic activation is required (Abernethy et al 2003), a change that would not occur if cardiac dilatation was the mechanism of the reduced basal function to begin with. Third, when correcting ejection fraction for wall stress in dilated hearts of endurance athletes, an approach which potentially eliminates the negative impact of cardiac dilatation on pump function, a significant number of athletes still have reductions in pump function (Abergel et al 2004, Colan et al 1987). If cardiac dilatation was the cause of the reduced pump function, then ejection fraction is likely to be normalized after corrections for wall stress. Fourth, relative wall thickness was noted to be increased in athletes with pump dysfunction and a dilated chamber (Abergel et al 2004). According to

the law of La Place, cardiac dilatation is likely to reduce pump function only if the relationship between wall thickness and internal radius is reduced. Fifth, against a role for exercise-induced cardiac dilatation in promoting pump dysfunction is the evidence that an increased stroke volume may occur in endurance athletes with increases in cardiac chamber dimensions (Arbab-Zadeh et al 2004, Cox et al 1986, D'Andrea et al 2002, DeMaria et al 1978, Levine et al 1991, Levy et al 1993, Rerych et al 1980; see Table 1.3). Thus, the impact of exercise-induced cardiac dilatation on pump function is uncertain.

1.6 Summary of problem statement and aims of the dissertation.

From the above discussion it should be apparent that marked increases in cardiac cavity dimensions can occur with chronic exercise under certain circumstances. Although this has not been proven, presumably pathological levels of increases in cardiac cavity dimensions with exercise occur partly due to right shifts and increased volume intercepts of diastolic pressure-volume relations. It should also be evident that this could be mediated through the well-recognized effects of chronic sympathetic activation, changes that are not necessarily secondary to contractile disturbances, but which could lead to pump dysfunction.

Although increases in cardiac cavity dimensions have been shown to occur in association with pump dysfunction after prolonged medium-to-high intensity endurance exercise training (Colan et al 1987, Abernethy et al 2003, Abergel et al 2004), the obvious question is whether pump dysfunction under these circumstances is the cause or the consequence of exercise-induced chamber dilatation? This question has not been

answered to-date for a number of potential reasons. First, there are no animal models of marked exercise-induced cardiac dilatation (increased volume intercept of diastolic pressure-volume relations) that have been described. Second, in human studies it is difficult to identify subjects with marked cardiac dilatation in the absence of a pathological cause. Third, in human studies it is not clear whether increases in cavity volume are simply through marked increases in preload, or whether they are associated with right shifts in diastolic pressure-volume relations. Last, in human studies intrinsic myocardial contractile function cannot be assessed. Hence, it is difficult to assess the relative roles of intrinsic myocardial contractile disturbances and cardiac dilatation as causes of pump dysfunction in human studies. Therefore, further studies are required to determine the pathophysiological significance of exercise-induced cardiac dilatation. The question is whether an appropriate study design indeed exists to solve this conundrum?

Following habitual exercise for prolonged periods in rats, our group have recently noted that a proportion of rats do indeed develop degrees of cardiac dilatation (right shifts in diastolic pressure-volume relations with increased volume intercepts) that are equivalent to those produced by chronic β-adrenoreceptor activation (Woodiwiss and Norton, personal communications). This observation provided an ideal opportunity to study the functional consequences of marked exercise-induced cardiac dilatation. The data described in this dissertation are the outcome of this study.

The aim of my dissertation was therefore to determine whether pump dysfunction occurs in rats with exercise-induced cardiac dilatation and whether the extent of which is comparable with that produced by pathological dilatation. The models of pathological dilatation that I used as comparators in this study were those produced by chronic β-

adrenoreceptor activation in rats, where our group has previously established the importance of cardiac dilatation as a cause of pump dysfunction (Woodiwiss et al 2001, Badenhorst et al 2003b, Veliotes et al 2005, Osadchii et al 2007).

Chapter 2

Methods

2.1 Animal models of cardiac dilatation.

The studies were approved by the Animal Ethics Committee of the University of the Witwatersrand (approval numbers 99:01:2b, 2002:37:5 and 2002:39:5). All rats used in these studies were housed in the Central Animal Services of the University of the Witwatersrand. The room in which the rats were housed was temperature controlled at 22°C and was lighted between 0600 and 1800. Standard laboratory rat chow and water were provided *ad libitum.*

Two models of cardiac dilatation were used in these studies, namely: (1) a model of pathological cardiac hypertrophy and dilatation (induced by chronic β-adrenoreceptor agonist administration to either Sprague-Dawley or spontaneously hypertensive rats), and (2) a model of physiological cardiac hypertrophy and dilatation (induced in Sprague-Dawley rats by 4-5 months of voluntary running activity on exercise wheels).

2.1.1 β-adrenoreceptor agonist-induced cardiac dilatation

The rodent model of pathological cardiac hypertrophy and dilatation studied in this dissertation was that induced by chronic administration of the β-adrenoreceptor agonist, isoproterenol (ISO) to either Sprague Dawley rats (Woodiwiss et al 2001) or to spontaneously hypertensive rats (SHR) with compensated left ventricular hypertrophy (Badenhorst et al 2003b). As the model of exercise-induced cardiac dilatation available to me is best produced in Sprague Dawley rats, Sprague-Dawley rats receiving ISO for prolonged periods is obviously the most appropriate comparator of pathological

dilatation. However, SHR as well as normal Sprague Dawley rats were utilized as comparator groups in the present dissertations for the following reasons. First, the SHR model receiving ISO for prolonged periods is the model of pathological dilatation where our group has established the importance of chamber dilatation over that of myocardial dysfunction in determining pump dysfunction (Badenhorst et al 2003b, Veliotes et al 2005). At the time of initiating this dissertation, the relative roles of chamber dilatation and myocardial dysfunction as determinants of pump dysfunction following chronic ISO administration to Sprague Dawley rats had not been established. Second, I was uncertain as to whether the transition to cardiac dilatation in physiological cardiac hypertrophy involves separate mechanisms from those involved in producing cardiac hypertrophy to begin with. Hence, I wished to employ an animal model of a sympathetic-induced cardiac dilatation which evolved from an initial hypertrophic state (Badenhorst et al 2003b) as an additional comparator group. A group of Wistar Kyoto rats was also included as these rats are the normotensive genetic control rats for SHR (Tsotetsi et al 2001).

In the present study, either 250 g Sprague Dawley rats (n=20) or 10-month old SHR (n=43) and age-matched Wistar Kyoto (WKY) controls (n=17) were randomized. All rats were males. SHR and WKY were subsequently studied over a time period (10-to-17 months of age) prior to that when left ventricular decompensation occurs in the SHR colony which is bred by the Central Animal Services of the University of the Witwatersrand (Tsotetsi et al 2001). Sprague-Dawley rats (SD) and SHR were assigned to groups that received either twice daily intraperitoneal injections of ISO (Imuprel: Adcock Ingram, 0.02 mg/kg per injection subcutaneously ≈0.2 ml) for 7 months (SD-ISO: n=10; SHR+ISO: n=22) (Figure 2.1) or twice daily intraperitoneal injections of the

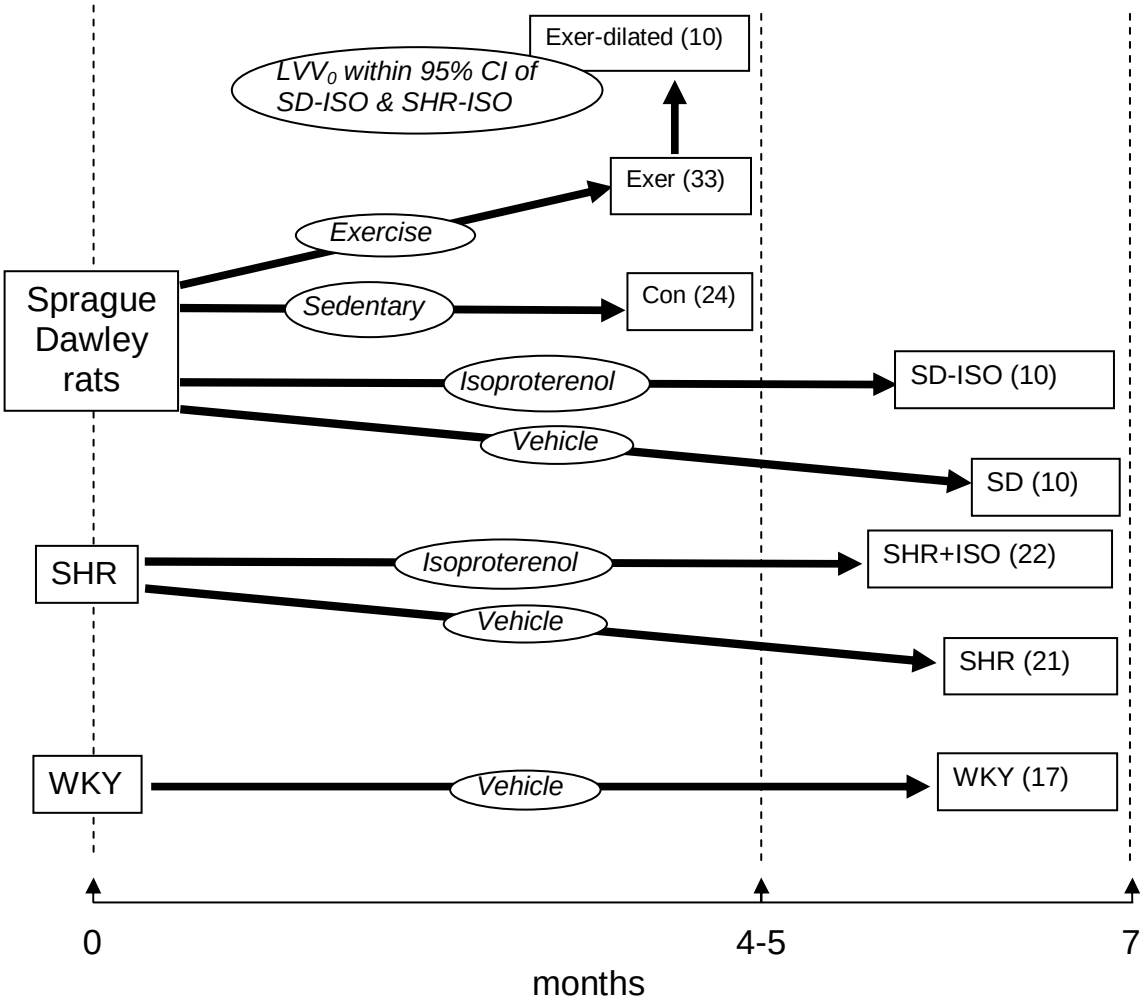

Figure 2.1. Flow chart showing random assignment of Sprague-Dawley, SHR and WKY rats to study groups (Exer: Sprague-Dawley exercise; Con: Sprague-Dawley sedentary controls; SD-ISO: Sprague-Dawley receiving daily isoproterenol; SD: Sprague-Dawley receiving daily vehicle of isoproterenol; SHR+ISO: SHR receiving daily isoproterenol; SHR: SHR receiving daily vehicle of isoproterenol; WKY: WKY receiving daily vehicle of isoproterenol). Exer-dilated are those Sprague-Dawley exercise rats with equivalent extents of dilatation as in SD-ISO and SHR+ISO (intercept of the left ventricular diastolic pressure-volume relationship within 95% CI of SD-ISO and SHR+ISO).

saline vehicle for 7 months (SD: n=10; SHR: n=21) (Figure 2.1). Ten-month-old WKY rats received twice daily intraperitoneal injections of the saline vehicle of ISO for 7 months prior to data collection (WKY: n=17) (Figure 2.1). ISO was not given to WKY as our group has previously shown that ISO has little effect on left ventricular geometry and function in WKY controls (Badenhorst et al 2003b).

2.1.2 Exercise model.

The rodent model of physiological cardiac hypertrophy and dilatation studied in this dissertation was that induced by 4-5 months of voluntary running activity on exercise wheels designed in our laboratory (Woodiwiss and Norton 1995). Using this method of voluntary exercise training, Woodiwiss and Norton (1995) have shown that 4 months of exercise training resulted in the development of significant LV hypertrophy (10% difference in LV mass in exercise-trained compared to sedentary control groups) which is equivalent to the mean increase in LV mass of 9.8% noted in longitudinal human studies (Wolfe et al 1986).

As not all Sprague Dawley rats will voluntarily run, rats first needed to be selected before they were randomly assigned to exercise or control groups. For this purpose, 102 male Sprague-Dawley rats weighing 75-90g were placed individually in cages with free access to voluntary running wheels with a circumference of 1 meter (Figures 2.2 and 2.3) (Woodiwiss and Norton 1995), for a ten day period of voluntary running. Daily running distance was monitored using odometers (CatEye) attached to the wheels (Woodiwiss and Norton 1995) (Figures 2.2 and 2.3). Only those rats that ran on

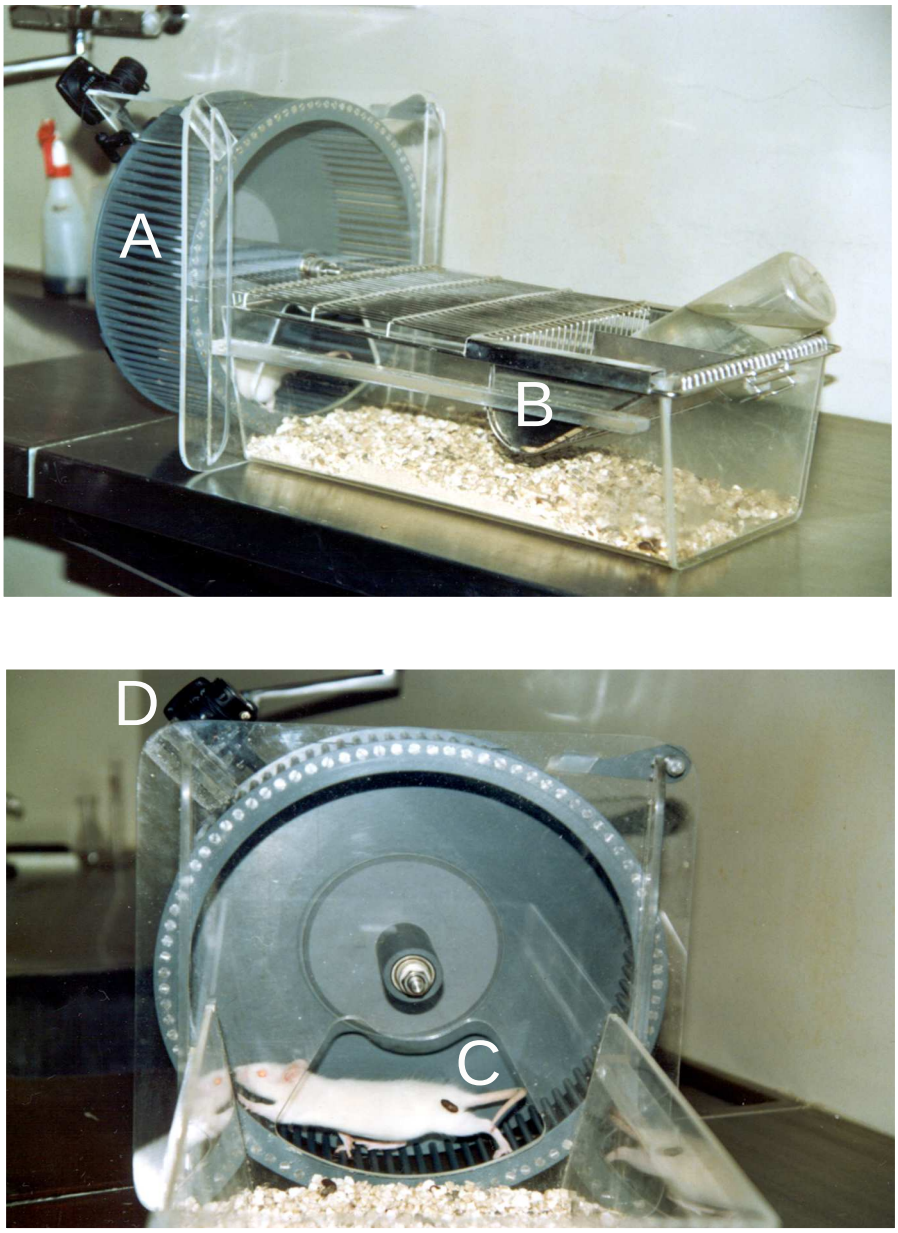

Figure 2.2. Photographs of voluntary running wheel (A) with a circumference of 1m, attached to standard rat cage (B). Rats had free access to the running through the opening in the cage (C). Distance run was monitored using CatEye odometers (D).

