

**Left Ventricular Function After Ultra-
Distance Triathlon:
Response is Dependent on the Cardiac
Loading Conditions**

A dissertation prepared by

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**(Student No. HSSMUH001) in partial fulfilment of the
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List of abbreviations

A Late transmitral valve flow velocity

AO Aorta

AV Atrio-ventricular

BP Blood pressure

B-receptor Beta receptor

CK Creatine kinase

CONTR Contraction

cTnI Cardiac troponin I

cTnT Cardiac troponin T

D Diastole

DD Diastolic dimension

DV Diastolic volume

E Early transmitral valve flow velocity

E/A Ratio of Early/Late Transmitral valve flow velocity

EDV End diastolic volume

EF Ejection fraction

ESV End systolic volume

FS Fractional shortening

IC Isovolumetric contraction

IR Isovolumetric relaxation

IVSd Interventricular septum diameter

LA Left atrium

LV Left ventricle

LVPWd Left ventricle posterior wall diameter

MV Mitral valve

RA Right atrium

RFP Rapid filling phase

RV Right ventricle

S Systole

sBP Systolic blood pressure

SV Stroke volume

TnI Troponin I

TnT Troponin T

CHAPTER ONE

INTRODUCTION AND SCOPE OF THE THESIS

CHAPTER 1

Introduction and scope of the thesis

In 1978 two runners developed acute pulmonary edema during the 90-km Comrades Marathon foot race in South Africa (McKechnie et al 1979). The absence of any medical and cardiac condition, together with the rapidity with which these abnormalities regressed despite negligible therapy, suggested transient pulmonary edema of cardiac origin. This is a rare phenomenon and has subsequently led to a variety of studies that investigated for cardiac dysfunction after prolonged exercise.

Subsequently, a number of echocardiographic studies have shown a variety of changes in left ventricular function after prolonged exercise (Upton et al 1980, Niemelä et al 1984, Perrault et al 1986, Douglas et al 1987, Niemelä et al 1987, Seals et al 1988, Douglas et al 1990, Vanoverschelde et al 1991, Manier et al 1991, Ketelhut et al 1992, Palatini et al 1994, Lucia et al 1999, Whyte et al 2000, Goodman et al 2001). These athletes were asymptomatic, however they had echocardiographic changes indicative of diastolic and systolic dysfunction. The diastolic dysfunction was shown by changes in the cardiac Doppler flow characteristics while systolic dysfunction was shown by changes in contractility as shown by the altered changes in the fractional shortening or ejection fraction after exercise. The presence of either diastolic (Douglas et al 1987, Vanoverschelde et al 1991, Lucia et al 1999, Whyte et al 2000) or systolic abnormalities (Niemelä et al 1984, Douglas et al 1987, Niemelä et al 1987, Seals et al 1988, Douglas et al 1990, Vanoverschelde et al 1991, Ketelhut et al 1992, Whyte et al 2000) after prolonged endurance exercise has given rise to the concept that prolonged exercise produces a reversible “cardiac fatigue”. The “cardiac fatigue” represents a temporary, altered cardiac function as shown by the changes observed by the echocardiographic measurements after prolonged exercise, but there are no clinical manifestations of cardiac disease.

However, an important but overlooked weakness of all studies that have described cardiac fatigue after prolonged exercise is that the loading conditions on the heart were not standardized before and after exercise, in a way that might control for the significant changes in peripheral vascular function that are known to develop after very prolonged exercise (Niemelä et al 1984, Perrault et al 1986, Niemelä et al 1987, Douglas et al 1987, Seals et al 1988, Douglas et al 1990, Vanoverschelde et al 1991, Manier et al 1991, Ketelhut et al 1992, Lucia et al 1999, Whyte et al 2000). Thus changes in both preload and afterload after prolonged exercise (Niemelä et al 1984, Douglas et al 1987, Niemelä et al 1987, Seals et al 1988, Vanoverschelde et al 1991, Manier et al 1991, Ketelhut et al 1992, Lucia et al 1999, Whyte et al 2000) might be sufficient to produce what appears to be “cardiac fatigue” but which may be an artefact of different ventricular loading conditions before and after exercise.

It is also relevant to note that three previous studies (Upton et al 1980, Palatini et al 1994, Goodman et al 2001) found no evidence for “cardiac fatigue” during as opposed to after exercise. These studies measured cardiac function during exercise using radionuclide isotope imaging and found no cardiac dysfunction during exercise when the expected cardiac work load is at its peak. This is surprising if post-exercise cardiac fatigue is a real phenomenon which develops during exercise and which is therefore not simply an artefact of the act of stopping exercise since the changes in the cardiac loading conditions after exercise can cause altered echocardiographic changes similar to cardiac dysfunction (Choong et al 1987, Bhatia et al 1987, Courtois et al 1988, Stoddard et al 1989, Berk et al 1990).

Importantly in the studies performed during exercise, systolic blood pressure rose significantly and the preload was maintained. Ejection fraction was either maintained (Goodman et al 2001)

or increased (Upton et al 1980, Palatini et al 1994) during exercise. These findings contrast with results from studies that assessed cardiac function only after the cessation of exercise and in which the ejection fraction had decreased (Niemelä et al 1984, Douglas et al 1987, Niemelä et al 1987, Seals et al 1988, Douglas et al 1990, Vanoverschelde et al 1991, Ketelhut et al 1992, Whyte et al 2000). Thus, paradoxically, “cardiac fatigue”, as defined earlier, has been reported in the post-exercise period when the expected cardiac work load declined due to the reduction in the rate-pressure product and in the peripheral requirements for blood flow.

The purpose of this thesis is to establish if there is any evidence to support the hypothesis that altered ventricular loading conditions after the cessation of exercise may cause “cardiac fatigue”. The studies that have shown post-exercise “cardiac fatigue” have not controlled for either preload or afterload or both, before and after exercise. These studies may rather have identified the effects of alterations in peripheral vascular function on left ventricular function after prolonged exercise.

The research study in this thesis is to evaluate if the loading conditions of the heart affect the echocardiographic measurements after exercise that may be misinterpreted as “cardiac fatigue”. Echocardiography as a tool of cardiac evaluation cannot be done during exercise because of the technical difficulty of doing a cardiac ultrasound on a human being in motion. The studies that have investigated post exercise “cardiac fatigue” have therefore measured cardiac function after exercise and retrospectively assumed that the cardiac dysfunction was present during exercise since the cardiac demands are at their peak during exercise. However, the post exercise period may be associated with altered loading conditions that may cause changes in the echocardiographic measurements that are similar to cardiac abnormalities. Echocardiographic studies at rest have shown that reduced preload causes abnormal diastolic function similar to

post exercise “cardiac fatigue” (Choong et al 1987, Bhatia et al 1987, Courtois et al 1988, Stoddard et al 1989, Berk et al 1990). Since the post exercise period may be associated with reduced venous return and therefore reduced preload (Holtzhausen et al 1994) and since this is shown in the studies assessing cardiac function after exercise (Niernalä et al 1984, Douglas et al 1987, Niernalä et al 1987, Seals et al 1988, Manier et al 1991, Vanoverschelde et al 1991, Lucia et al 1999), the differentiation in physiological changes and pathological changes is necessary to ascertain if cardiac dysfunction is a real phenomenon. The research study was designed to maximize venous return by leg elevation before and after exercise in an attempt to maintain preload during cardiac measurements before and after exercise.

I begin with my review of the normal physiology of cardiac function as assessed with echocardiography measurements and follow this with a review of any abnormal findings. The influence of the loading conditions on cardiac function and the measurements are discussed in relation to studies that found post exercise “cardiac fatigue”. The research study was conducted to identify any possible effects of these peripheral vascular changes on left ventricular function after prolonged exercise. This is followed by an assessment of the influence of prolonged exercise on the cardiac beta-receptor response after prolonged exercise that could not be controlled for during this or other similar studies. The abnormal cardiac enzyme measurements and the reliability of using serum enzyme analysis to assess reversible and irreversible myocardial ischaemia after prolonged exercise is discussed in relation to its role after prolonged exercise (Saggin et al 1990, Kobayashi et al 1992, Muller-Bardorff et al 1997).

Summary:

Some changes in left ventricular function after prolonged exercise may reflect changes in left ventricular loading conditions. Since most of the previous studies assessing cardiac dysfunction

lacked standardization in their study design to maintain left ventricular loading conditions, “cardiac fatigue” may have been the result of changes in the peripheral vascular function induced by prolonged exercise. The aim of my thesis is to assess for this possibility and the research study was conducted to test this hypothesis.

CHAPTER TWO

METHOD OF ASSESSING CARDIAC FUNCTION

CHAPTER 2

Methods of assessing cardiac function

In the study reported in chapter 4, echocardiography was used to evaluate cardiac function before and after exercise. This chapter present a review of echocardiographic measurements of diastolic and systolic left ventricular function.

(1) The cardiac cycle and mitral valve blood flow pattern

Figure 2.1 shows the Doppler flow pattern across the mitral valve in relation to the cardiac cycle. The cardiac cycle refers to the blood flow through the heart during which a series of electrical and mechanical events take place. The original Wiggers diagram that defines diastole and systole (figure 2.1) divides the cardiac cycle into a sequence of eight defined events during systole (S) and diastole (D).

At the onset of systole the pressures inside the left ventricle and left atrium are equal. The pressure in the ventricle rises and the atrio-ventricular (AV) valves close completely giving rise to the first heart sound. The ventricle contracts isovolumetrically (IC). Since both the mitral and aortic valves are closed, the ventricular pressure rises rapidly during this isovolumetric contraction phase. When the intra-ventricular pressure exceeds the aortic pressure, the aortic valve opens and blood flows across the open aortic valve. Following the end of ventricular systole, the onset of ventricular relaxation produces a sharp drop in pressure in the ventricle and aorta. The lower intra-ventricular pressure causes the aortic valve to close causing the second heart sound. Within the ventricle there is a rapid reduction in pressure during this phase of isovolumetric relaxation (IR) and the point of opening of the mitral valve represents the end of IR and ventricular systole. The intra-ventricular pressure declines to a level lower than that in the atrium and the mitral valve is opened by the pressure difference. The drop in the intra-

ventricular pressure causes a phase of rapid filling (RFP) represented by the E wave flow pattern when measured using Doppler echocardiography.