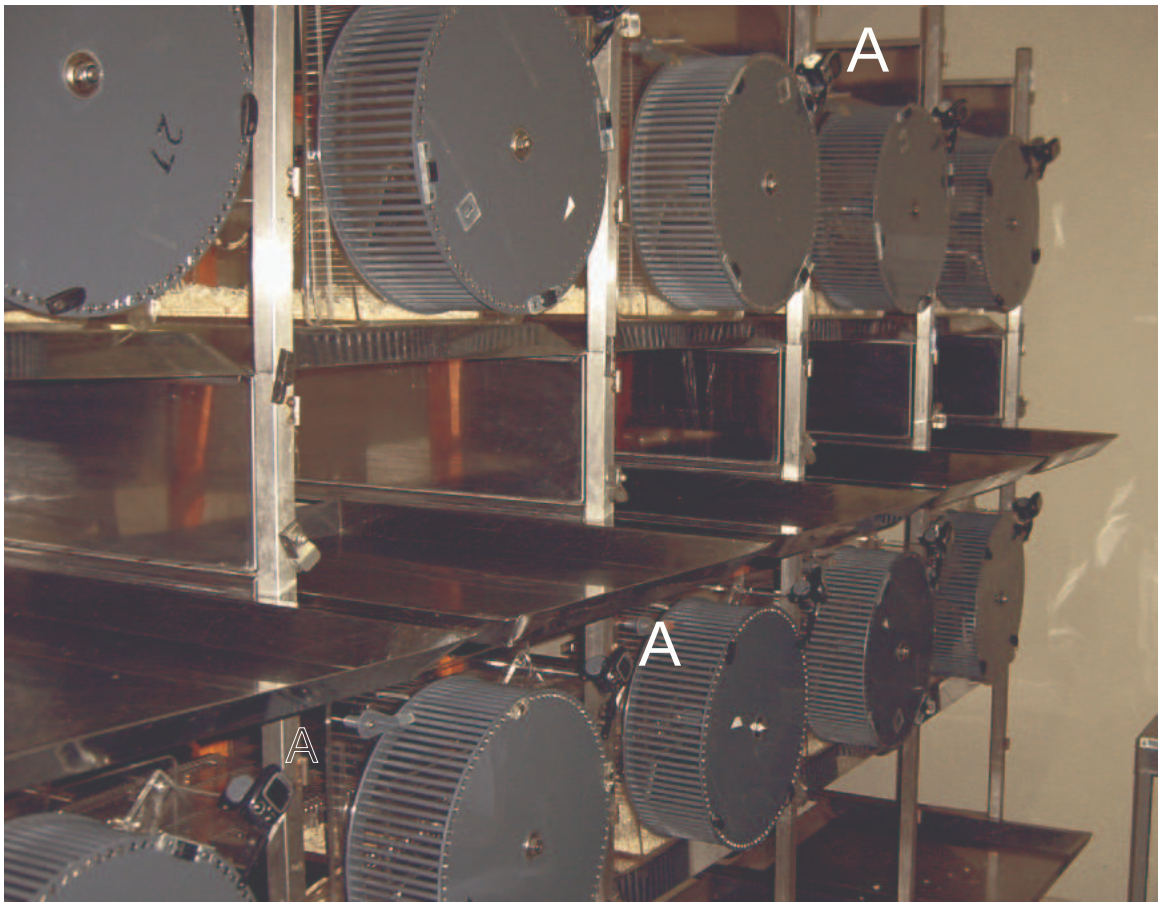

Figure 2.3. Photograph showing arrangement of voluntary running wheels in a room in the Central Animal Services of the University of the Witwatersrand. Sedentary control rats were housed individually in cages on the opposite of the room. Daily running distance was monitored using CatEye odometers (A).

average more than 2km/day were selected. These 57 selected rats were then assigned to exercise (Exer: n=33) or sedentary control (Con: n=24) groups (Figure 2.1). The rats assigned to the exercise group were placed individually in cages with free access to voluntary running wheels for a 4 to 5 month period of voluntary running. The sedentary control rats were housed individually in the same room in similar cages but without access to voluntary running wheels.

Although right shifts in LV diastolic pressure-volume relations and increments in the mean volume intercept for these relations (LV V_0, see 2.2.1) were noted to occur in exercised rats, thus providing evidence of eccentric LV remodeling, the extent of these changes was not as marked as those noted to occur in rats with pathological eccentric LVH. Therefore a cohort of exercised rats with LV V_0 values within 95% confidence intervals of rats with pathological eccentric LVH was selected (Exer-dilated: n=10), for the purposes of assessing pump function at comparable degrees of eccentric LV remodeling.

2.2 Isolated, perfused heart preparation

The degree of left ventricular dilatation as well as systolic chamber and myocardial function were determined in an isolated, perfused organ system (Norton et al 2002, Woodiwiss et al 2001, Badenhorst et al 2003b). In contrast to *in vivo* assessments, where the impact of fluctuating heart rates, loading conditions, neurohumoral activity and coronary flow is difficult to control, an isolated, perfused organ system allows for the

measurement of cardiac structure and function in the absence of neurohumoral activation and whilst controlling for heart rate, preload, afterload and coronary flow.

At least 24-hours after the last period of exercise or ISO injection, rats were anaesthetized with ketamine ($75mg.kg^{-1}$) and xylazine ($15mg.kg^{-1}$) and a thoracotomy was performed. Hearts were immediately excised and placed in an ice-cold perfusion solution (Table 2.1) to maintain their viability prior to perfusion. Hearts were subsequently placed on a Langendorff apparatus and retrogradely perfused via the aorta.

A Langendorff technique, rather than a working heart perfusion system was selected to determine function, as coronary flow in a working heart system depends on the function of the left ventricle as well as the function of the coronary vasculature. Using a Langendorff apparatus, perfusion fluid travels down the aorta toward the heart, the aortic valve stays in a closed position because of the pressure gradient produced across the aortic valve, and perfusion fluid flows down the coronary arteries rather than into the left ventricular lumen. Thus myocardial viability is maintained via constant coronary perfusion without relying on the function of the left ventricular chamber to determine coronary flow and myocardial tissue viability.

The perfusion solution employed to maintain myocardial tissue viability (Table 2.1) was saturated with 95% O_2 and 5% CO_2 gas and filtered through a size 0.45μm Millipore Durapore membrane filter before buffering the solution to achieve a pH of 7.40. The solution was constantly gassed with 95% O_2 and 5% CO_2 for the duration of each study. Hearts were perfused at a constant flow of 12 ml/min.g wet heart weight. To obtain this flow rate a crude heart weight (heart weight with left ventricle, right ventricle, atria and large vessels) was determined before perfusing the heart. Once the

Table 2.1. Constituents of the perfusion solution as well as the purpose for the inclusion of each ingredient.

Constituent	[mM]	Reason for constituent
NaCl	118.0	To maintain transmembrane osmolarity gradients.
KCl	4.7	To maintain a stable resting membrane potential.
$CaCl_2$	2.5	To sustain Ca^{2+}-induced Ca^{2+} release and maintain a stable resting membrane potential.
$NaHCO_3$	25.0	To maintain pH
KH_2PO_4	1.2	To provide additional buffering capacity
$MgSO_4$	1.2	To maintain a stable resting membrane potential and to provide additional buffering capacity.
Glucose	10.0	To provide an energetic substrate.

heart was on the perfusion apparatus, the speed on a peristaltic pump was then adjusted to achieve the appropriate coronary flow. Coronary flow rate was measured from timed samples obtained of the coronary effluent. The perfusate was maintained at 37^{o}C by passing the perfusion solution through a water jacket (Figure 2.4). A bubble trap was placed proximal to the heart to prevent air entering the coronary artery (Figure 2.4).

Platinum electrodes were attached to the right atrium and the apex of the heart and the heart paced at 360 beats/min using a Grass (Astro Med Inc.) model SD9 pacing device (Figure 2.4). This heart rate is approximately 150 beats/min less than that noted to occur *in vivo* in rats. A lower heart rate was employed as this is a crystalloid rather than a blood perfused preparation. It is only in blood perfused preparations in which physiological heart rates can be employed because of the presence of a greater arterial oxygen content. The heart rate selected for the present study was one aimed to achieve maximal systolic function without producing demand-induced ischemia. Demand-induced ischemia was eliminated as the pacing rate is well below that which results in an increase in diastolic left ventricular pressures, a change that characterizes this form of ischaemia (Umeda et al 2003). Hearts were paced at a voltage that was estimated to be 10% above threshold for spontaneous excitation (Norton et al 2002).

A latex balloon coupled to a catheter was placed through the mitral valve into the left ventricular chamber (Figure 2.4) in order to measure left ventricular developed pressures and diastolic pressures. The catheter was coupled to both a pressure transducer and a micromanipulator. The balloon used in these studies had a pressure-volume relationship where the pressure in the balloon only started to increase well beyond that of the maximal left ventricular volume of a normal rat or a rat with a dilated

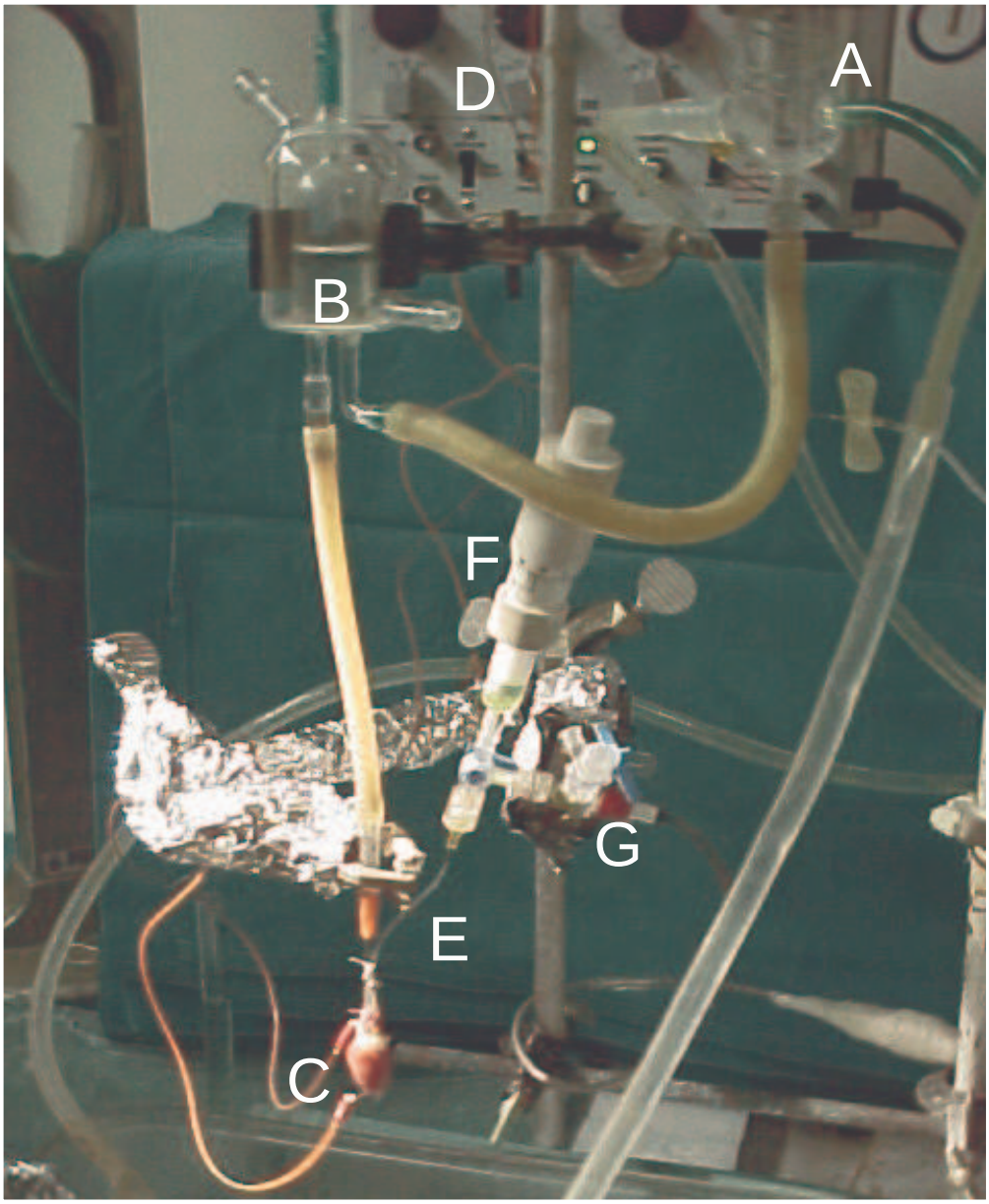

Figure 2.4. Photograph showing apparatus used in the isolated, perfused heart system. A, water jacket; B, bubble trap; C, platinum electrodes attached to isolated heart; D, pacing device; E, fluid filled catheter with balloon attached which has been inserted into the left ventricular lumen; F, micromanipulator; G, pressure transducer.

ventricle. The volume of the balloon material was calculated using a volume displacement technique and included as part of the intra-ventricular volume assessment. Left ventricular pressures were determined at as many multiple small increments in volume as were practically possible.

Left ventricular developed pressures and diastolic pressures were recorded on a Hellige recorder (Figure 2.5). Left ventricular diastolic pressures were recorded on a different channel and with a higher amplification to that of the channel used to record left ventricular developed pressures, to enhance the sensitivity of diastolic recordings (Figure 2.5). The channel used to record left ventricular developed pressures was calibrated using a mercury manometer whereas the channel used to record left ventricular diastolic pressures was calibrated with a water-filled U-tube system designed to calibrate low pressure systems (Norton et al 1996). Calibrations for both left ventricular developed pressure and diastolic pressure recordings were performed both before and after each heart preparation. As the isolated, perfused heart preparation employed is isovolumic, left ventricular minimum pressures (diastolic pressures) were assumed to be the equivalent of left ventricular end diastolic pressures.

2.2.1 Assessment of cardiac chamber dilatation and systolic function.

To assess the degree of cardiac dilatation, left ventricular diastolic pressure-volume relations were constructed. For statistical comparisons of the degree of left ventricular dilatation, left ventricular volumes obtained at a left ventricular diastolic pressure of 0 mm Hg were compared (i.e. the volume intercept of the left ventricular

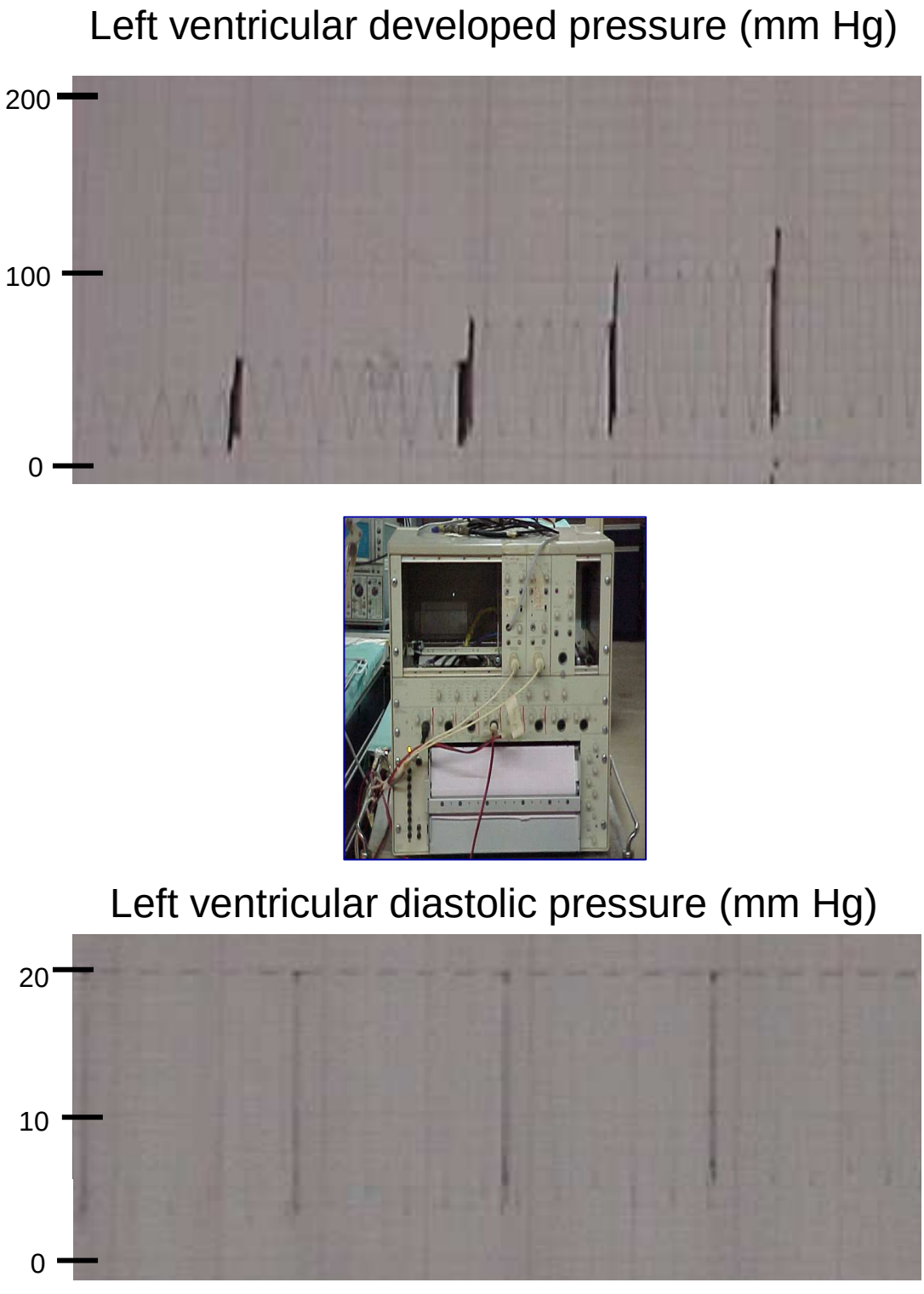

Figure 2.5. Typical recordings obtained of left ventricular developed pressures and left ventricular diastolic pressures in isolated, perfused heart preparations. Each recording was obtained at incremental filling volumes.

diastolic pressure-volume relationship-LV V_0) (Norton et al 2002, Badenhorst et al 2003a, Woodiwiss et al 2001, Badenhorst et al 2003b).

To assess systolic chamber function, left ventricular developed pressures were compared at specific filling volumes. To determine intrinsic systolic myocardial function, the slope of the systolic developed stress-strain relationship was compared (myocardial systolic elastance) (Norton et al 2002, Badenhorst et al 2003b, Veliotes et al 2005). By converting pressures and volumes into stress and strain values, the impact of alterations in left ventricular chamber geometry on systolic function are eliminated. Hence, the left ventricular developed pressure-volume relation is used to assess chamber function (which is influenced by alterations in chamber geometry); whereas the slope of the left ventricular developed stress-strain relation assesses intrinsic myocardial independent of alterations in chamber geometry.

Left ventricular developed stress and strain values were calculated from previously described formulae (Norton et al 2002, Badenhorst et al 2003b) assuming a thick-walled spherical geometry of the left ventricle as follows:

$$\text{LV systolic stress} = \frac{1.36 \times \text{LV}_{dev}\text{ pressure} \times (\text{LV volume})^{2/3}}{[\text{LV volume} + (0943 \times \text{LV mass})]^{2/3} - \text{LV volume}^{2/3}}$$

$$\text{LV systolic strain} = \frac{\{\text{LV volume}^{1/3} + [\text{LV volume} + (0.943 \times \text{LV mass})]^{1/3}\} - 1}{\text{LV } V_0{}^{1/3} + [\text{LV } V_0 + (0.943 \times \text{LV mass})]^{1/3}}$$

where LV, is left ventricle, LV_{dev}pressure is LV developed pressure and LV V_0 is the volume intercept of the systolic developed pressure-volume relationship.

2.3 Cardiac weights

After completion of data collection from isolated, perfused hearts, hearts were removed from the apparatus and blotted dry. The left and the right atria as well as the aorta and pulmonary artery were removed. The free wall of the right ventricle was removed from the septum of the heart. The left ventricle with the septum was then weighed and left ventricular weight was expressed as an absolute value.

2.4 Data analysis.

Differences in left ventricular weight, LV V_0 of the diastolic pressure-volume relations, left ventricular developed pressures at specific filling volumes, and the slopes of the left ventricular developed stress-strain relationships and the left ventricular diastolic pressure-volume relations were assessed by either a one-factor ANOVA followed by a Tukey *post hoc* test when data from more than two groups were compared or a Student's unpaired t-test when data from two groups were compared. To attempt to identify the determinants of the degree of left ventricular dilatation regression analysis was performed with LV V_0 for the diastolic pressure-volume relationship as the primary outcome. All values in the text are represented as mean ± SEM.

Chapter 3

Results

3.1 Running distance and running speed.

Rats selected for their ability to run on average more than 2 kilometres per day (Woodiwiss and Norton 1995) ran on average 3.00±0.33 km/day with an average running speed of 1.00±0.05 km/h. Rats with an LV V_0 value for diastolic pressure-volume relations within the 95% confidence interval for rats with pathological dilatation (Exer-dilated) had an average running distance of 3.09±0.49 km/day and an average running speed of 1.03±0.08 km/h. The distance run and average speed by the Exer-dilated group of rats was similar to that of rats with LV V_0 value for diastolic pressure-volume relations less than the lower 95% confidence interval for rats with pathological dilatation (Exer: 2.96±0.43 km/day and 0.99±0.07 km/h). Hence, rats with cardiac dilatation within pathological ranges (Exer-dilated) did not have a greater running speed or running distance than exercised rats in general. Moreover, running speed and distance were not determinants of the degree of pathological dilatation (LV V_0 for the diastolic pressure-volume relationship) in the whole group of exercised rats ($r=0.18$, $p=0.32$, $n=33$).

3.2 Left ventricular weight.

The left ventricular weights of the study groups are summarised in Figure 3.1. Habitual exercise and the presence of spontaneous hypertension resulted in an increase in left ventricular weight (Figure 3.1). Moreover, chronic ISO administration to Sprague Dawley rats resulted in an increased left ventricular weight (Figure 3.1). Although ISO administration to SHR produced a modest further increase in left ventricular weight, this

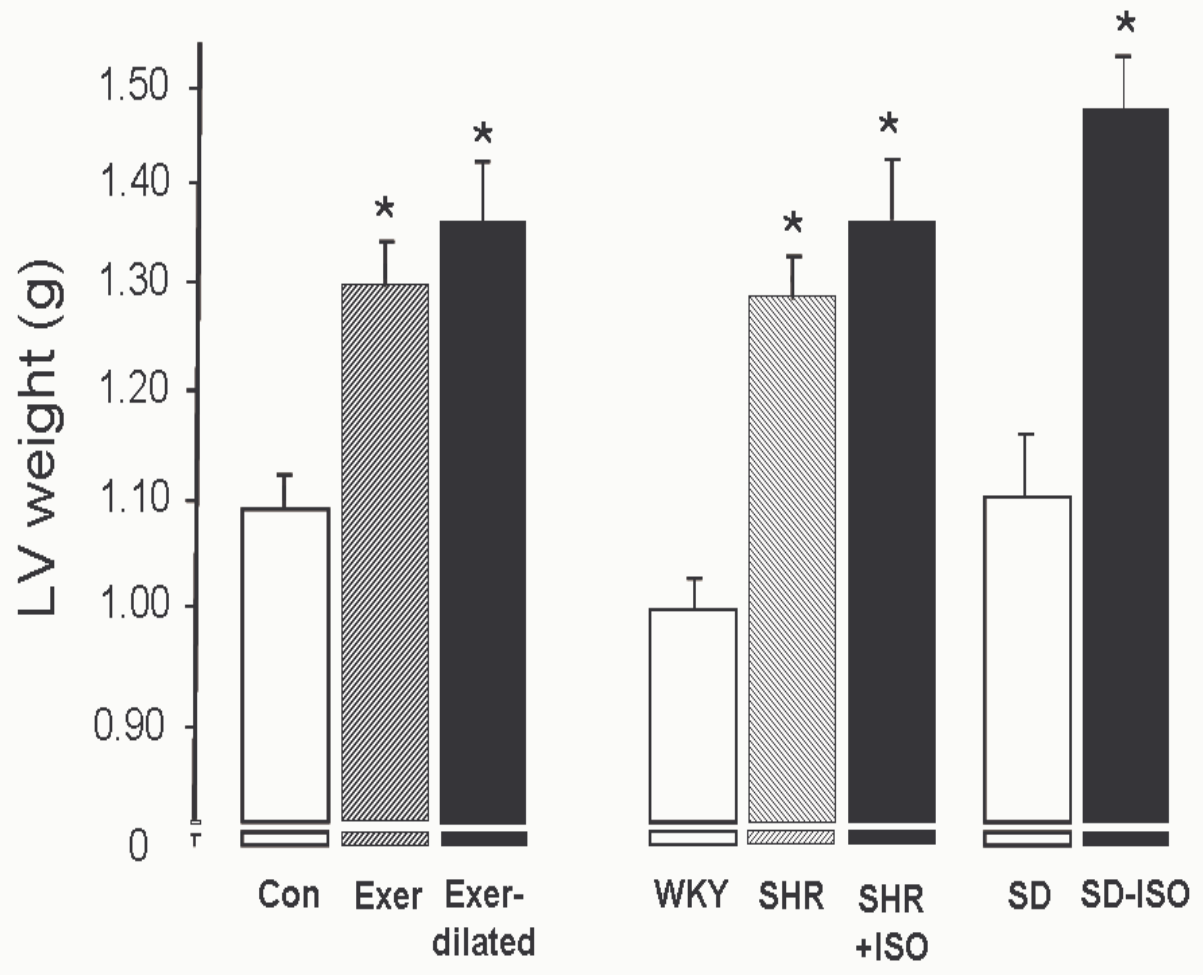

Figure 3.1. Left ventricular (LV) weight in study groups. Con, sedentary control rats; Exer, exercised rats; Exer-dilated, exercised rats with pathological levels of dilatation; WKY, Wistar Kyoto control rats; SHR, spontaneously hypertensive rats; SD, Sprague Dawley rats; ISO, isoproterenol treated rats. Sample sizes; Con=24, Exer=33, Exer-dilated=10, WKY=17, SHR=21, SHR+ISO=22, SD=10, SD-ISO=10. * $p<0.01$ versus either Con, WKY or SD groups.

did not reach statistical significance (Figure 3.1). Importantly, left ventricular weight was similar in the exercise-dilated, SHR-ISO treated and Sprague Dawley ISO-treated groups (Figure 3.1). Left ventricular weight was not a determinant of the degree of pathological dilatation (LV V_0 in the exercised rats; r=0.06, p=0.74, n=33).

3.3 Left ventricular diastolic pressure-volume relations.

Figure 3.2 shows the effect of habitual exercise on left ventricular diastolic pressure-volume relationships. Habitual exercise in all rats studied resulted in a right shift and an increased volume intercept of the relationship (LV V_0 in mls: Sedentary controls=0.18±0.01; Exercised rats=0.22±0.01, $p<0.005$), changes consistent with cardiac chamber dilatation. Importantly, the slope of the diastolic pressure-volume relationship was not altered by exercise (Figure 3.2).