The E wave represents the rapid flow across the mitral valve due to the large pressure gradient between the ventricle and atrium. Atrial contraction then produces the A wave pattern (A) identified by Doppler flow measurement across the mitral valve and this atrial contraction may be audible clinically as the fourth heart sound.

The pressure and flow changes during the Cardiac Cycle

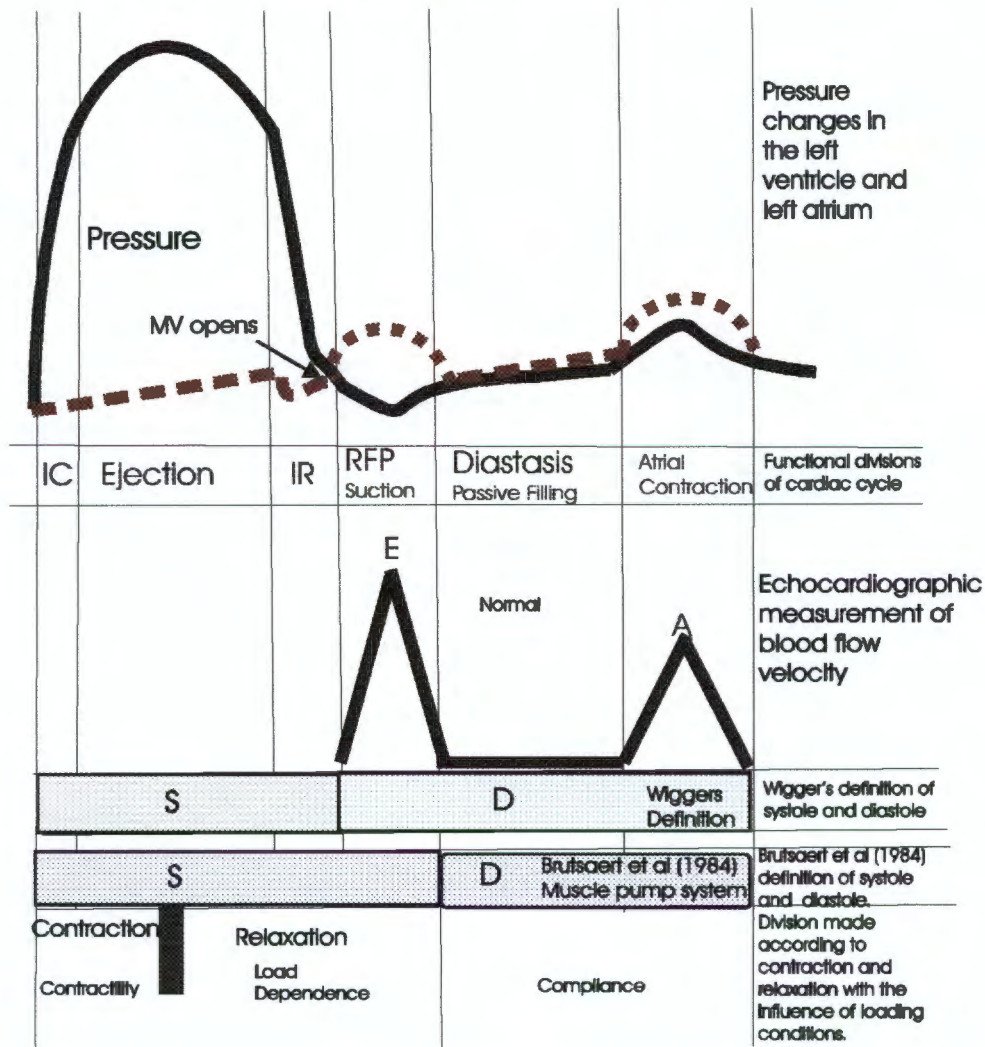


Figure 2.1. The normal blood flow pattern across the mitral valve as determined by echocardiography in relation to the cardiac cycle. The top panel shows the pressure changes in the left ventricle (solid line) and the left atrium (dotted line). After the mitral valve (MV) opens (arrowed), the velocity of blood flow across the mitral valve increases to reach an initial peak- the E wave as measured by Doppler echocardiography. The rate of blood flow then decreases before the flow rate again increases during atrial systole to reach a second peak value represented by the A wave. The size of the E wave is normally greater than the size of the A wave. In the classic Wiggers model of the cardiac cycle, the E wave occurs during the diastolic period while it is included in systole as defined by the load dependent model by Brutsaert et al (1984). In this model the cardiac cycle is divided into systole that includes LV contraction and relaxation represented by systole. Since LV relaxation extends into the RFP, the end of systole is defined after RFP. The LV contraction is dependent on contractility while relaxation is load dependent and diastole is dependent on the LV compliance during LV filling. IC = Isovolumetric contraction, IR = Isovolumetric relaxation, RFP = Rapid filling phase. For details, see text.

Mechanical aspects of cardiac relaxation:

The performance of the heart during the contraction phase is controlled according to heterometric and homeometric autoregulation. Heterometric autoregulation refers to the control by changes in load and hence in the length of the sarcomeres in response to changes in volume and pressure. This is the Starling mechanism where optimal sarcomere lengths produces activation of all the actin-myosin cross bridges. Homeometric autoregulation is the control by change in contractility at the level of the individual actin-myosin cross bridges resulting from the increase in cytosolic calcium or cyclic AMP effects.

Brutsaert et al (1984) postulated a third component of cardiac control defined as “nonuniform distribution”. Control of relaxation is continuously modulated by the regional and temporal nonuniform distribution of load and inactivation due to the multicellular and nonuniform structure of the heart. Since systole includes contraction and relaxation which are dependent on the cardiac loading conditions, they proposed systole includes the processes of relaxation that extends into the early part of diastole so that a functional categorization of the cardiac cycle should be more clearly defined by the different loading conditions present at different moments in the cardiac cycle. They therefore proposed that the rapid filling phase should be considered an integral part of systole since it is part of and a continuation of the cardiac muscle relaxation phase (Figure 2.1). The cardiac contraction is the initial phase of systole followed by cardiac relaxation that is still part of systole. Diastole, according to the classic Wigger’s definition, is defined according to the opening and closure of the mitral valve and not according to the cardiac contraction and relaxation processes.

Using their postulated model based on load dependence, systole and diastole are defined according to an integrated “ muscle-pump system” in which the rapid filling phase is considered to be an integral part of cardiac muscle relaxation. Systole therefore encompasses contraction

that includes isovolumetric contraction (IC) and the first part of ejection while relaxation includes a large portion of the second half of ejection, isovolumetric relaxation and the rapid filling phase. Since exercise causes changes in the peripheral circulation and loading conditions of the heart and cardiac relaxation extends into the rapid filling phase (RFP), the integrated muscle-pump system seems more appropriate to define the systolic and diastolic cardiac response to the changing loading conditions of the heart during and after exercise.

(2) Measuring left ventricular function using echocardiography.

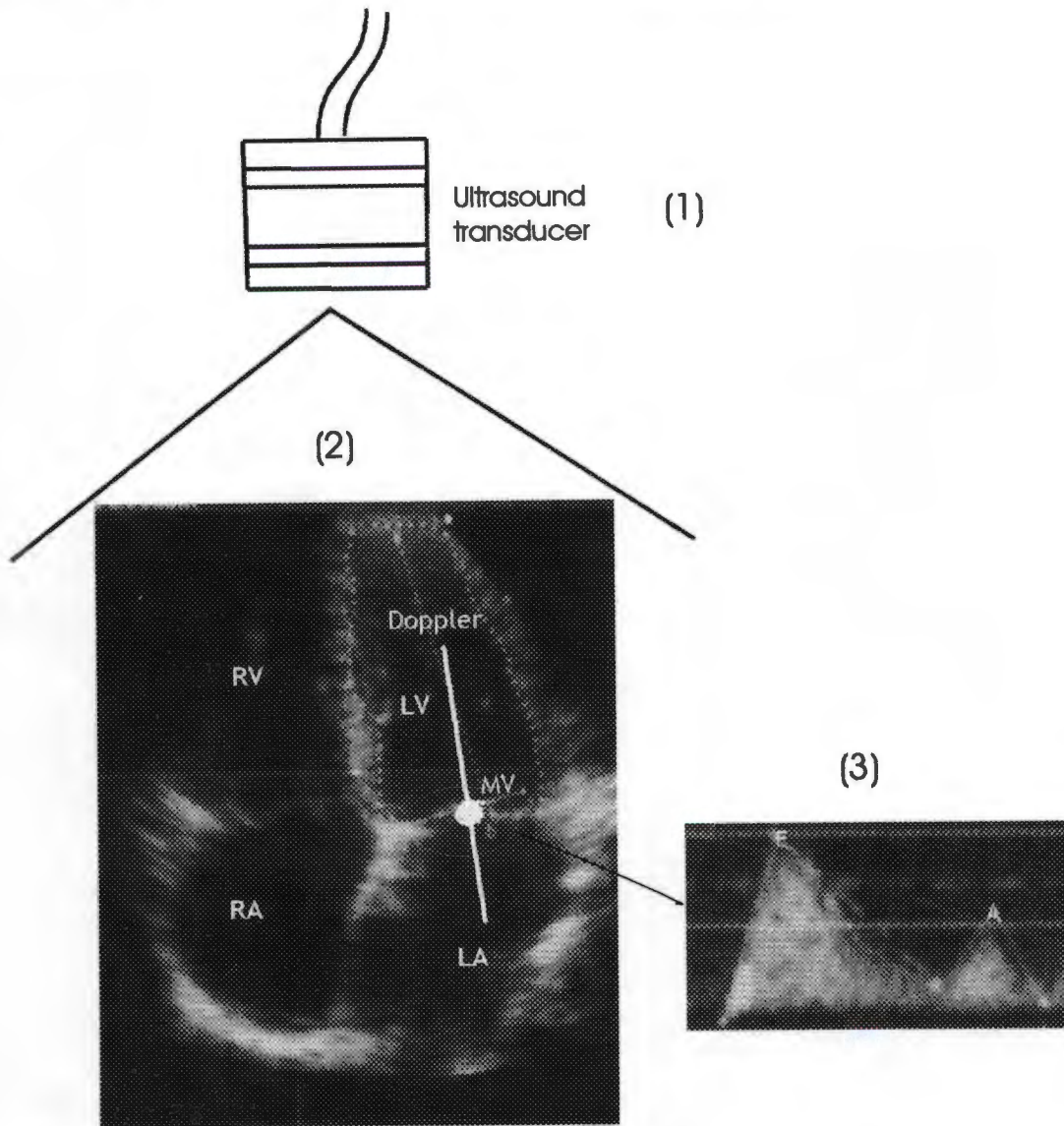
Diastolic left ventricular function measured with echocardiography.

Doppler Echocardiography:

Doppler echocardiography has made it possible to measure blood flow patterns as well as blood velocity in humans in vivo. Doppler echocardiography is a technique for recording the manner in which blood moves within the cardiovascular system. The reflected sound waves from the heart are used to determine the motion of blood that reflects the ultrasound energy. The receiving transducer records the reflected echoes and the intensity of the received frequency is dependent on the direction and velocity of the blood.

Using Doppler velocity measurements, the pressure gradient across an orifice can be calculated by modifying the Bernoulli equation (Stam et al 1983). The pressure gradient across the orifice is equal to 4 times the velocity². When measuring blood flow across a valve it is important that the Doppler examination allows the ultrasound beam to be parallel to the moving column of blood. The Doppler flow pattern of the mitral valve is measured with the transducer at the apex of the heart using an apical two or four-chamber view (Figure 2.2). At the end of systole, as defined by the Wiggers definition of the cardiac cycle (Figure 2.1), the mitral valve opens and blood flows across the mitral valve. There are essentially two phases to the flow across the valve. The first occurs in early diastole (E) and the second after atrial systole (A). Normally the early transmitral flow velocity is greater than the second due to the larger pressure gradient across the mitral valve that results from the “atrial suction” during the rapid filling phase.

Echocardiographic 4-chamber view of the heart with the transducer at the apex of the heart.



Key: LA = left atrium, LV = left ventricle, RA = right atrium,
 RV = right ventricle, E = early transmitral flow velocity,
 A = late transmitral flow velocity, MV = mitral valve annulus.

Figure 2.2. The normal Doppler blood flow pattern across the mitral valve. The apical 4-chamber view of the heart is shown with the transducer (1) positioned at the apex of the heart. Doppler blood flow measurements are taken with the blood flow sample at the valve annulus taken perpendicular to the mitral valve annulus (MV). The normal diastolic blood flow pattern is shown on the right (3). The early (E) and late (A) transmitral flow patterns are shown with the E wave being greater than the A wave under normal loading conditions at rest.

The transmitral pressure-flow relationship can be described qualitatively by the following equation of motion: $\Delta P = (A) d (MiF) / dt + (B) (MiF)$ in which ΔP = instantaneous atrio-ventricular pressure; ΔP = Pressure difference, MiF = mitral flow, A = inertial coefficient, B = resistive coefficient.

At time of peak flow (Figure 2.2 [3]), the rate of change of flow, $d (M: F)/dt$, is zero and therefore ΔP which is the atrioventricular pressure difference at the time of peak flow, is proportional to the maximum flow rate (E).

The principle determinants of the atrioventricular pressure difference during diastole are the following:

- Left ventricular end systolic volume
- Left atrial pressure at the onset of mitral inflow
- Compliance of the left atrium
- Rate and duration of left ventricular relaxation
- Passive left ventricular compliance

These determinants are dependent on the loading conditions of the heart including the preload and afterload.

Preload and afterload:

Preload can be defined as a cardiac load that stretches a muscle before it is stimulated to contract while afterload is encountered only after the muscle has started to contract (Katz et al 1992). Afterload is therefore a load that is not apparent to the muscle when it is in a resting state but which is encountered by the muscle when it begins to contract. The volume of blood at the end of diastole is responsible for the length of the cardiac muscle prior to contraction, thereby defining the length tension/preload conditions of the heart. The length tension relationship of cardiac muscle is responsible for the cardiac response to the prevailing loading conditions. The Frank Starling law describes the relationship of volume and pressure and stipulates that the systolic pressure developed in a series of isovolumic contractions increases

with increasing left ventricular end diastolic volume. The end diastolic volume of the left ventricle is dependent on the venous return and the atrial response. Steady state is when venous return has to equal cardiac output. Exercise increases the venous return to the heart due to the muscle pump action of the lower limbs. After exercise this muscle pumping action decreases significantly and as a result, venous return and thus preload may decline causing a mismatch to the steady state.

The atrium acts as a “primer pump” since atrial contraction augments the volume of blood in the ventricles thereby influencing the length of the ventricular muscle at the end of diastole. The end diastolic volume and activation of the Frank Starling mechanism then determines the strength of the ventricular contraction. Atrial systole as a primer system therefore allows a mechanism for increasing end diastolic volume at any given physiological instant when diastolic volume determines ventricular performance.

Echocardiographic measurement of left ventricular systolic function:

Measurement of the cardiac ejection fraction provides indirect assessment of left ventricular function. The ejection fraction represents the percentage or fraction of left ventricular diastolic volume that is ejected in systole. The ejection fraction can be measured with echocardiography from either volume changes or from linear dimension changes to calculate the fractional shortening of the left ventricle.

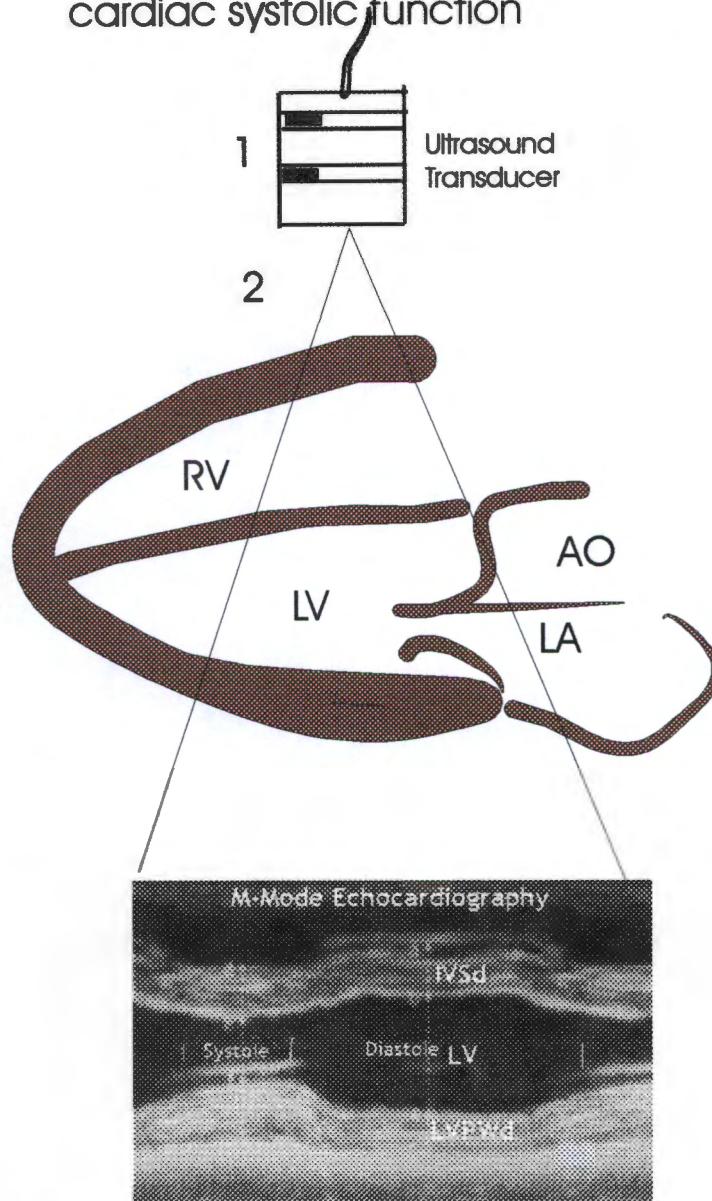
Hence:

Ejection fraction (volume change) = Stroke volume/Diastolic volume multiply by 100 (%)

Fractional shortening (linear dimension) = (Diastolic dimension – Systolic dimension)/Diastolic dimension multiply by 100 (%).

Fractional shortening is measured echocardiographically using the M-Mode or two-dimensional linear dimensions with the left parasternal long-axis view (Figure 2.3).

Parasternal long axis view of the heart in M-mode for the measurement of cardiac systolic function



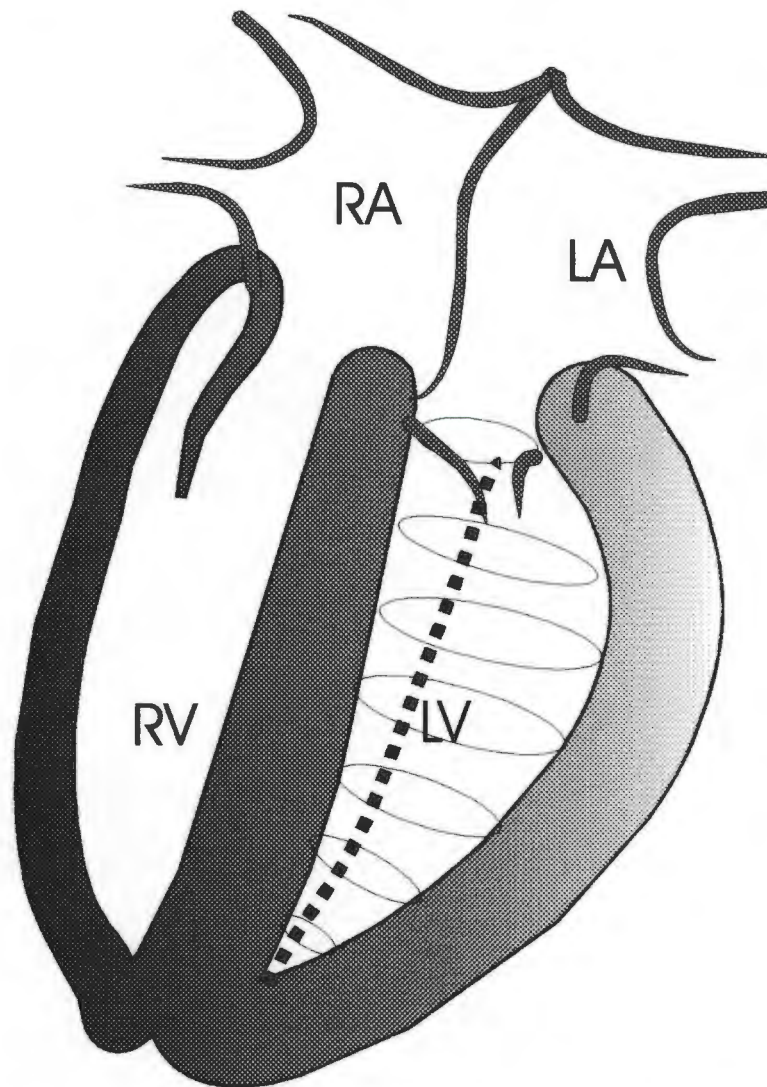
Key: RV=Right ventricle, LV=Left ventricle, AO=Aorta, LA=Left atrium, IVSd=Interventricular septum diameter, LVPWd= Left ventricular posterior wall diameter.