The effect of chronic ISO administration to Sprague Dawley rats on left ventricular diastolic pressure-volume relationships is shown in Figure 3.3. ISO resulted in a right shift and an increased volume intercept of the relationship (LV V_0 in mls: Controls=0.20±0.01; ISO-treated rats=0.27±0.02, $p<0.005$), changes consistent with chamber dilatation. Importantly, the degree of chamber dilatation produced by chronic ISO administration was greater than that produced by habitual exercise (LV V_0 in mls: Sprague Dawley rats receiving ISO=0.27±0.02; Exercised rats=0.22±0.01, $p< 0.005$), despite similar effects on LV weight (Figure 3.1).

Figure 3.4 shows the effect of chronic ISO administration on left ventricular diastolic pressure-volume relations (Figure 3.4a) and the volume intercept of the

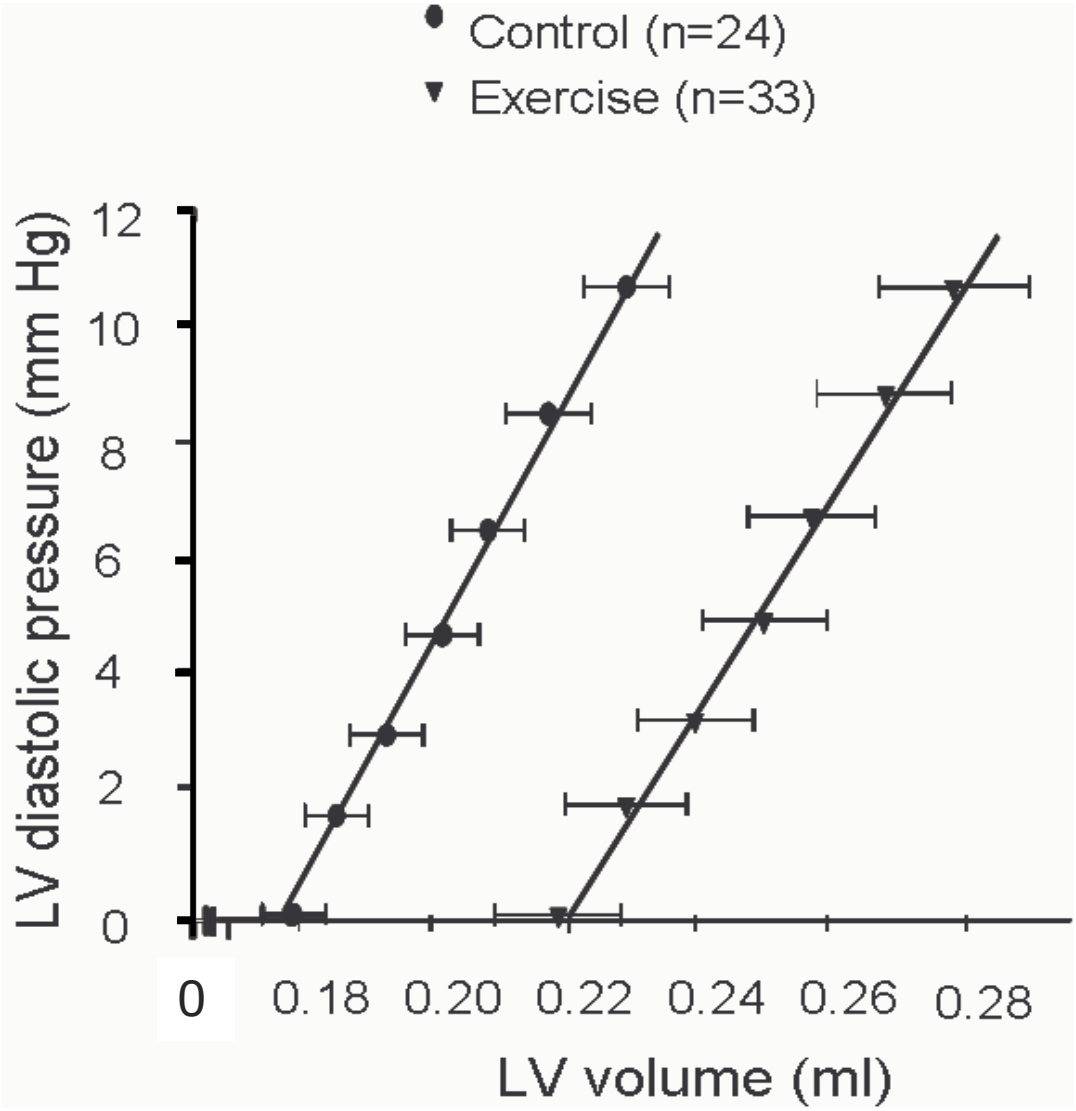

Figure 3.2. Effects of chronic exercise on left ventricular (LV) diastolic pressure-volume relations in Sprague Dawley rats. Statistical comparisons of the volume intercepts of these relations are given in the text.

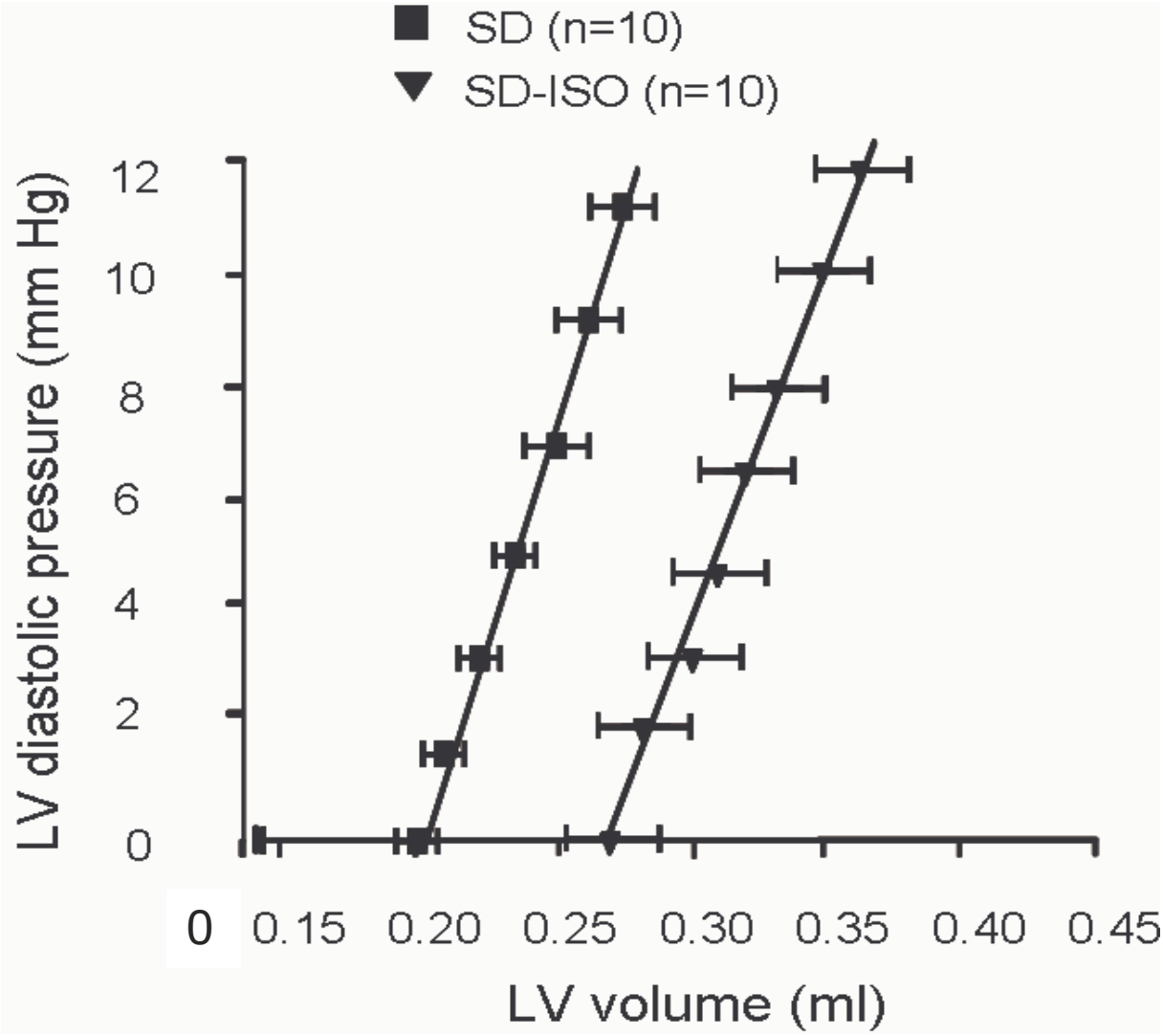

Figure 3.3. Effects of chronic isoproterenol (ISO) administration on left ventricular (LV) diastolic pressure-volume relations in Sprague Dawley rats (SD). Statistical comparisons of the volume intercepts of these relations are given in the text.

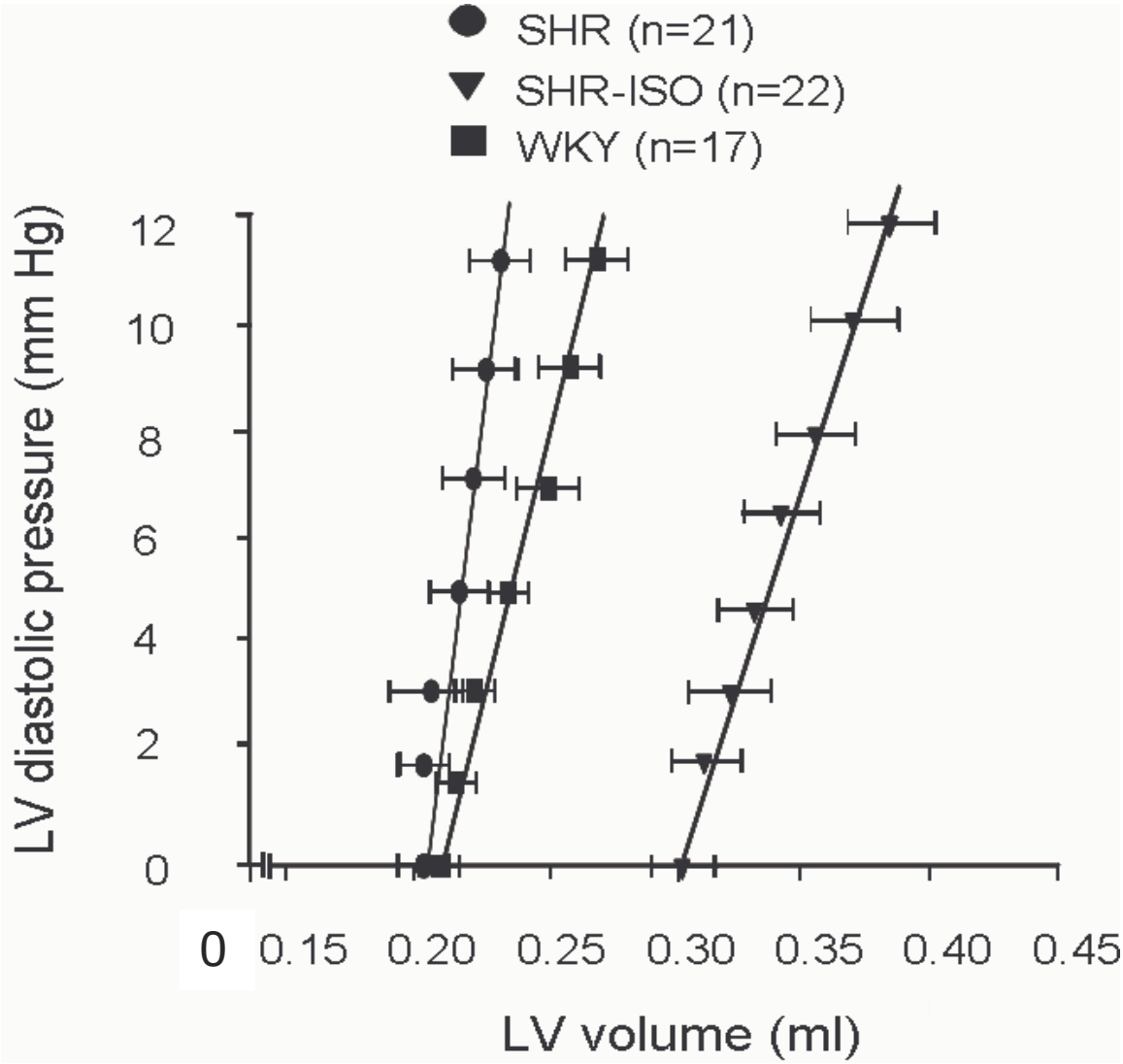

Figure 3.4a. Effects of chronic isoproterenol (ISO) administration on left ventricular (LV) diastolic pressure-volume relations in spontaneously hypertensive rats (SHR). WKY, Wistar Kyoto control. Statistical comparisons of the volume intercepts of these relations are provided in Figure 3.4b.

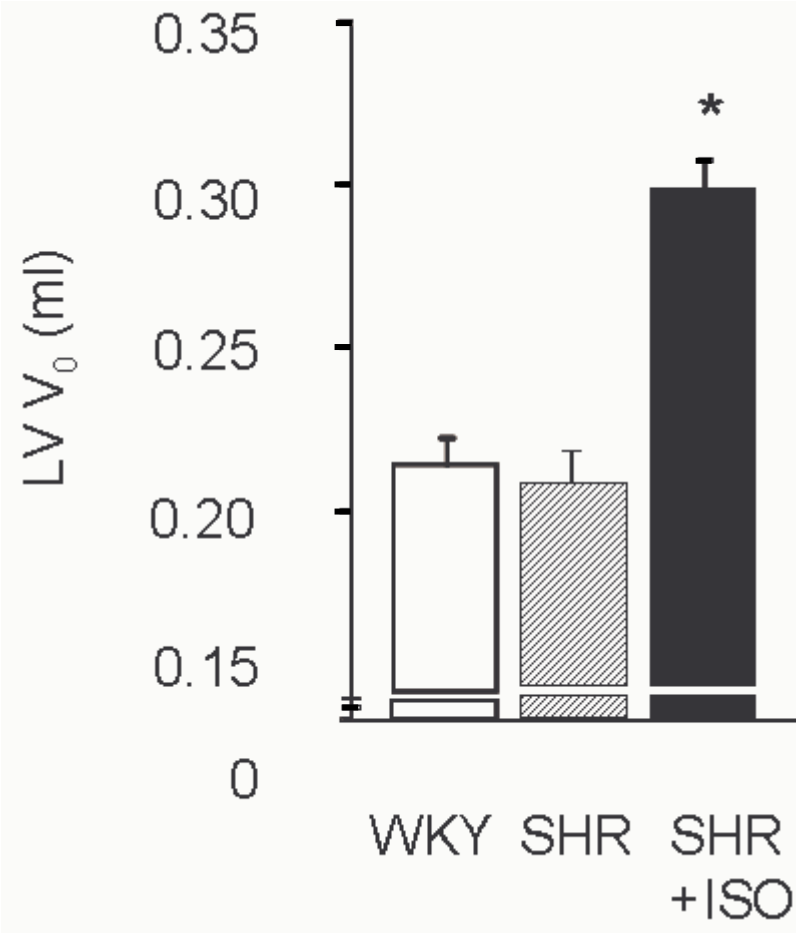

Figure 3.4b. Effects of chronic isoproterenol (ISO) administration on the volume intercept (LV V_0) of the left ventricular diastolic pressure-volume relations (shown in the previous page) in spontaneously hypertensive rats (SHR). Data are compared to Wistar Kyoto control (WKY) rats. * $p<0.01$ versus other groups. Sample sizes are indicated in Figure 3.4a.

relationship (Figure 3.4b) in SHR. Although there was a trend for an increased slope of the relationship, untreated SHR at 17 months of age had a similar left ventricular diastolic pressure-volume relationship as WKY controls (Figure 3.4a). Importantly however, untreated SHR at 17 months of age had the same volume intercept of the relationship (LV V_0) as WKY controls (Figure 3.4b). Nevertheless, ISO administered to SHR for 7 months resulted in a marked right shift in the left ventricular diastolic pressure-volume relationship (Figure 3.4a) and an increase in LV V_0 (Figure 3.4b), changes consistent with chamber dilatation. However, again the degree of chamber dilatation produced by chronic ISO administration to SHR was greater than that produced by habitual exercise (LV V_0 in mls: SHR receiving ISO=0.30±0.01; Exercised rats=0.22±0.01, $p<0.005$), despite similar effects on LV weight (Figure 3.1).