Figure 2.3. M-mode visualization of the long axis view of the heart. The transducer (1) is positioned at the left parasternal area with the ultrasound M-mode beam through the right ventricle (RV) and left ventricle (LV). The M-Mode beam (2) provides an ultrasound recording of the contracting heart for calculation of fractional shortening of the left ventricle. The M-mode image is a continuous recording of the contracting heart and a selected clip of diastole and systole is used for the determination of either the fractional shortening or the ejection fraction.

An important limitation in the measurement of fractional shortening is that fractional shortening does not provide a true reflection of global left ventricular function if the heart is not contracting symmetrically as a consequence of wall motion abnormalities in the left ventricle.

A more reliable assessment of left ventricular function, the ejection fraction can also be measured using the long-axis measurements of the heart from the apical views of the left ventricle using the area length technique (Figure 2.4). The area length method is used from two-or-four-chamber apical examination. Simpson's rule provides a more accurate method to calculate ventricular volume (Schiller et al 1989). The principle of the Simpson's rule for volume measurement is to divide the heart into slices of known thickness. The summation of the volume of calculated slices is equal to the total volume, derived from the short axis view. The modified Simpson's approach uses the apical 2 or 4 chamber view of the ventricle and the volume measurements calculated.

Left ventricular volume measurement using the Modified Simpson rule



Key: RA = right atrium, RV = right ventricle, LA = left atrium, LV = left ventricle.

Figure 2.4 Left ventricular volume measurements using the modified Simpson's method of summation by the plane area length method. Cardiac volumes are calculated during diastole and systole. The summation of discs is taken from the mitral valve annulus to the apex (dotted line). This volume measurement is independent of asymmetrical ventricular contraction. The calculation equations using the Modified Simpson method to calculate LV volumes are as follows:

$$EDV = (LVLd/9) \times \{4 \times LVSAMVd + 2 \times LVSAPMd + (LVSAMVd \times LVSAPMd)^{1/2}\},$$

$$ESV = (LVLs/9) \times \{4 \times LVSAMVs + 2 \times LVSAPMs + (LVSAMVs \times LVSAPMs)^{1/2}\},$$

$SV = EDV - ESV$ and Ejection fraction = Stroke volume/Diastolic volume multiply by 100 (%), (Schiller et al 1989).

When performing an ultrasound examination of the heart, the echo transmitted is constantly moving and as a result the echo position changes constantly with reference to the transducer. The motion is recorded using a technique of intensity modulation in which the amplitude of the echo is converted to intensity and the signal is converted to a dot. This representation is called B-mode. Since the heart is moving, time can be added as a second dimension during the recording and this technique is called “M-mode” where the M stands for motion.

M-mode echocardiography allows assessment of only a small portion of the heart and makes the assumption that the limited area visualized with the M-mode beam is representative of overall cardiac function. The modified Simpson’s method of systolic cardiac evaluation is a more reliable indicator of global systolic function especially when asymmetrical cardiac contraction is present.

Summary: Cardiac volume and function can therefore be measured using either the fractional shortening or ejection fraction method. Since the modified Simpson’s method is a more reliable indicator of cardiac function when the heart is contracting asymmetrically, for the purpose of the research study, I used the latter technique for cardiac assessment.

CHAPTER THREE

CARDIAC RESPONSE TO CARDIAC LOADING CONDITIONS

CHAPTER 3

Cardiac response to loading conditions

The hypothesis under evaluation in this thesis is that loading conditions on the heart may change after prolonged exercise. Studies assessing cardiac function after exercise may reflect changes in the circulatory system that may be misinterpreted as “cardiac fatigue”.

Doppler echocardiography has been used to describe changes in transmitral Doppler flow patterns in pathological conditions such as hypertrophic cardiomyopathy (Bryg et al 1987), dilated cardiomyopathy (Takenaka et al 1986), hypertrophy secondary to hypertension (Inouye et al 1984, Snider et al 1985) or obesity (Chakko et al 1991), coronary artery disease (Wind et al 1987) and valvular heart disease (Otto et al 1989). It has been shown that a reduction or increase in preload may induce a diastolic filling pattern at rest that can either mimic or mask diastolic dysfunction (Stoddard et al 1989). Since exercise may cause a change in the loading conditions of the heart causing postural hypotension (Holthausen et al 1995) or post exercise collapse (Noakes et al 2003), the changes in the post exercise period may mimic the same changes seen when using echocardiography to measure the cardiac function of pathological conditions at rest.

This chapter discusses the influences of the loading conditions on left ventricular function and are reviewed in relation to the echocardiographic measurements used to define cardiac dysfunction.

Left ventricular Cardiac responses to changes in the cardiac loading conditions

Cardiac relaxation:

Brutsaert et al (1984) developed the concept of triple control of cardiac relaxation as discussed in Chapter 2. The cardiac relaxation is dependent on the prevailing cardiac loading conditions, the process of contractile inactivation and the arrangement of cardiac muscle fibers. Relaxation of the heart is governed by the contractile system response to the prevailing loading conditions. According to this model, the control of myocardial relaxation can be classified accordingly

(Triple Response):

1. Control by load
2. Control by inactivation
3. Control by non-uniformity

Control by load:

At a higher afterload or at a higher preload, the onset of relaxation is delayed. Any increase in preload or afterload, once established during the first two-thirds (Figure 2.1) of the CL (contraction loading) phase, will delay the onset of relaxation. The shifts in pressure and volume load from late to early ejection will therefore delay relaxation, while shifts from early to late ejection will induce premature relaxation. The four major loading conditions of the heart during relaxation includes the deformation during cardiac contraction, impedance alterations late in the ejection process, coronary artery filling during isovolumetric relaxation and the Laplace relationship after mitral valve opening, with the diastolic suction during the rapid filling phase a mere consequence of the cardiac loading conditions (Brutsaert et al 1984). Laplace states that the wall tension is equal to the pressure within a cylinder times the radius of curvature of the wall. The wall tension at any given pressure increases as the radius of the cylinder increases, the cardiac wall tension therefore dependent on the loading conditions.

curvature of the wall. The wall tension at any given pressure increases as the radius of the cylinder increases, the cardiac wall tension therefore dependent on the loading conditions.

Control by inactivation:

Contraction and relaxation of cardiac muscle is dependent on the availability of myoplasmic calcium concentrations. Relaxation is governed by the detachment of the cardiac cross-bridges under the prevailing loading conditions. The inactivation process modulates the cardiac relaxation process in a subtle interplay with the load, with the load predominating over inactivation at sufficiently lowered levels of myoplasmic calcium concentration. The availability of cardiac cross-bridging is dependent on the inactivation process under the prevailing loading conditions and this may be influenced by metabolic control of the coronary circulation, neurohumeral control or the use of drugs (Brutsaert et al 1980) that affect the availability of oxygen, nutrients and energy available for cardiac function.

Control by Non-uniformity:

Non-uniformity of cardiac muscle is a third physiologic concept determining cardiac response to the prevailing loading conditions. This refers to the spatial orientation of cardiac muscle fibers that are arranged in a non-uniform arrangement with cardiac muscle sarcomeres varying in length at any given work-load. This is most marked during relaxation and at higher contraction loads. Non-uniformity of contraction contributes further to load dependence since actively shortening fibers in some areas add to the external load of already relaxing fibers in other areas.

Summary:

Based upon the influences of load, inactivation and non-uniformity, variables affecting left ventricular function include preload, afterload, neuroendocrine changes and the sensitivity of the cardiac Beta-receptors to agonist stimulation.

Studies assessing cardiac function after prolonged exercise have shown a reduction in preload and afterload (Vanoverschelde et al 1991, Manier et al 1991, Lucia et al 1999), normal preload with decreased afterload (Whyte et al 2000) and normal afterload with reduced preload (Douglas et al 1987). These changes in the loading conditions are therefore influenced by the heart's response through the physiological process of cardiac "control of load, inactivation and non-uniformity." The shifts in the loading conditions of the left ventricle during ejection, from early to late may induce premature relaxation that may manifest as "cardiac fatigue", manifesting asymptotically with echocardiographic Doppler changes of relaxation abnormalities. Furthermore, the control by inactivation is influenced by the possible metabolic changes in the coronary circulation (Brutsaert et al 1984), together with the cardiac Beta-receptor desensitisation after prolonged exercise (Friedman et al 1986, Eysmann et al 1996)(Figure 5.2).

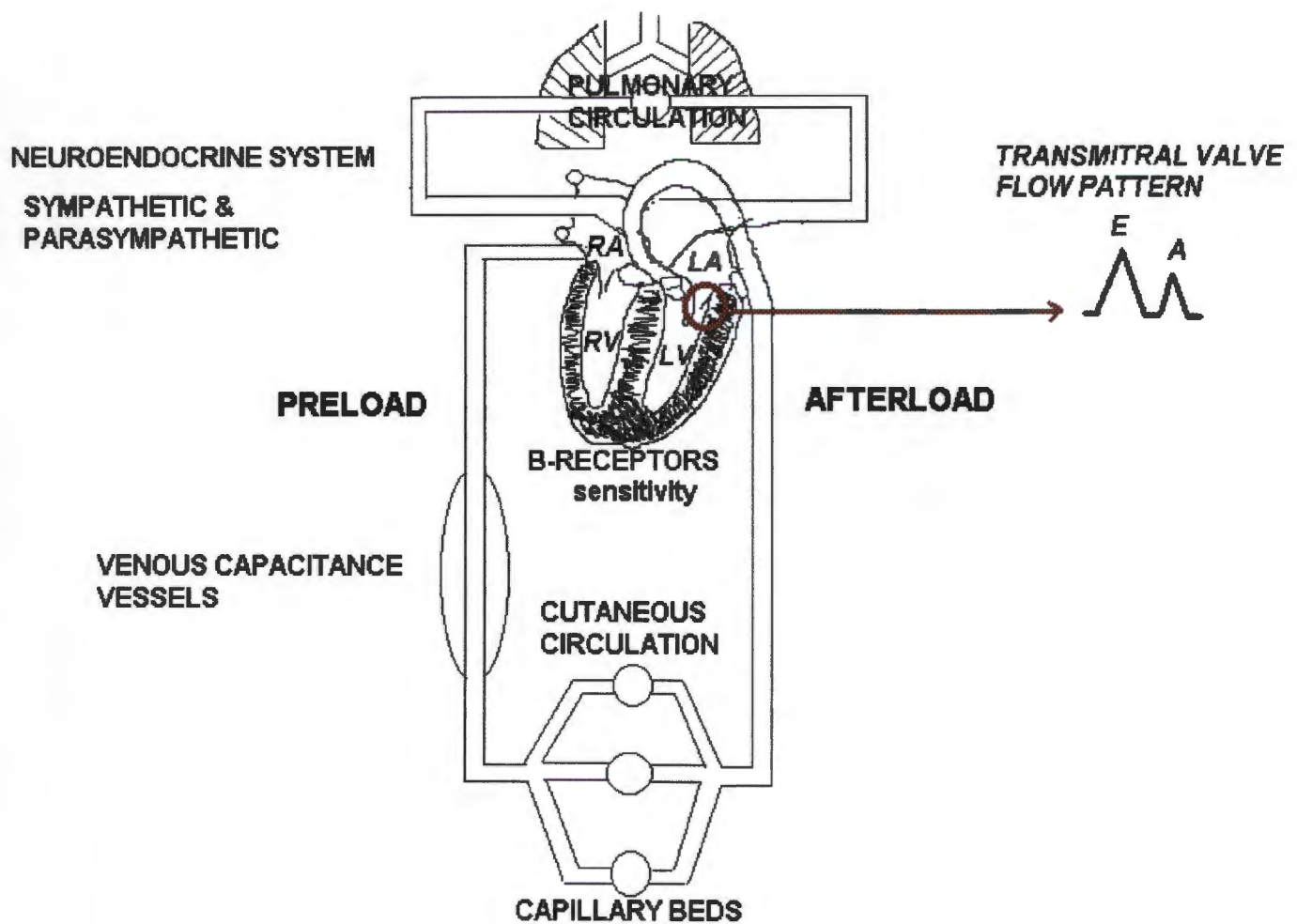


Figure 3.1 Factors that affect the measurements of left ventricular function with echocardiography. The role of the components of the peripheral circulation that affect the cardiac loading conditions of the heart and subsequently the effects of Doppler flow across the mitral valve. One of the determinants of preload during exercise includes the “muscle pump system”. The muscle contraction during exercise pumps blood from the venous capacitance vessels back to the heart and this may be inoperable immediately after exercise when muscle blood pooling may develop. The cutaneous circulation is an additional compartment where venous pooling occurs especially when exercising in the heat and the redistribution of blood back to the general circulation may be difficult to control. The cardiac response to the loading conditions is also dependent on the sympathetic nervous system and the efficiency of the cardiac response is dependent on the sensitivity of the cardiac B-receptor to both the circulating norepinephrine concentrations and to neurally released norepinephrine concentrations.

(A) Changes in diastolic characteristics as a result of exercise training

Training does not alter the diastolic filling properties of the left ventricle. In particular, physiologic left ventricular hypertrophy is not accompanied by any alteration in left ventricular diastolic filling characteristics (Shapiro et al 1983, Granger et al 1985).

(B) Echocardiography evidence of left ventricular diastolic dysfunction:

Conceptually, diastole encompasses the time period during which the myocardium loses its ability to generate force and shorten and returns to an unstressed length and force. By extension, diastolic dysfunction occurs when these processes are prolonged, slowed or incomplete.

Relaxation abnormalities:

Relaxation abnormalities of the heart are one of the earliest manifestations of cardiac dysfunction. Early relaxation abnormalities have been found in various cardiac diseases and frequently precede evidence of systolic dysfunction (Brutsaert et al 1984). Doppler echocardiography is used as a non-invasive modality that shows changes of the left ventricular intra-cavity filling pattern in patients with diastolic dysfunction and the Doppler-derived indexes of intra-ventricular flow have been proposed as markers of diastolic dysfunction.

Abnormal flow pattern:

Doppler transmitral flow velocity pattern in patients with diastolic dysfunction usually shows decreased peak early diastolic filling velocity, slowed deceleration of the early diastolic filling wave and increased peak filling velocity at atrial contraction (Yamamoto et al 1993). The early stages of diastolic dysfunction measured by Doppler echocardiography shows a decline in E velocity and prolongation of deceleration time because of impaired or slowed left ventricular relaxation. If left ventricular relaxation is not rapid enough to produce the early diastolic

gradient across the mitral valve, rapid early diastolic filling will not occur. The left atrial pressure will not decrease after mitral valve opening so that little flow will occur. Thus the E wave will be small, and the left ventricle will almost totally be dependent on atrial contraction (Nikolic et al 1988).

Abnormal left ventricular relaxation causes a reduction in the height of the E wave causing a rapid rise in left atrial pressure to produce a tall A wave (Figure 3.2) as seen in abnormal diastolic filling conditions such as dilated cardiomyopathy (Takenaka et al 1986), hypertension (Inouye et al 1984, Snider et al 1985), left ventricular hypertrophy of obesity (Chakko et al 1991), coronary artery disease (Wind et al 1987) and valvular heart disease (Otto et al 1989).

If the pathological relaxation abnormality progresses, left ventricular compliance may decrease, which results in increased left atrial pressure with an increase in size of the E wave velocity and decreased deceleration time. This may mimic the normal transmitral flow pattern and this “pseudonormal” filling pattern with increased left ventricular filling pressure is difficult to differentiate from the normal left ventricular filling pattern.

The pressure and flow changes during the Cardiac cycle

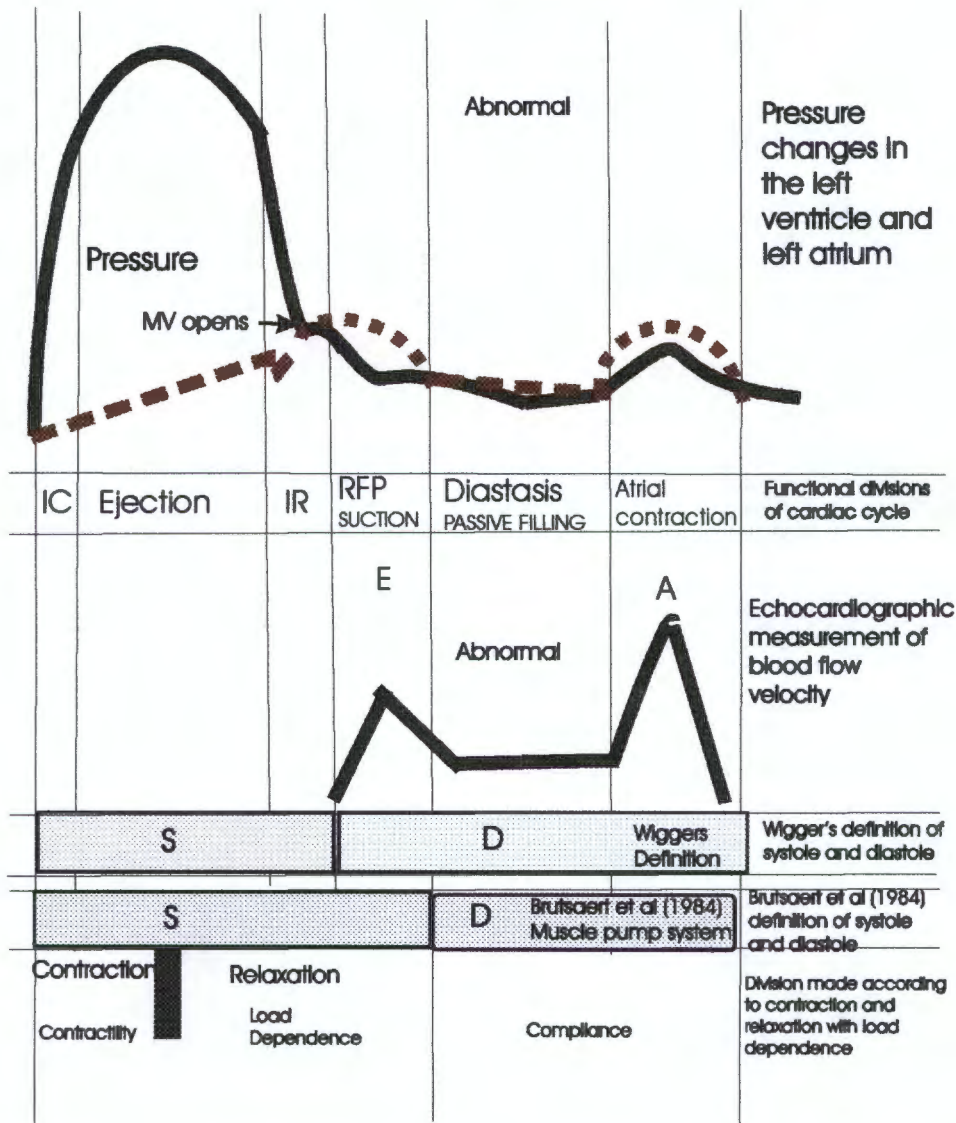


Figure 3.2 The abnormal diastolic filling pattern across the mitral valve determined by echocardiography in relation to the cardiac cycle. Comparison of ventricular (solid line) and atrial (dotted line) pressure changes during the cardiac cycle using the classic Wiggers definition of systole (S) and diastole (D) compared to the muscle pump system defined by Brutsaert et al (1984). The changes in the pressure gradient between the atrium and ventricle resulting from left ventricular relaxation abnormalities such as ischaemic heart disease, hypertrophic cardiomyopathy, hypertrophy secondary to hypertension and obesity and valvular heart disease, causes an alteration of the Doppler flow pattern with a reduction in the early transmitral flow velocity and an increase in the late transmitral flow velocity pattern causing the E/A ratio to be less than 1. IC = Isovolumetric contraction, IR = Isovolumetric relaxation, RFP = Rapid filling phase.