The left ventricular diastolic pressure-volume relationships in exercised rats with volume intercepts (LV V_0 values) within the 95% confidence intervals of both Sprague Dawley rats and SHR receiving ISO for prolonged periods (rats with pathological dilatation) are shown in Figure 3.5a. Figure 3.5b shows the volume intercepts of exercised rats with LV V_0 values within the 95% confidence intervals of both Sprague Dawley rats and SHR receiving ISO for prolonged periods (rats with pathological dilatation). The LV V_0 values of exercised rats with pathological levels of cardiac dilatation are compared to the LV V_0 values of rats with pathological dilatation in Figure 3.5b. Importantly, exercised rats with LV V_0 values within pathological ranges had similar LV V_0 values as rats with pathological dilatation.

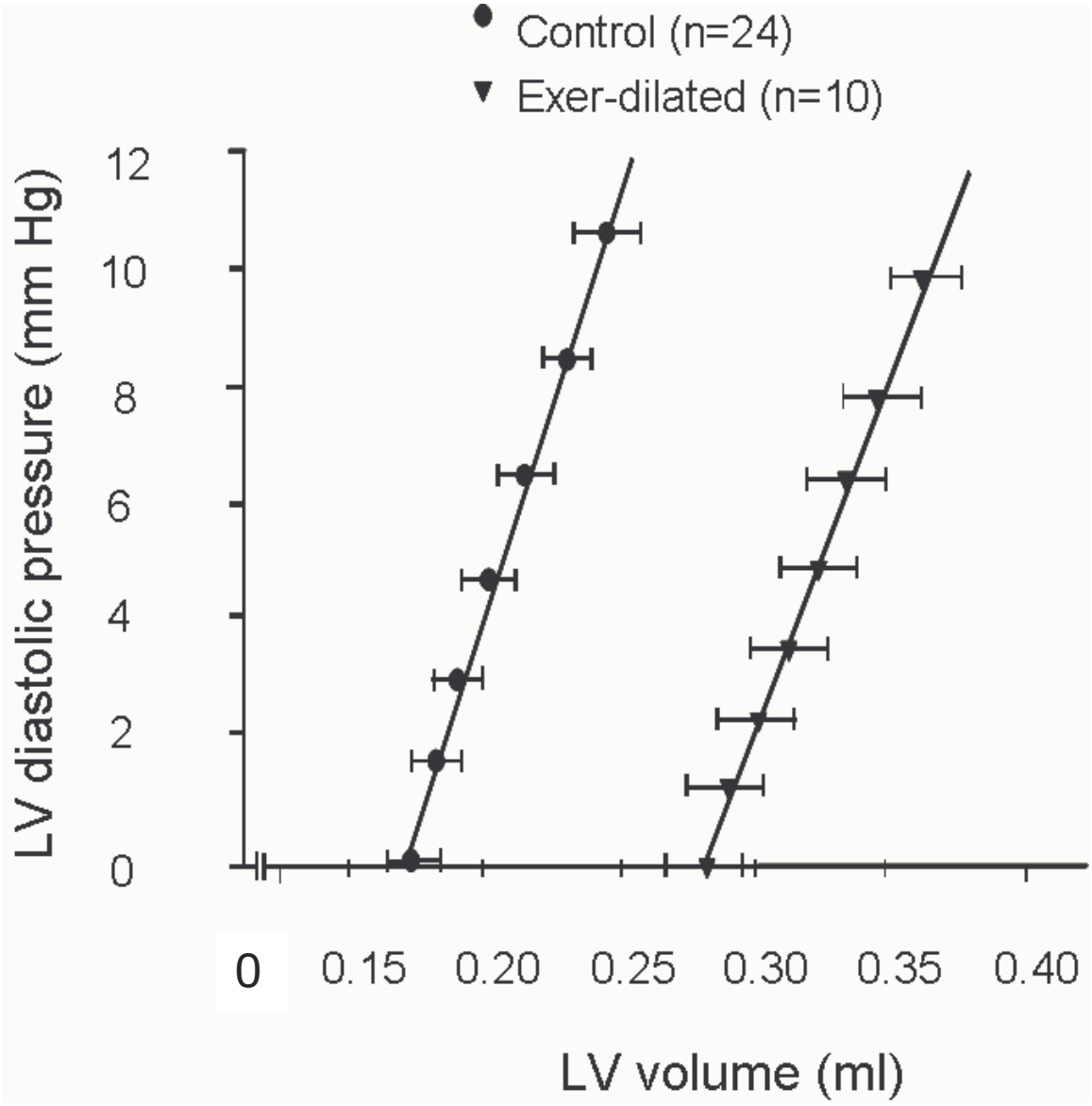

Figure 3.5a. Left ventricular (LV) diastolic pressure-volume relations in exercised rats with volume intercepts within the 95% confidence intervals of rats with pathological dilatation (Exer-dilated). Statistical comparisons of the volume intercepts of these relations are given in Figure 3.5b.

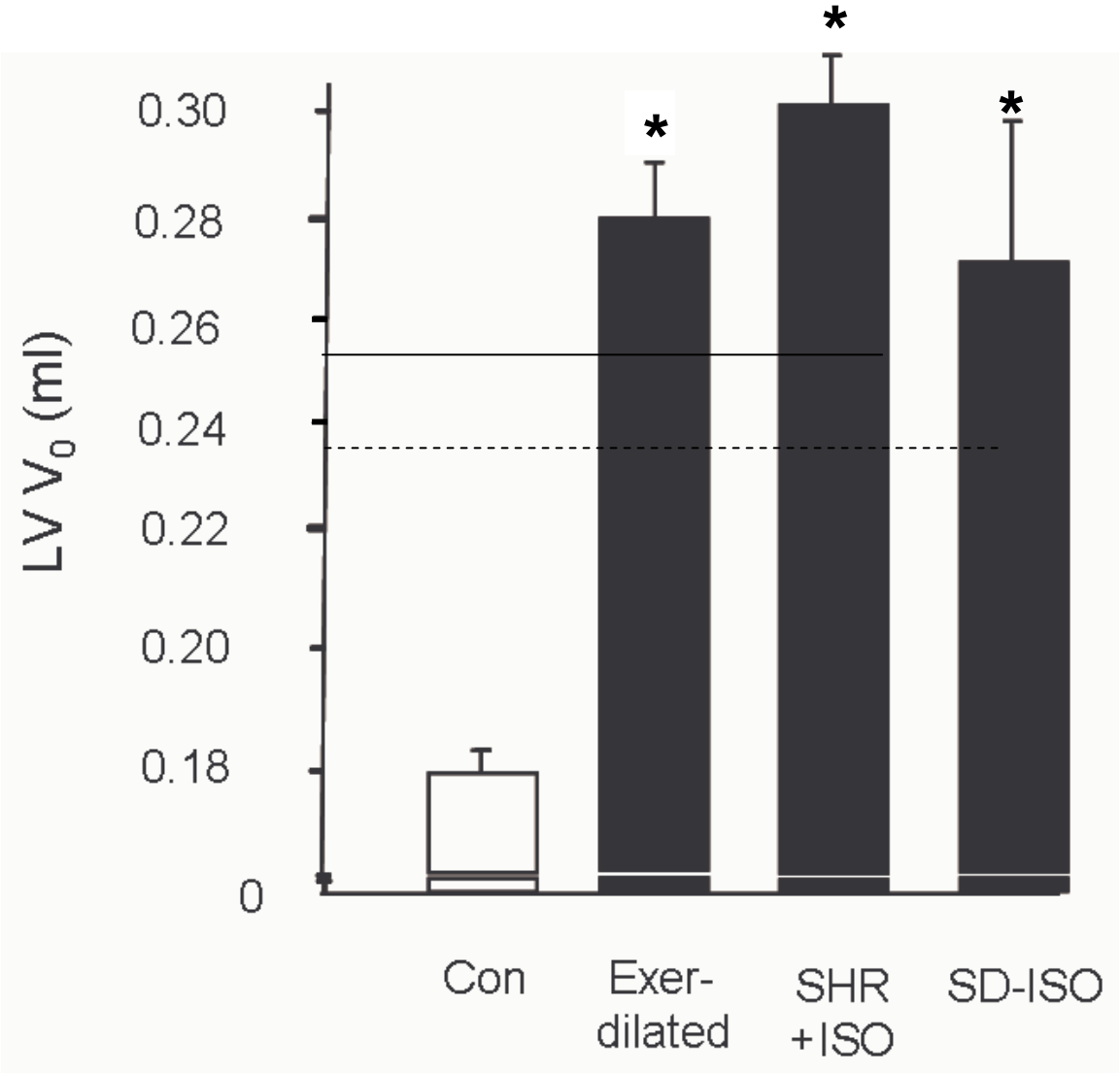

Figure 3.5b. Volume intercept (LV V_0) of the left ventricular diastolic pressure-volume relations shown in Figure 3.5a and of rats with pathological dilatation (Sprague Dawley [SD] and spontaneously hypertensive rats [SHR] having received isoproterenol [ISO] for 7 months). *$p<0.0001$ versus control group (ANOVA followed by Tukey *post-hoc* test). Sample sizes are indicated in Figure 3.1. Horizontal lines represent the lower 95% confidence intervals for the SHR+ISO (continuous line) and SD-ISO (interrupted line) groups.

3.4 Systolic chamber function.

The effect of chronic ISO administration to SD rats on left ventricular systolic chamber function (developed pressures at incremental filling volumes) is shown in Figure 3.6. Chronic ISO administration to SD produced a marked decrease in left ventricular developed pressures at incremental filling volumes (Figure 3.6). Thus ISO administration to SD rats resulted in left ventricular dilatation in association with pump dysfunction.

Figure 3.7 shows the effect of chronic ISO administration to SHR on left ventricular systolic chamber function. Left ventricular chamber systolic function (pump function) was maintained in untreated SHR as compared to WKY controls. However, chronic ISO administration to SHR produced a marked decrease in left ventricular developed pressure at incremental filling volumes (Figure 3.7). Thus ISO administration to SHR rats also resulted in left ventricular dilatation in association with pump dysfunction.

Left ventricular systolic chamber function in exercised rats with volume intercepts (LV V_0 values) within the 95% confidence intervals of both Sprague Dawley rats and SHR receiving ISO for prolonged periods (rats with pathological dilatation) is shown in Figure 3.8. Importantly, exercised rats with LV V_0 values within pathological ranges had a similar systolic chamber function as compared to control rats (Figure 3.8). Similar outcomes were noted when comparing pump function in all exercised rats (non-selected rats) with pump function of controls (data not shown).

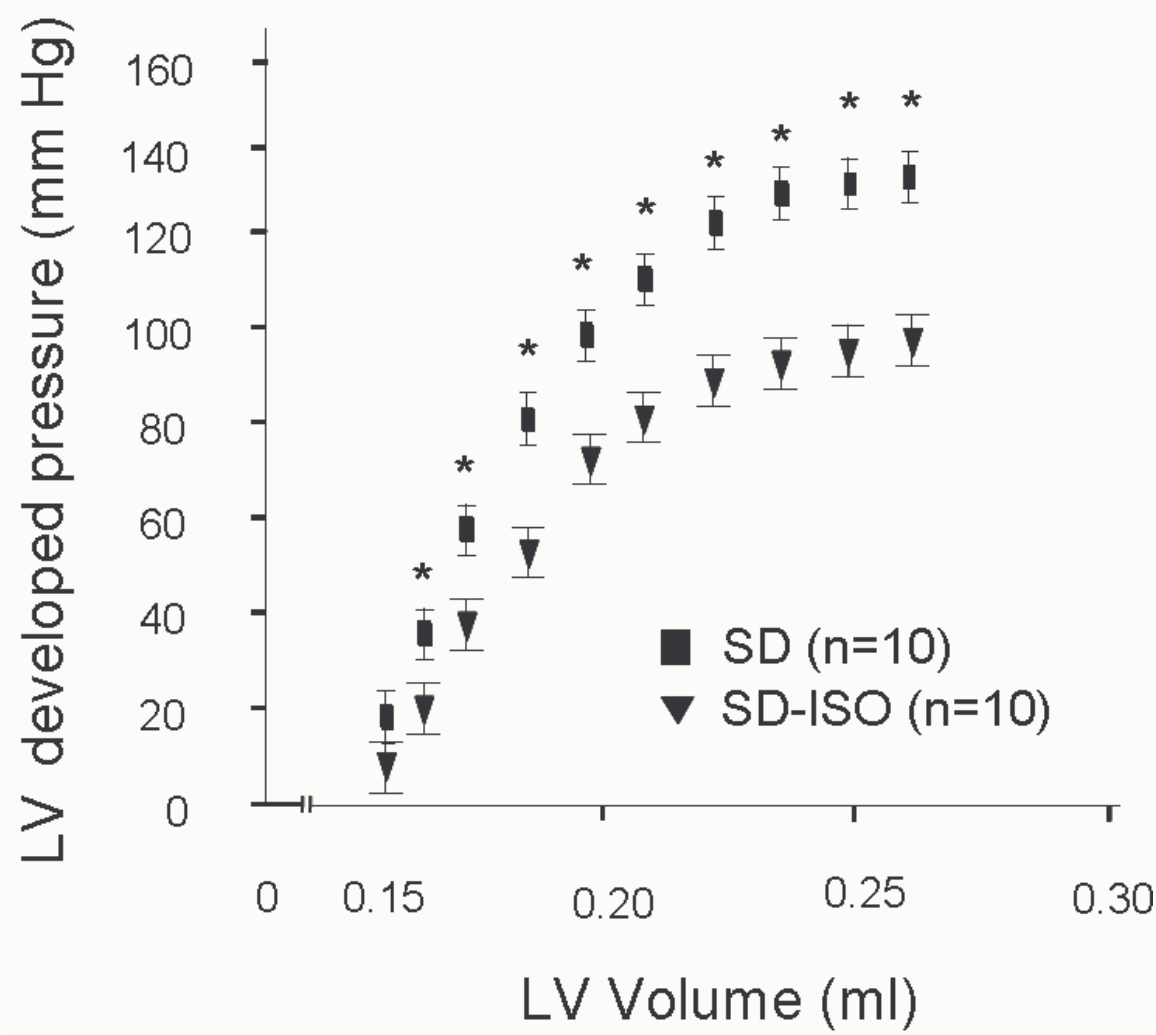

Figure 3.6. Effects of chronic isoproterenol (ISO) administration on left ventricular (LV) developed pressure-volume relations in Sprague Dawley rats (SD). *p<0.01 versus SD group.