The third transmitral flow pattern includes a tall E wave with a small A wave. This pattern is a result of a high initial filling pressure in the left atrium causing rapid left ventricular filling. Filling stops relatively early in diastole with little contribution from late atrial systole; hence there is a reduction in the height of the A wave. This process occurs when the ventricle loses its compliance.

(C) Studies assessing diastolic function in healthy subjects:

Studies describing diastolic function in trained athletes using radionuclide angiography (Granger et al 1985), M-mode echocardiography (Colan et al 1985) and Doppler echocardiography (Finkelhor et al 1985) have shown that the various indexes of diastolic function were within normal limits at rest. The left ventricular diastolic function in athletes with physiologic cardiac hypertrophy show Doppler flow patterns that are similar to sedentary subjects (Granger et al 1985, Colan et al 1985, Nixon et al 1991, Levy et al 1993) (Figure 2.1), unlike left ventricular hypertrophy due to hypertrophic cardiomyopathy (Takenaka et al 1986), hypertension (Inouye et al 1984, Snider et al 1985), obesity (Chakko et al 1991) or valvular heart disease (Otto et al 1989) (Figure 3.2).

Doppler flow velocity waveform is altered by changes in left ventricular preload at rest as shown by studies (Choong et al 1987, Bhatia et al 1987, Courtois et al 1988, Stoddard et al 1989, Berk et al 1990) assessing the effect of preload reduction on transmitral flow pattern. Courtois et al (1988) showed a decline in early and late transmitral flow pattern when they assessed the effect of preload reduction on transmitral flow pattern after inferior vena cava occlusion. The three nitro-glycerine infusion studies at rest by Choong et al (1987), Bhatia et al (1987) and Stoddard et al (1989) that decreases preload and the preload reduction with lower negative pressure by Berk et al (1990), showed a reduced early transmitral flow pattern with an unchanged late transmitral flow pattern.

Table 3.1 Studies assessing diastolic function in healthy subjects at rest with altered loading conditions:

Study	Intervention protocol to reduce preload	Preload	Amplitude of the E wave	Amplitude of the A wave
Choong et al 1987	Nitro-glycerine infusion	reduced	reduced	unchanged
Bhatia et al 1987	Nitro-glycerine infusion	reduced	reduced	unchanged
Courtois et al 1988	Inferior vena cava occlusion	reduced	reduced	reduced
Stoddard et al 1989	Nitro-glycerine infusion	reduced	reduced	unchanged
Berk et al 1990	Lower body negative pressure	reduced	reduced	unchanged

The study of Berk et al (1990) reduced venous return by placing the lower body of the tested subjects in an airtight glass chamber connected to a vacuum system to produce negative body pressure thereby reducing preload in the tested subjects. The possible explanations for the difference in late transmitral flow pattern are that nitroglycerine infusion and lower body negative pressure produce a more gradual reduction in preload than inferior vena cava occlusion. Since increasing heart rate may negate any decrease in A wave peak velocity that might accompany a decrease in preload (Gillian et al 1987, Parker et al 1987), the second possible explanation is that the heart rate increased in the studies that had no change in late transmitral flow pattern (Choong et al 1987, Bhatia et al 1987, Stoddard et al 1989, Berk et al 1990) whereas the heart rate remained unchanged in the study of Courtois et al (1988).

(D) Studies assessing diastolic function during exercise

Relatively few studies have investigated diastolic filling characteristics during exercise (Iskandrian et al 1986; Bianco et al 1987; Schulman et al 1992). Bianco et al (1987) found that the peak-filling rate during exercise is related linearly to the heart rate in young subjects. The peak filling rate increases with an increase in workload during exercise. Exercise training further exacerbates this increase in peak filling rate and this process may therefore be more pronounced in athletes. At all matched heart rates to a specific work-load, the peak filling rate is higher after exercise training. Longitudinal data from Levy et al (1993) shows that physiological left ventricular hypertrophy due to exercise training, is associated with an improvement of absolute early diastolic filling rates at rest and at all heart rates during exercise in both the young and the elderly.

Mechanisms augmenting diastolic filling during exercise include an increase in “diastolic suction” of the left ventricle and an increase in left atrial pressure (Levy et al 1993).

I. Diastolic Suction:

Studies (Miyazaki et al 1990, Cheng et al 1992) assessing diastolic filling in dogs have shown that diastolic filling at sub-maximal exercise is augmented by a marked downward shift (refer to Figure 2.1 to see where this change occurs) of the early portion of the left ventricular pressure volume curve (-1 to -3 mmHg) and this results in an increased transmitral pressure gradient.

Diastolic suction seems to be related to sympathetic activation since isoproterenol in humans or dobutamine in dogs enhances this effect while B-blockers prevents the diastolic suction in dogs and eliminates the age related differences in diastolic filling during exercise in young and older men (Udelson et al 1990, Schulman et al 1992, Cheng et al 1992).

II. Increase in left atrial pressure:

An increase in transmitral pressure gradient due to an increase in mean pulmonary capillary wedge pressure that occurs at peak exercise in humans, may augment diastolic filling (Kitzman et al 1991) because it will increase left atrial filling pressure.

Transmitral flow pattern is dependent on “diastolic suction” and left atrial pressure, both of which are influenced by the cardiac loading conditions at rest, during and especially after exercise. The early transmitral flow pattern (E wave) occurs during early diastole is dependent on the “diastolic suction” mechanism. Since the sympathetic nervous system affects the “diastolic suction” (Udelson et al 1990, Schulman et al 1992, Cheng et al 1992) by its direct effect on the cardiac relaxing system (augmenting myocardial cAMP and increasing sarcoplasmic reticulum uptake of calcium) and since B-receptor desensitisation occurs after prolonged exercise (Friedman et al 1986, Eysmann et al 1996), changes in the E wave pattern after prolonged exercise may reflect the influence of this physiological process, independent of changes in left ventricular contractile function.

Except for one study (Goodman et al 2001), all the studies assessing cardiac function during exercise (Table 3.2) have reported that the preloading conditions were maintained with either an increased systolic blood pressure (Upton et al 1980, Palatini et al 1994, Goodman et al 2001) and normal (Goodman et al 2001) or an elevated ejection fraction (Upton et al 1980, Palatini et al 1994). These studies assessed cardiac function during exercise and showed no cardiac dysfunction when the cardiac loading conditions are maintained.

Table 3.2 Studies assessing cardiac function during exercise

Study	EF	EDV or DD	sBP or mean BP
Upton et al 1980	increased	increased	increased
Palatini et al 1994	increased	increased	increased
Goodman et al 2001	unchanged	decreased	increased

Most of the studies assessing cardiac function during exercise (Upton et al 1980, Palatini et al 1994, Goodman et al 2001) have shown that the loading conditions during the exercise period were maintained and none showed any evidence of systolic dysfunction during exercise.

(E) Studies assessing diastolic function after exercise

Table 3.3 Studies assessing diastolic function after prolonged exercise including the prevailing cardiac loading conditions

Study	Distance	Amplitude of the E wave	Amplitude of the A wave	E/A ratio	EDV or DD	sBP or mean BP
Douglas et al 1987	224 km Triathlon	unchanged	increased	decreased	decreased	unchanged
Vanoverschelde et al 1991	20 km run	decreased	increased	decreased	decreased	decreased
Manier et al 1991	42.2 km Marathon	unchanged	unchanged	unchanged	decreased	decreased
Lucia et al 1999	42 km marathon	decreased	increased	decreased	decreased	decreased
Whyte et al 2000 Triathlon	112 km	decreased	increased	decreased	unchanged	decreased
	224 km Marathon	decreased	increased	decreased	unchanged	decreased
Hassan et al 2003 Triathlon	224km Marathon	decreased	unchanged	decreased	unchanged	unchanged

All five studies that described “cardiac fatigue” after prolonged exercise (Douglas et al 1987, Vanoverschelde et al 1991, Manier et al 1991, Lucia et al 1999, Whyte et al 2000) measured the

diastolic function after the exercise period. Loading conditions were not maintained and controlled for in studies assessing diastolic function since the end diastolic volume (Douglas et al 1987, Vanoverschelde et al 1991, Manier et al 1991, Lucia et al 1999) and blood pressure (Vanoverschelde et al 1991, Manier et al 1991, Lucia et al 1999, Whyte et al 2000) decreased after exercise as these parameters reflect preload and afterload respectively. Studies (Brutsaert et al 1984, Rokey et al 1985, Ishida et al 1986, Choong et al 1987) have shown that the loading conditions of the heart affect the diastolic flow pattern across the mitral valve. If the studies that investigated post exercise “cardiac fatigue” did not maintain the cardiac loading conditions to prevent post exercise postural hypotension (Holtzhausen et al 1995) and post exercise collapse (Holtzhausen et al 1994, Noakes et al 2003), then the transmitral Doppler flow characteristics may merely represent the altered loading conditions associated with the recovery period after prolonged exercise.

Table 3.3 shows the studies including the left ventricular loading conditions at the time when the echocardiographic measurements were taken. When these studies are sub-categorized according to the specific pattern of prevailing loading conditions at the time that the echocardiographic measurements were taken, three studies showed decreased end diastolic volume and systolic blood pressure (Vanoverschelde et al 1991, Manier et al 1991, Lucia et al 1999), (Table 3.4). Except for the study of Manier et al (1991) that showed no change in early and late transmitral flow pattern and Douglas et al (1987) that showed no change in early transmitral flow pattern with an increase in late transmitral flow pattern, all (Vanoverschelde et al 1991, Lucia et al 1999, Whyte et al 2000) showed a decrease in the size of the E wave and an increase in the size of the A wave without reversal of the E/A ratio. This is compatible with changes in transmitral flow pattern caused by altered loading conditions (Rokey et al 1985,

Ushida et al 1986, Choong et al 1987, Bhatia et al 1987, Berk et al 1987, Courtois et al 1988, Stoddard et al 1989).

Table 3.4 Studies showing diastolic Doppler flow pattern with a decreased preload and afterload as shown by the changes in end diastolic volume and blood pressure respectively

Study	Distance	E	A	E/A	EDD or DD	sBP or mean BP
Vanoverschelde et al 1991	20 km run	decreased	increased	decreased	decreased	decreased
Manier et al 1991	42.2 km Marathon	unchanged	unchanged	unchanged	decreased	decreased
Lucia et al 1999	42 km Marathon	decreased	increased	decreased	decreased	decreased

Studies which reported a normal preload and a decrease afterload (Table 3.5) also showed changes in Doppler flow patterns, including a decrease in the size of the E and an increase in the size of the A wave with a reduction in the E/A ratio.

Table 3.5 Studies of diastolic Doppler flow pattern with a normal preload and a decreased afterload as shown by the changes in end diastolic volume and blood pressure respectively

Study	Distance	E	A	E/A	EDD or DD	sBP or mean BP
Whyte et al 2000	112 km	decreased	increased	decreased	unchanged	decreased
	224 km Marathon	decreased	increased	decreased	unchanged	decreased

Only one study (Table 3.6) showed no change in blood pressure despite the decreased end diastolic volume. The transmitral blood flow pattern showed no change in the size of the E wave. However the size of the A wave was increased.

Table 3.6 Study showing diastolic Doppler flow pattern with a decreased preload and normal afterload as shown by the changes in end diastolic volume and blood pressure respectively

Study	Distance	E	A	E/A	EDV or DD	sBP or mean BP
Douglas et al 1987	224 km Triathlon	unchanged	increased	decreased	decreased	unchanged

It is apparent that only the study by Manier et al (1991) showed no change in the sizes of the E and A waves despite the decrease in preload and afterload. In all others, changes in the normal Doppler flow pattern with the altered loading conditions after exercise may be related to the post exercise changes in loading conditions since studies showed that transmitral Doppler flow characteristics at rest are influenced by the loading conditions (Brutsaert et al 1984, Rokey et al 1985, Ishida et al 1986, Choong et al 1987, Bhatia et al 1987, Courtois et al 1988, Stoddard et al 1989).

Conclusion:

1. Left ventricular loading conditions change as a result of exercise.
2. Changes in loading conditions are associated with altered left ventricular function.
3. Hence it cannot be concluded with absolute certainty that “cardiac fatigue” is due to changes in left ventricular function independent of changes caused by altered loading conditions.

Therefore the aim of my research study was to repeat diastolic echocardiography measurements before and after exercise with the maintenance of preload and afterload. This was achieved by testing the athletes in a head down position before and after prolonged exercise. The outcome

of the research study (Table 3.7) showed that the E wave decreased while the A wave remained unchanged, similar to the three nitroglycerine infusion studies (Choong et al 1987, Bhatia et al 1987, Stoddard et al 1989). Despite equivalent loading conditions, the decrease in the size of the E wave may have been as a result of the altered sympathetic nervous system response after prolonged exercise since prolonged exercise induces Beta-receptor desensitisation (Friedman et al 1986, Eysmann et al 1996). It has been shown that a decrease in the sympathetic nervous system causes a decrease in the E wave pattern by affecting the “diastolic suction” mechanism (Udelson et al 1990, Schulman et al 1992, Cheng et al 1992). Accordingly in Chapter 5 of this thesis, I review this effect of altered sympathetic sensitivity of the cardiac B-receptors after prolonged exercise.

Table 3.7 Studies showing diastolic Doppler flow pattern with normal preload and normal afterload as shown by the changes in end diastolic volume and blood pressure respectively

Study	Distance	E	A	E/A	EDV or DD	sBP or mean BP
Hassan et al 2003	224km Triathlon	decreased	unchanged	decreased	unchanged	unchanged

(F) STUDIES ASSESSING SYSTOLIC DYSFUNCTION POST EXERCISE

Studies assessing systolic function after prolonged exercise (Niemelä et al 1984, Niemelä et al 1987, Seals et al 1988, Douglas et al 1990, Vanoverschelde et al 1991, Ketelhut et al 1992, Whyte et al 2000) have shown a reduction in ejection fraction or fractional shortening or both. These studies showed either a reduced preload together with a reduced afterload after exercise (Niemela et al 1984, Niemela 1987, Seals 1988, Vanoverschelde 1991, Whyte et al 2000); a normal preload with a reduced afterload (Ketelhut 1992) after exercise; or a reduced preload with normal afterload after exercise (Douglas et al 1987). Douglas et al (1990) reported an

unchanged preload after exercise, however blood pressure was not listed in their data. No previous study excluded the possibility that changes in the loading conditions of the heart may affect left ventricular systolic performance after prolonged exercise.

Table 3.8 Studies assessing cardiac function in the recovery period after exercise

STUDY	DISTANCE/ DURATION	EDV or DD	EF or FS	s-BP
Ketelhut et al 1992	60 min cycling	unchanged	decreased	decreased
Vanoverschelde et al 1991	20km run	decreased	decreased	decreased mean BP
Perrault et al 1986	42km	unchanged	unchanged	decreased
Lucia et al 1999	42km	decreased	Increased	decreased
Manier et al 1991	42.2km	decreased	unchange	decreased
Douglas et al 1987	224 km Triathlon	decreased	decreased	unchanged
Douglas et al 1990	224 Triathlon	unchanged	decreased	Not listed
Whyte et al 2000	224 km Triathlon	decreased	decreased	decreased
	112 km Triathlon	decreased	unchanged	decreased
Niemalä et al 1984	227km	decreased	decreased	decreased
Niemalä et al 1987	146 – 227km run	decreased	decreased	decreased
Seals et al 1988	Treadmill run to fatigue	decreased	decreased	decreased
Hassan et al 2003	224 km Triathlon	unchanged	unchanged	unchanged

Key: EDV = end diastolic volume, DD = diastolic dimension, EF = ejection fraction, FS = fractional shortening,

BP = blood pressure, s-BP = systolic blood pressure. Grouped according to increasing distance of exercise.

Except for one study (Douglas et al 1990) that showed no change in preload and that did not report the arterial blood pressures before and after prolonged, all the studies assessing cardiac dysfunction echocardiographically after prolonged exercise did not control for changes in the loading conditions of the heart before and after exercise (Table 3.8). These studies can be sub-categorized according to the specific combination of the cardiac loading conditions that were reported.

Table 3.9 Studies of cardiac function after prolonged exercise showing systolic dysfunction after exercise: associated loading conditions

Study	EF or FS	EDV	s-BP or mean BP
Niemela et al 1984	decreased	decreased	decreased
Douglas et al 1987	decreased	decreased	unchanged
Niemela et al 1987	decreased	decreased	decreased
Seals et al 1988	decreased	decreased	decreased
Douglas et al 1990	decreased	unchanged	Not listed
Vanoverschelde et al 1991	decreased	decreased	decreased
Ketelhut et al 1992	decreased	unchanged	decreased
Whyte et al 2000	decreased	decreased	decreased

Studies of cardiac function after prolonged exercise showing systolic dysfunction in which EDV and BP decreased after exercise:

Table 3.10 shows the studies that reported reduced end diastolic volume and reduced systolic blood pressure during cardiac assessment after prolonged exercise. Five studies showed ejection fraction or fractional shortening was reduced after exercise, suggestive of “cardiac fatigue”. Despite the decrease in end diastolic volume and systolic blood pressure, Manier et al

(1991) showed no change in ejection fraction, Lucia et al (1999) showed an increase in ejection fraction and Whyte et al (2000) showed no change in ejection fraction after a half distance (112km) Ironman Triathlon. The latter authors did however show a decrease in ejection fraction after the full 224 km Triathlon. Of note is the discrepancy in timing of cardiac parameter measurements in the design protocol of these studies. The significance of this is that those studies also showed that the systolic and diastolic measurements normalized when the measurements were repeated 1 to 2 days after exercise by which time the left ventricular loading conditions had normalized (Douglas et al 1987, Whyte et al 2000). The lack of standardization of timing of the echocardiographic measurements after the exercise and the effects of peripheral venous pooling that may occur after exercise (Holthausen et al 1995) may lead to erroneous echocardiographic conclusions on cardiac function since a reduction in preload mimics echocardiographic changes indicative of cardiac dysfunction (Choong et al 1987, Bhatia et al 1987, Courtois et al 1988, Stoddard et al 1989, Berk et al 1990).

Table 3.10 Studies of cardiac function after prolonged exercise in which EDV and BP decreased after exercise

Study	Distance	EDV or DD	EF of FS	s-BP
Niemelä et al 1984	227 km run	decreased	decreased	decreased
Niemelä et al 1987	146-227 km run	decreased	decreased	decreased
Seal et al 1988	Treadmill run to fatigue	decreased	decreased	decreased
Vanoverschelde et al 1991	20 km run	decreased	decreased	decreased mean BP
Manier et al 1991	42.2 km run	decreased	unchanged	decreased
Lucia et al 1999	42 km run	decreased	increased	decreased
Whyte et al 2000	112 km half	decreased	unchanged	decreased
	vs. 224km Triathlon	decreased	decreased	decreased

Studies in which EDV was normal after exercise with a decrease in s-BP:

Except for the study of Douglas et al (1990) that did not report the systolic blood pressures, the other two studies reported normal end diastolic volumes with reduced systolic blood pressures after prolonged exercise (Table 3.11). Perrault et al (1986) showed no change in ejection fraction while Ketelhut et al (1992) and Douglas et al (1990) showed reduced ejection fraction after exercise.

Table 3.11 Studies of cardiac function after prolonged exercise in which EDV was normal after exercise with a decrease in s-BP

Study	Distance	EDV or DD	EF of FS	s-BP
Perrault et al 1986	42 km run	unchanged	unchanged	decreased
Ketelhut et al 1992	60 min cycle	unchanged	decreased	decreased
Douglas et al 1990	224 Triathlon	unchanged	decreased	Not listed

Studies in which EDV decreased post exercise with normal s-BP:

The only study (Douglas et al 1987) that maintained systolic blood pressure with a reduced end diastolic volume showed a decrease in ejection fraction after exercise (Table 3.12).

Table 3.12 Study of cardiac function after prolonged exercise in which EDV decreased after exercise with normal s-BP

Study	Distance	EDV or DD	EF of FS	s-BP
Douglas et al 1987	224 km run	decreased	decreased	unchanged

Summary of Tables 3.9-3.12:

It is apparent that all of the studies that assessed systolic function after prolonged exercise did not control for equal end diastolic volumes and systolic blood pressures before and after

exercise. Hence, it cannot be concluded that the altered cardiac function after prolonged exercise was a result of “cardiac fatigue” rather than due to the altered loading conditions induced by prolonged exercise. Subsequently, we repeated the cardiac echocardiographic measurements controlling for these loading conditions by testing the athletes in the head down (Trendelenberg) position (Chapter4). The design protocol ensured that the end diastolic volume and systolic blood pressure were maintained after the race. We showed no change in left ventricular ejection fraction, thereby showing that left ventricular function was normal after prolonged exercise when the appropriate control was in place before and after exercise to ensure optimum left ventricular loading conditions.