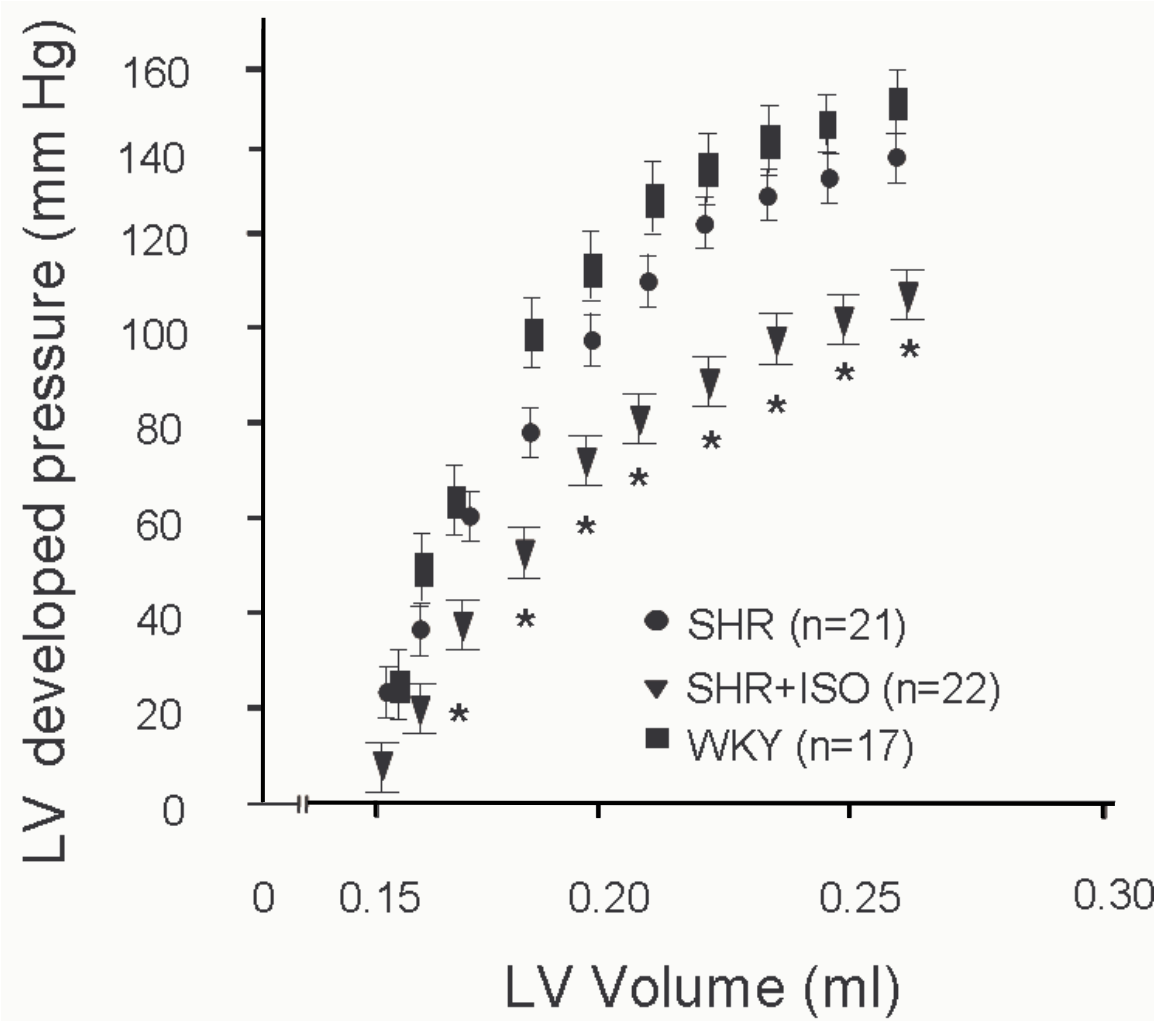

Figure 3.7. Effects of chronic isoproterenol (ISO) administration on left ventricular (LV) developed pressure-volume relations in spontaneously hypertensive rats (SHR). WKY, Wistar Kyoto control. * $p<0.01$ versus the SHR and WKY groups.

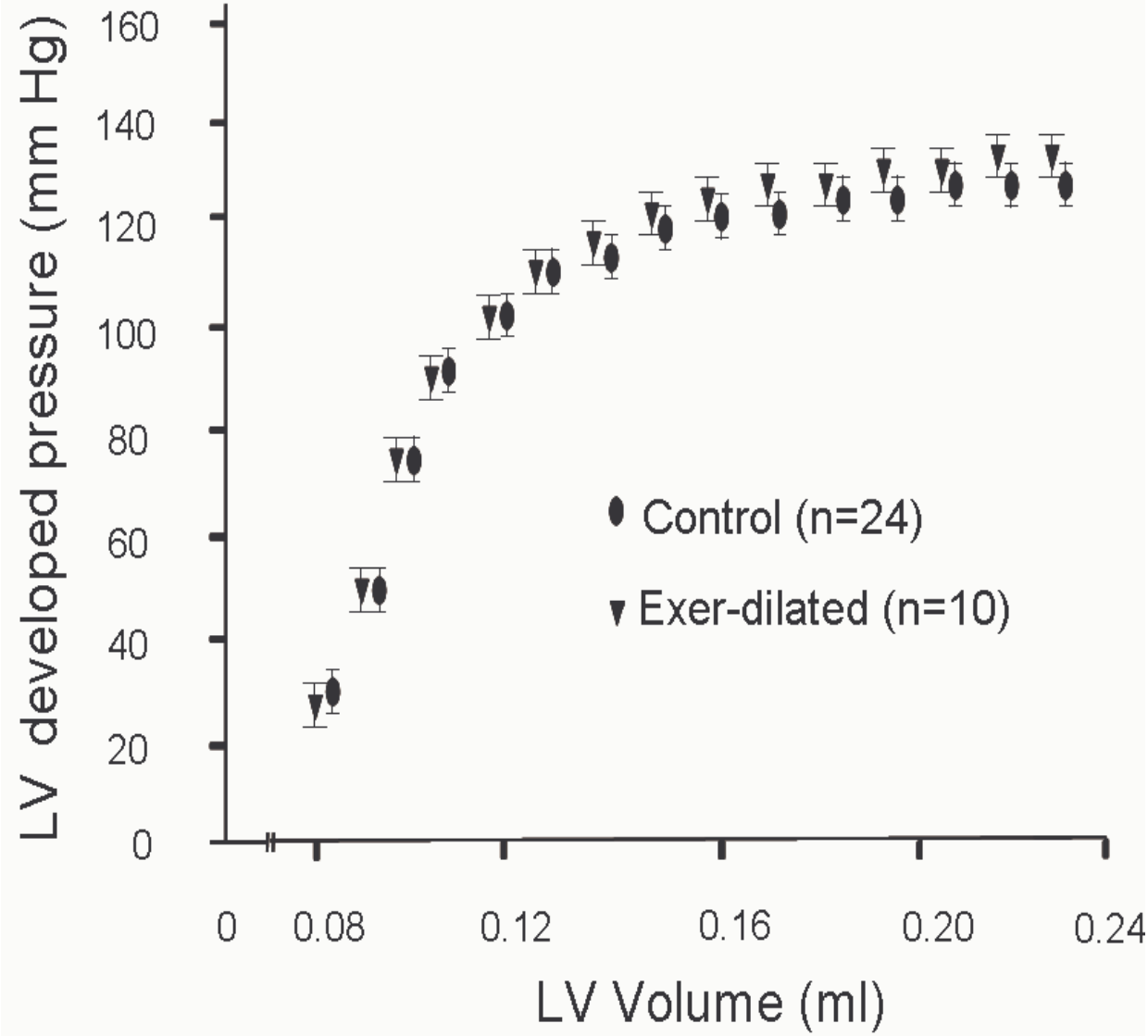

Figure 3.8. Left ventricular (LV) developed pressure-volume relations in exercised rats with diastolic volume intercepts within the 95% confidence intervals of rats with pathological dilatation (Exer-dilated). No differences were noted between Exer-dilated and sedentary control rats at any filling volume.

3.5 Systolic myocardial function

Figure 3.9 shows the effect of chronic ISO administration to SD rats on left ventricular systolic myocardial function as determined from left ventricular developed stress-strain relationships. Chronic ISO administration to SD produced a decrease in myocardial systolic function as noted from the reduced slope of the left ventricular developed stress-strain relation (in g/cm^2: Control=712.8±53.2, ISO=415.4±53.8, $p<0.005$) (Figure 3.9).

The effect of chronic ISO administration to SHR on left ventricular systolic myocardial function as determined from left ventricular developed stress-strain relationships is shown in Figure 3.10. Left ventricular myocardial systolic function was maintained in untreated SHR as compared to WKY controls (in g/cm^2: SHR=1114.6±29.3, WKY=1180.0±52.8, p=0.26) (data not shown). Moreover, chronic ISO administration to SHR failed to influence myocardial systolic function as noted from the slope of the left ventricular developed stress-strain relation (in g/cm^2: SHR=1114.6±29.3, SHR+ISO=1085.0±35.8, p=0.53) (Figure 3.10). Thus although ISO administration to SHR reduced systolic chamber function, this change was not associated with decreases in intrinsic myocardial contractility.

Figure 3.11 shows left ventricular systolic myocardial function as determined from left ventricular developed stress-strain relationships in exercised rats with volume intercepts (LV V_0 values) within the 95% confidence intervals of both Sprague Dawley rats and SHR receiving ISO for prolonged periods (rats with pathological dilatation).

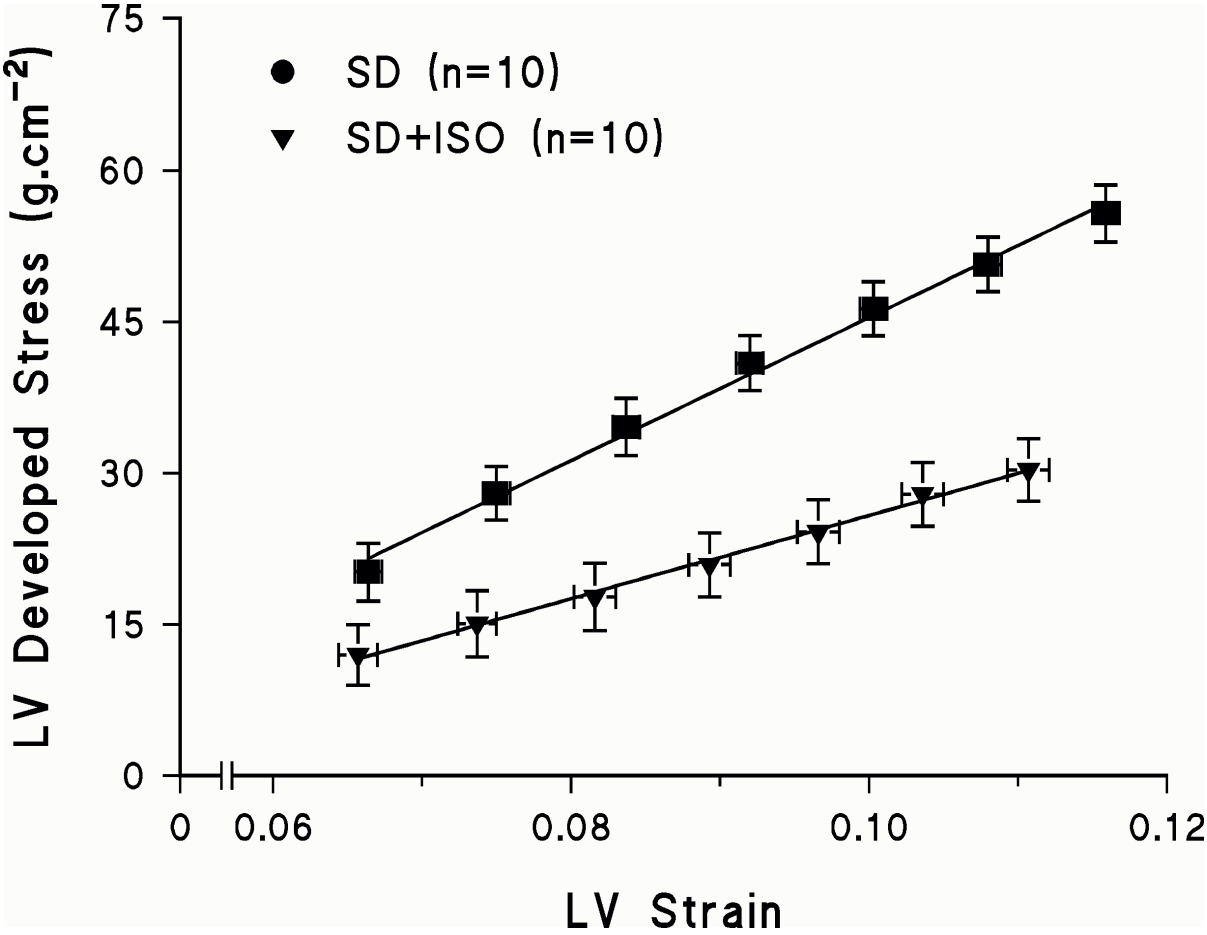

Figure 3.9. Effect of chronic isoproterenol administration (ISO) on left ventricular (LV) developed stress–strain relations in Sprague Dawley rats (SD). Comparisons of the mean slopes of the relations (systolic myocardial elastance) are provided in the text.

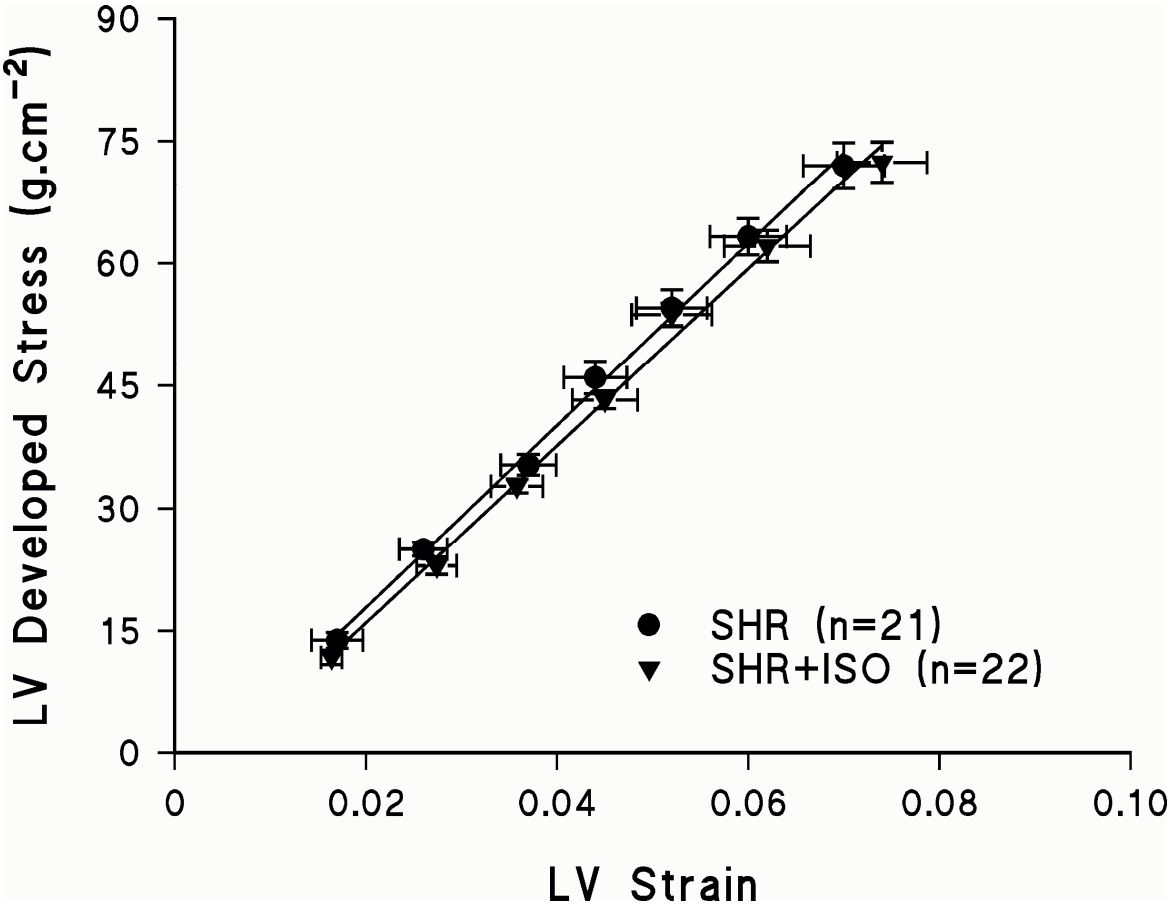

Figure 3.10. Effects of chronic isoproterenol administration (ISO) on left ventricular (LV) developed stress-strain relations in spontaneously hypertensive rats (SHR). The mean slopes of the relations (systolic myocardial elastance) are compared in the text.

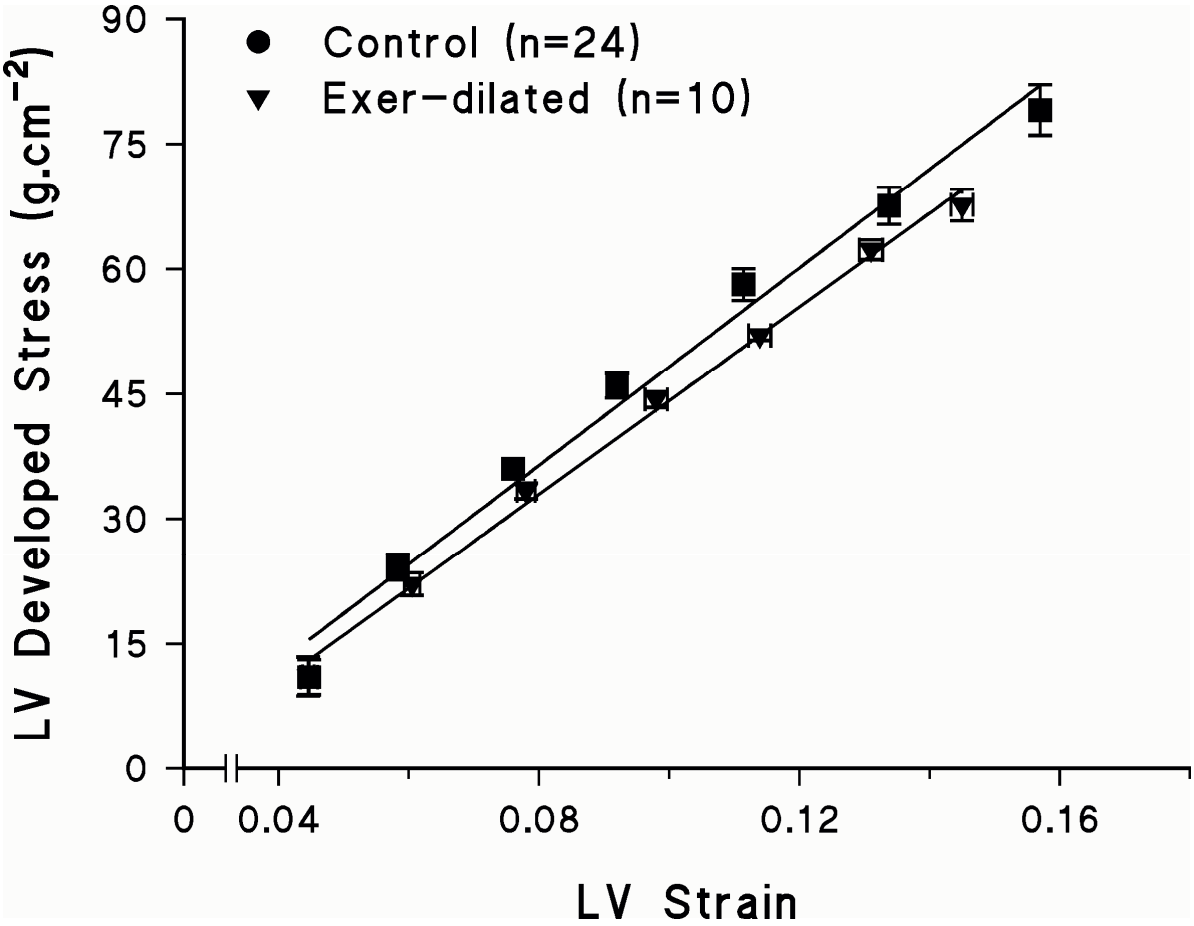

Figure 3.11. Left ventricular (LV) developed stress-strain relations in exercised rats with diastolic volume intercepts within the 95% confidence intervals of rats with pathological dilatation (Exer-dilated). The mean slopes of the relations (systolic myocardial elastance) are compared in the text.

Importantly, exercised rats with LV V_0 values within pathological ranges had a similar myocardial systolic function as noted from the slope of the left ventricular developed stress-strain relation as sedentary control rats (in g/cm^2: Control=620.6±53.6, Exer-dilated=615.8±93.5, p=0.96) (Figure 3.11). Similar outcomes were noted when comparing myocardial systolic function in all exercised rats (in g/cm^2: Ex=608.4±63.4, Exer-dilated=615.8±93.5, p=0.95) (data not shown).

Chapter 4

Discussion

4.1 Summary of main findings

The main findings of the present study are as follows. Habitual exercise is associated with right shifts in cardiac diastolic pressure-volume relations (Figure 3.2). Although the mean degree of left ventricular dilatation produced by habitual exercise is markedly lower than that noted in pathological forms of left ventricular dilatation, just under one third of the exercising animals assessed had increases in cavity dimensions that are within pathological ranges (Figures 3.5a and 3.5b). Importantly however, rats with exercise-induced increases in cavity dimensions within pathological ranges, nevertheless still had no evidence of left ventricular pump dysfunction (Figure 3.8). The lack of impact of pathological levels of chamber dilatation on pump function in exercised rats could not be attributed to an enhanced myocardial systolic function (Figure 3.11) opposing the potentially deleterious effects of increases in cavity dimensions.

4.2 Comparison with previous studies

4.2.1 Exercise conditioning and cardiac chamber dimensions.

Most previous studies conducted in humans assessing the impact of exercise programs on cardiac chamber dimensions have determined dimensions *in vivo* at a single preload and heart rate (see chapter 1 and Table 1.3 for a review of this scientific literature). As outlined in the introduction to this dissertation, increases in cardiac internal dimensions may not only occur as a result of chamber dilatation (rights shifts in diastolic

pressure-volume relations) but also through reductions in heart rate and increases in cardiac preloads. As exercise programs may produce profound reductions in heart rate (Gilbert et al 1977, Nishimura et al 1980) and marked increases in blood volume (Claybaugh et al 1986, Freund et al 1988), the degree to which chamber dilatation contributes to increases in cardiac cavity dimensions with exercise cannot be determined from these studies.

Recent evidence suggests that increases in cardiac cavity dimensions as measured *in vivo* are within pathological ranges after medium-to-high intensity endurance training (Abergel et al 2004, Abernethy et al 2003, Basavarajaiah et al 2008, Douglas et al 1997, Pelliccia et al 1999). Moreover, these increases in cardiac cavity dimensions were associated with pump dysfunction (Abergel et al 2004, Abernethy et al 2003, Pelliccia et al 1999). However, again, these measurements were obtained at lower heart rates and potentially increased preloads (Abergel et al 2004, Colan et al 1987, Pelliccia et al 1999). Further, these measurements were obtained in athletes in whom contractile function could have been attenuated through reductions in sympathetic tone, as evidenced by marked decreases in heart rate (Abergel et al 2004, Colan et al 1987). The increases in cardiac cavity dimensions under these circumstances could therefore have been secondary to a reduced contractile function and heart rate and increased preloads, rather than through cardiac dilatation *per se*.

Although, two studies conducted in humans have demonstrated a right shift in diastolic pressure-volume relations (Arbab-Zadeh et al 2004, Levine et al 1991); whether these changes were attributed to chamber dilatation or to alterations in myocardial material properties influencing chamber compliance was not assessed. Previous studies

conducted in animal models have provided clear evidence that myocardial and chamber compliance are altered after habitual exercise (Woodiwiss and Norton 1995, Woodiwiss et al 1998). Nevertheless, in these studies (Woodiwiss and Norton 1995, Woodiwiss et al 1998) the impact of chamber dilatation on the volume intercept of diastolic pressure-dimension relations was not assessed, as cardiac dimension measurements were of external diameters. In the present study conducted in a large sample of rats selected for their desire to exercise, I have provided clear evidence to indicate that rights shifts in diastolic pressure-volume relations do indeed occur (Figure 3.2), and that these changes are associated with an increased volume intercept of the diastolic pressure-volume relationship and not because of alterations in the slope of the relationship (Figure 3.2). Moreover, I have provided evidence to indicate that the increases in volume intercepts of diastolic pressure-volume relations are within pathological ranges in a proportion of rats (Figures 3.5a and 3.5b).

An inability to show alterations in the slope of the diastolic pressure-volume relationships in exercised rats in the present study (Figure 3.2) is in apparent contrast to changes in diastolic pressure-dimension relations following habitual exercise previously demonstrated by our group (Woodiwiss and Norton 1995). These data are however not contradictory. The slope of the diastolic pressure-volume relationship may be determined by both increases in ventricular wall thickness, which restricts filling and may increase the slope, and alterations in the myocardial material properties, with a stiffer muscle also contributing toward a greater slope (Gilbert and Glantz 1989). Exercise may increase wall thickness, but decrease myocardial stiffness (Woodiwiss and Norton 1995) the ultimate result being that the wall thickness effects negate the opposing influence of

alterations in myocardial material properties. The only effective means of assessing myocardial material property effects would have been to calculate myocardial stiffness constants. In the present study I did not calculate myocardial diastolic stiffness, as in an isovolumic preparation, where end diastole and end isovolumic relaxation are the same time periods, diastolic stiffness constants may be influenced by both relaxation forces as well as by myocardial material properties. Hence, changes in diastolic stiffness constants based on data obtained in an isovolumic preparation, such as that used in this dissertation, could have been attributed to either changes in material properties or changes in relaxation properties.

4.2.2 Pump function and exercise conditioning

As highlighted in the introduction to this dissertation, there has, in the past been much controversy regarding the impact of repeated periods of exercise on cardiac pump function. An improved preload-recruitable stroke work may follow increases in cardiac chamber compliance (Woodiwiss and Norton 1995, Arbab-Zadeh et al 2004). In this regard, there is an improved systolic function for a given filling pressure, but not for a given filling volume in the left ventricle (Woodiwiss and Norton 1995). Importantly, in general, systolic function when measured at rest is apparently neither increased nor decreased following exercise programs (see introductory chapter, Table 1.1), although this seems at odds with a lower sympathetic tone in subjects who are physically conditioned (Janssen et al 1993, Pluim et al 1999a). However, whether pump dysfunction

occurs in those individuals who develop pathological levels of cardiac dilatation, has not been given appropriate consideration.

Some studies conducted in humans suggest that pathological levels of cardiac dilatation may be achieved following medium-to-high intensity exercise training (Abergel et al 2004, Abernethy et al 2003, Douglas et al 1997, Pelliccia et al 1999). These changes in chamber size were associated with pump dysfunction (Abergel et al 2004, Abernethy et al 2003, Pelliccia et al 1999). However, it is not certain whether the associated pump dysfunction (Abergel et al 2004, Abernethy et al 2003, Pelliccia et al 1999) is through an attenuated myocardial contraction mediated by a reduced sympathetic activity known to occur with endurance training (Janssen et al 1993, Pluim et al 1999a), or through cardiac dilatation *per se*. In one of these prior studies (Abergel et al 2004), there was also an associated reduction in myocardial dysfunction (reduced midwall fractional shortening). This would suggest that pump dysfunction was the consequence of a reduced contractile function and not necessarily because of increases in cavity dimensions. However, a decrease in myocardial function may still have been as a consequence of cardiac dilatation, as wall stress was markedly increased, and midwall shortening assessments were not corrected for increments in wall stress. Nevertheless, when ejection fraction was corrected for wall stress, an approach that potentially accounts for the impact of cardiac dilatation, a considerable number of athletes still had a reduced pump function (Abergel et al 2004). Moreover, relative wall thickness was noted to be increased in athletes with pump dysfunction and a dilated chamber (Abergel et al 2004). According to the law of La Place, cardiac dilatation is likely to reduce pump function only if the relationship between wall thickness and internal radius is reduced. Lastly,

against a role for exercise-induced cardiac dilatation in promoting pump dysfunction is the evidence that an increased stroke volume may occur in endurance athletes with increases in cardiac chamber dimensions (see Table 1.3).

If a reduced pump function was the consequence of a reduced sympathetic activity (or some other unidentified disturbance) and subsequent reductions in myocardial contraction (Abergel et al 2004), cardiac dilatation could have been a consequence rather than a cause of pump dysfunction. Alternatively, exercise could promote increases in cardiac cavity size and subsequently produce pump dysfunction. This notion is supported by data showing a reduced pump function in association with an increased cavity size, despite a normal index of cardiac contraction (Colan et al 1987).

The results of the present study provide some insight into the conundrum of whether exercise-induced cardiac dilatation can promote pump dysfunction. The results described in the present dissertation suggest that even pathological levels of cardiac dilatation associated with habitual exercise are not associated with pump dysfunction (Figure 3.8). Thus, it is possible that pathological levels of cardiac dilatation following endurance exercise previously reported on (Abergel et al 2004, Abernethy et al 2003, Douglas et al 1997, Pelliccia et al 1999) are the consequence rather than a cause of pump dysfunction.

In the present study it could be argued that reductions in pump function mediated by cardiac dilatation are counter-balanced by increases in contractile function following habitual exercise. However, the sustained pump function noted in the present study was associated with a normal intrinsic myocardial contractility (normal slope of end systolic

myocardial elastance, Figure 3.11). This is consistent with the notion that endurance training does not enhance myocardial function (see introduction).

4.2.3 Pathological cardiac dilatation and pump function

It may be argued that the ability of habitual exercise to promote pathological levels of cardiac dilatation without mediating pump dysfunction is evidence against a pathophysiological role of cardiac dilatation in contributing toward pump dysfunction. However, there is now substantial evidence to implicate pathological dilatation as a determinant of pump dysfunction in cardiac pathology. Indeed, as reproduced by data obtained in the present study, our group have previously shown that chronic administration of a β-adrenoreceptor agonist to SHR induces pump dysfunction as determined from load and heart rate-dependent and -independent assessments of systolic chamber function (pump function) (Figure 3.7) without altering load and heart rate-dependent and -independent assessments of intrinsic myocardial systolic function (Figure 3.10) (Badenhorst et al 2003, Veliotes et al 2005). Moreover, as recently shown by our group, chronic administration of a β-adrenoreceptor agonist to Sprague Dawley rats induces pump dysfunction as determined from load and heart rate-dependent and -independent assessments of systolic chamber function (pump function) without altering load and heart rate-dependent and -independent assessments of intrinsic myocardial systolic function (Osadchii et al 2007). Consequently, the reduction in pump function in these studies (Badenhorst et al 2003, Veliotes et al 2005, Osadchii et al 2007) could not be attributed to decreases in myocardial function. Rather, the effect of chronic β-

adrenoreceptor activation on pump function could only be attributed to cardiac dilatation (Figures 3.3, 3.4a and 3.4b) (Badenhorst et al 2003, Veliotes et al 2005, Osadchii et al 2007). These data support the concept originally proposed by Cohn (1995), and subsequently substantiated by data obtained in human (Vasan et al 1997) and animal (Norton et al 2002, Badenhorst et al 2003) studies, that pump dysfunction can occur mainly as a consequence of cardiac dilatation rather myocardial contractile disturbances.

Although our group have recently demonstrated that daily administration of a β-adrenoreceptor agonist for three months to Sprague Dawley rats induces pump dysfunction without altering intrinsic myocardial systolic function (Osadchii et al 2007), in the present study daily administration of a β-adrenoreceptor agonist to Sprague Dawley rats for seven months produced a decrease in both chamber (Figure 3.6) and intrinsic myocardial systolic function (Figure 3.9). This difference between the present study and a previous study (Osadchii et al 2007) is most likely attributed to the longer duration of ISO administration in the present study (seven months) as opposed to that employed in a previous study (three months) (Osadchii et al 2007). The effect of longer periods of ISO administration on intrinsic myocardial contractile function in Sprague Dawley rats could be attributed to reduced β-adrenoreceptor-mediated contractile responses and cardiomyocyte apoptosis induced by chronic ISO administration (Osadchii et al 2007). The ability to maintain a normal intrinsic myocardial systolic function after three months of ISO administration to Sprague Dawley rats despite reduced β-adrenoreceptor-mediated contractile responses and cardiomyocyte apoptosis has recently been explained (Osadchii et al 2007). Our group have been able to show that intrinsic myocardial contractility is sustained in-part through enhanced myocardial α-

adrenoreceptor mediated contractile responses and an increased presynaptic myocardial norepinephrine release (Osadchii et al 2007). I assume that the ability to maintain a normal intrinsic myocardial systolic function after five (Badenhorst et al 2003) and seven (the present study (Figure 3.10), Veliotes et al 2005) months of ISO administration to SHR is in-part through the same mechanisms.

4.3 Potential mechanisms that explain the lack of impact of exercise-induced cardiac dilatation on pump function.

A fundamental question that emerges from the data obtained in the present dissertation is why marked cardiac dilatation following habitual exercise does not translate into an impaired pump function? Two possibilities may be envisaged. First, any detrimental effects that cardiac dilatation may have on pump function may have been offset by increases in intrinsic myocardial systolic function produced by habitual exercise. However, as indicated by data obtained in this dissertation, this possibility is unlikely as intrinsic myocardial systolic function was maintained at control levels after habitual exercise (Figure 3.11). A second and more likely possibility that should be considered is that cardiac dilatation produced by exercise is through different pathophysiological mechanisms from that which occur in pathological states, mechanisms that do not reduce pump function. There are several reasons to believe that different mechanisms account for cardiac dilatation in exercise as compared to pathological states, and that this may explain the lack of impact of exercise-induced

increases in cardiac cavity dimensions on pump function. These reasons may be summarized as follows.

As indicated in the introductory chapter to this dissertation, two cellular mechanisms may account for cardiac dilatation. These are cardiomyocyte cell lengthening or side-to-side slippage. These fundamental cellular changes may produce different functional effects. In contrast to cardiomyocyte side-to-side slippage, cardiomyocyte cell lengthening is a process which requires the addition of sarcomeres, (Gerdes 2002, Gerdes et al 1992 and 1995), a change that increases the volume of the contractile apparatus and thus could potentially counter-balance the negative impact of a dilated chamber geometry on pump function (increases in wall stress). This would not necessarily be detected by measurements of intrinsic myocardial contractile function, which are designed to assess systolic function for a given volume of myocardium. Moreover, unlike cardiomyocyte cell lengthening, side-to-side slippage of cardiomyocytes may produce effects on chamber systolic function that are not necessarily related to increases in wall stress. Indeed, our group have demonstrated that cardiac dilatation in pathological hypertrophy is associated with decreases in load (stress)-independent measures of pump function and a normal intrinsic myocardial function (Norton et al 2002, Badenhorst et al 2003, Veliotes et al 2005, Gibbs et al 2004, Osadchii et al 2007). The possibility must therefore be entertained that inappropriate force transduction occurs in pathologically dilated ventricles during myocyte contraction which in-turn leads to pump dysfunction. Alternatively, a pathologically dilated chamber could simply be remodelled so that larger chamber volumes are required to produce cardiomyocyte stretch and hence recruit the Frank-Starling effect. Both of these

possibilities are easier to conceive of in conditions where cardiomyocyte side-to-side slippage rather than cell lengthening occur. These changes that occur in pathological states may not accompany physiological cardiac hypertrophy. However, is there evidence to support the notion that physiological cardiac dilatation is a different cellular process to pathological cardiac dilatation? To my knowledge, despite a thorough search of the literature, there is no such evidence. These studies are presently underway in our laboratory.

4.4 Clinical relevance of the present study

What is the clinical relevance of discovering that pathological levels of cardiac dilatation following habitual exercise do not necessarily translate into pump dysfunction? From a clinical stand-point there is much data to suggest that marked increases in cardiac cavity dimensions (well within pathological ranges) in endurance athletes may not be associated with pump dysfunction (see introductory chapter). Yet the data demonstrating pump dysfunction in association with increases in cardiac cavity dimensions (Abergel et al 2004, Abernethy et al 2003, Colan et al 1987, Pelliccia et al 1999) raises the question as to whether exercise-induced cardiac dilatation within pathological ranges may occur, and whether this is a cause of pump dysfunction? The present study provides evidence to support the notion that increases in cardiac cavity dimensions following endurance exercise programs are indeed related to pathological levels of cardiac dilatation (increased volume intercept of the diastolic pressure-volume relationship, Figure 3.5b). However, data from the present dissertation also indicate that these pathological levels of

cardiac dilatation do not necessarily translate into pump dysfunction (Figure 3.8). Indeed, it is difficult to understand how decreases in pump function attributed to cardiac dilatation following endurance exercise programs do not translate into a reduced exercise performance (Abergel et al 2004, Abernethy et al 2003, Colan et al 1987, Pelliccia et al 1999), if the reduced pump function as measured at rest is indeed a pathological process. It is more likely that reductions in pump dysfunction as measured at rest after endurance exercise (Abergel et al 2004, Abernethy et al 2003, Colan et al 1987, Pelliccia et al 1999) are the consequence of reductions in sympathetic drive rather than through increases in cavity dimensions, and that during exercise, these decreases in pump function are negated by exercise-induced increases in sympathetic tone (Abernethy et al 2003).

4.5 Strengths and limitations of the present study

In the present study cardiac dilatation and pump dysfunction were assessed from measurements made in isolated, perfused heart preparations. The value of isolated, perfused heart measurements have already been emphasized in the methods section. Briefly, in an isolated perfused heart preparation, heart rate, afterload, preload and coronary flow are controlled for; left ventricular volume measurements are made using direct techniques; and the effects of anaesthesia and variations in neurohumoral activation are eliminated. The limitations of the use of isolated, perfused heart preparations include the fact that measurements are made under unphysiological conditions in a preparation that is not actively filling or emptying (it is an isovolumic

preparation in which volumes are adjusted using a micromanipulator attached to a balloon tipped catheter which is placed in the LV – see methods, section 2.2).

In the present study, as with other studies that we have conducted (Badenhorst et al 2003, Osadchii et al 2007), the left ventricular diastolic pressure-volume relationship was largely linear. This is in contrast to exponential relations normally reported on in blood perfused hearts (Norton et al 1997). Linear diastolic pressure-volume relations may occur in ischaemic/hypoxic hearts or over-perfused hearts when oedema occurs. Although I cannot exclude a degree of hypoxia mediated by the use of a crystalloid rather than a blood perfusate, or the possibility that demand-induced ischaemia is not present at higher than normal filling volumes, I can certainly exclude flow-induced ischaemia, demand-induced ischaemia mediated by high pacing rates and the presence of oedema. The following outlines these arguments.

In our laboratory we have established the flow rate at which the myocardium achieves maximal left ventricular developed pressures. Increasing flow rates above that used in the present study has no impact on left ventricular developed pressures. Hence, flow-induced ischaemia is an unlikely explanation for the linear diastolic pressure-volume relations. With respect to demand-induced ischaemia I have already outlined the approach adopted by members of our laboratory to avoid demand-induced ischaemia with respect to pacing rates. However, I cannot exclude the possibility that at high filling volumes, where wall tension will be high, demand-induced ischaemia may occur. Lastly, no differences in the ratio of dry-to-wet left ventricular weights were noted between hearts studied in this dissertation and those ratios observed in hearts which have not been

perfused with a crystalloid solution (Norton et al 1997). Hence oedema is an unlikely explanation for the linear diastolic pressure-volume relationships.

What then could explain the linear diastolic pressure-volume relationships shown in this dissertation? Although the characteristics of the cardiac balloon used in these studies was appropriate in that pressures only started increasing in the balloon well beyond maximal filling volumes of any single heart tested, I cannot exclude a possibility that interactions between the balloon and the myocardial wall contributed toward the diastolic pressure-volume relations. Hence, it is possible that the characteristics of the balloon possibly contributed toward the linear diastolic pressure-volume relations. Second, in isovolumic heart preparations, to avoid the impact of active properties of the heart influencing diastolic pressure-volume relations, these relations are normally constructed in K^+ arrested hearts. However, our group have shown that left ventricular diastolic pressure-dimension relations in K^+ arrested hearts are very different from end diastolic pressure-dimension relations obtained in filling and emptying hearts (Norton and Woodiwiss, personal communications). Hence, the value of diastolic pressure-volume relations obtained in K^+ arrested hearts is questionable.

4.6 Insights gained regarding appropriate use of SD vs. SHR

Although SHR have an increased LV weight compared to SD (Figure 3.1), the LV diastolic pressure-volume relation (Figures 3.3 and 3.4a), the volume intercept of this relation (Figures 3.3 and 3.4b) and the LV developed pressure-volume relation (Figures 3.6 and 3.7) were similar. In addition, SD and SHR show similar responses to chronic isoproterenol administration. In both rat strains LV dilatation occurs with a right-shift in

the pressure-volume relation (Figures 3.3 and 3.4a), there is a similar increase in the LV volume intercept (Figures 3.3 and 3.4b) and a decrease in systolic chamber function (developed pressure-volume relation, Figures 3.6 and 3.7). The only differences observed were a lower systolic myocardial function in SD (Figure 3.9) compared to SHR (Figure 3.10), and with isoproterenol administration systolic myocardial function was decreased in SD (Figure3.9) but unchanged in SHR (Figure 3.10). Hence except for the assessment of systolic myocardial function, SD could be used as a normotensive control for SHR in future studies of cardiac properties. Nevertheless, the correct genetic control for SHR is the normotensive WKY strain of rats (Tsotetsi et al 2001).

4.7 Conclusions

In conclusion, the data provided in the present study indicate that unlike pathological cardiac hypertrophy, where pump dysfunction can be attributed directly to cardiac dilatation, pathological levels of cardiac dilatation in physiological cardiac hypertrophy (in response to habitual exercise) do not translate into pump dysfunction. The mechanisms responsible for the contrasting ability of physiological and pathological cardiac dilatation to promote pump dysfunction require further investigation.

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