Study in which EDV and s-BP was normal post exercise:

Table 3.13 Study of cardiac function after prolonged exercise in which EDV and s-BP was normal after exercise

Study	Distance	EDV or DD	EF or FS	s-BP
Hassan et al 2003	224 km Triathlon	unchanged	unchanged	unchanged

Discussion:

Training does not alter left ventricular diastolic filling properties in athletes with physiological hypertrophy unlike hypertrophy secondary to hypertrophic cardiomyopathy (Takenaka et al 1986), hypertension (Inouye et al 1984, Snider et al 1985), obesity (Chakko et al 1991) and valvular heart disease (Otto et al 1989). The Doppler echocardiographic findings have been well described in these pathological conditions. The altered changes includes a reduced E wave with an elevated A wave with the E/A ratio less than 1. This results from abnormal relaxation of the left ventricle. Except for one study (Manier et al 1991), most studies in which cardiac

function was measured after prolonged exercise reported evidence for cardiac diastolic dysfunction (Douglas et al 1987, Vanoverschelde et al 1991, Lucia et al 1999, Whyte et al 2000) with changes in the E and A wave pattern. The E wave was either decreased with an increased A wave (Vanoverschelde et al 1991, Lucia et al 1999, Whyte et al 2000) or unchanged with an increased A wave (Douglas et al 1987). However, in all of these studies (Douglas et al 1987, Vanoverschelde et al 1991, Manier et al 1991, Lucia et al 1999, Whyte et al 2000) the ratio of the E/A remained greater than 1, unlike the pattern seen in hypertrophic cardiomyopathy, hypertension or in hypertrophy secondary to obesity and valvular heart disease. Thus, the mechanism causing these changes is different from those that occur in disease.

The cardiac loading conditions affect diastolic filling pattern and a reduction or increase in preload may induce a diastolic filling pattern that may either mimic or mask diastolic dysfunction (Stoddard et al 1989). All the studies assessing cardiac function before exercise showed normal baseline Doppler flow patterns under normal loading conditions at rest, thereby excluding any possible diastolic abnormalities at rest. The absence of false negative results of diastolic dysfunction is further supported by the absence of preload elevation as shown by the changes in the end diastolic volume in all of the studies assessing cardiac dysfunction after exercise. Since these athletes are involved in regular exercise, this also shows that if “cardiac fatigue” exists then it is transitory since there is no evidence for cardiac dysfunction prior to exercise during the preparatory training period, as determined by these non-invasive techniques.

An acute reduction in left atrial loading conditions significantly alters the diastolic transmitral pressure relation and thus profoundly affects the Doppler flow velocity profile (Courtois et al 1988). Abrupt preload reduction as shown by inferior vena cava obstruction (Courtois et al

1988) causes a decline in the size of both the E and A waves while gradual preload reduction as shown by nitro-glycerine infusion (Choong et al 1987, Bhatia et al 1987, Stoddard et al 1989) and lower body negative pressure (Berk et al 1990) produces a decline in the size of the E wave with an unchanged size of the A wave. Prolonged exercise may be associated with preload reduction (Niemelä et al 1984, Douglas et al 1987, Niemelä et al 1987, Seals et al 1988, Vanoverschelde et al 1991, Manier et al 1991, Lucia et al 1999, Whyte et al 2000) that may manifest as post exercise postural hypotension (Holtzhausen et al 1995) or an abrupt reduction in venous return manifesting as post exercise collapse (Holtzhausen 1994, Noakes 2003). The studies that assessed cardiac diastolic function after exercise showed abnormal transmitral diastolic flow patterns associated with altered loading conditions. The conclusion may be that the altered loading conditions may cause the abnormal transmitral flow pattern and may not necessarily indicate cardiac diastolic dysfunction since altered loading conditions have been shown to cause the same abnormal diastolic flow pattern in the absence of cardiac disease (Choong et al 1987, Bhatia et al 1987, Courtois et al 1988, Stoddard et al 1989, Berk et al 1990).

Further desensitisation to the sympathetic stimulation after exercise (Friedman et al 1986, Eysmann et al 1996) influence left ventricular function measurements since the reduced sympathetic stimulation influences the E wave pattern (Udelson et al 1990, Schulman et al 1992, Cheng et al 1992) and the A wave pattern (Gillam et al 1987, Harrison et al 1990). The sympathetic changes affect these parameters by its direct effects on the cardiac relaxing system. Sympathetic stimulation increases myocardial cyclic AMP levels and increases sarcoplasmic reticulum uptake of calcium and since desensitisation occurs after prolonged exercise, these processes are affected.

Conclusion:

Preload and afterload affects the inotropic (contractility) states of the ventricle (Katz 1992). Since prolonged exercise produces significant changes in the peripheral vascular function including a persistent reduction in total peripheral vascular resistance that influences preload and afterload, the cardiac response measured immediately after exercise may reflect the persistence of these circulatory changes rather than indicate acute cardiac dysfunction. These altered loading conditions and reduced cardiac inotropic and chronotropic changes may then cause echocardiographically measured changes that mimic cardiac dysfunction.

To differentiate between cardiac dysfunction and a normal cardiac physiological response to the reduced preload and/or afterload requires the maintenance of the loading conditions of the heart before and after exercise which has not controlled for in previous studies assessing cardiac dysfunction after prolonged exercise (Tables 3.10-3.12). However, even if the loading conditions are controlled for after exercise, an additional influence of cardiac beta-receptor desensitisation cannot be excluded. Therefore the aim of my research study was to test the hypothesis that cardiac function and the assessment thereof, using echocardiography may be influenced by the loading conditions after prolonged exercise. The maintenance of the loading conditions after exercise was achieved by testing athletes both before and after completing a 224km Ironman Triathlon competition in the head down position (Trendellenberg). This study is reported in Chapter 4.

CHAPTER FOUR

RESEARCH STUDY:

**CHANGES IN VENTRICULAR LOADING
CONDITIONS MAY EXPLAIN SOME CHANGES
IN LEFT VENTRICULAR FUNCTION AFTER
ULTRA-ENDURANCE EXERCISE**

CHAPTER 4

Introduction

A study to determine whether altered loading conditions of the heart after prolonged exercise influences the diastolic and systolic function as measured by echocardiography.

Altered loading conditions of the heart affect diastolic function that may mimic the diastolic dysfunction present in pathological conditions. Since prolonged exercise may be associated with altered loading conditions (Niemelä et al 1984, Douglas et al 1987, Niemelä et al 1987, Seals et al 1988, Vanoverschelde et al 1991, Manier et al 1991, Lucia et al 1999, Whyte et al 2000) that may manifest as post exercise postural hypotension (Holtzhausen et al 1995) or an abrupt reduction in venous return manifesting as post exercise collapse (Holtzhausen 1994, Noakes 2003), the studies that reported “cardiac fatigue” in athletes, may simply have identified the secondary effects on left ventricular function of an altered peripheral vascular function caused by prolonged exercise.

The aim of this research study was to identify any possible effects of these peripheral vascular changes on left ventricular function after prolonged exercise. Changes in peripheral vascular resistance could cause a reduced central blood volume and hence a reduced right atrial filling pressure after exercise. To control for pre- and after-load, all the echocardiographic tests were performed in the head down (Trendelenberg) position with the legs and pelvis elevated above the level of the heart. We assumed that this would ensure equivalent left ventricular loading conditions before and after prolonged exercise.

The remainder of this chapter is presented in the form of the scientific paper which has been submitted to the journal of Medicine and Science in Sports and Exercise for consideration for publication.

ABSTRACT

Purpose: Previous studies examining the effects of prolonged exercise on left ventricular function have not controlled for possible changes in loading conditions before and after exercise. The purpose of this study was to investigate the effects of a 224-km Ironman Triathlon on left ventricular function measured with echocardiography when the loading conditions of the heart were standardized before and after exercise. **Method:** Using M- mode and Doppler analysis, echocardiographic parameters were obtained from 44 triathletes, 2 – 5 days before and immediately after they completed a 224km Ironman Triathlon in Cape Town, South Africa. In addition, venous blood samples were collected before and after the race for the measurement of serum total creatine kinase (total CK) and for CK-MB isoenzyme (CK – MB) activity. **Results:** Heart rate was significantly higher on completion of the race (78 ± 13 vs. 58 ± 11 b.min⁻¹, $p < 0.01$; after vs. before the race). The systolic blood pressure was lower although insignificantly (116 ± 18 vs. 121 ± 13 mmHg; $p=0.09$) whereas the diastolic blood pressure was higher (63 ± 12 vs. 58 ± 9 mmHg; $p=0.03$). The end diastolic volume was insignificantly higher after the race (149 ± 33 vs. 145 ± 34 ml; $p=0.50$) indicating that this determinant of left ventricular preload was the same before and after exercise. End systolic volume (64 ± 21 vs. 57 ± 18 ml; $p=0.08$), stroke volume (85 ± 26 vs. 88 ± 24 ml; $p=0.60$) and the ejection fraction ($61\% \pm 8$ vs. $57 \pm 11\%$; $p=0.06$) did not change as a result of the race. The peak early transmitral filling (E) was significantly reduced after the race (0.97 ± 0.17 vs. 1.09 ± 0.15 m/s; $p < 0.0001$) whereas the late transmitral filling velocity (A) was unchanged (0.62 ± 0.12 vs. 0.65 ± 0.12 m/s; $p=0.33$). As a consequence, the E/A ratio declined significantly after the race (1.59 ± 0.31 vs. 1.72 ± 0.27 ; $p=0.04$). The E wave was higher than A wave both before and after the race. The total CK and CK-MB isoenzyme activity increased significantly during the race (65 ± 26 vs. 896 ± 873 mmol/l, $p=0.00$ and 2.6 ± 2.7 vs. 42.6 ± 41.9 ng/l, $p=0.00$ respectively). However, the CK-MB/Total CK

activity ratio did not change (4.5 ± 3.5 vs. $5.3 \pm 3.7\%$, $P= 0.09$). **Conclusion:** When specific loading conditions were chosen to maximize venous return to the heart both before and after exercise, there was no evidence for left ventricular systolic dysfunction in competitors who completed a 224km Ironman Triathlon in approximately 722.8 ± 100.3 min. The decreased peak E showed changes in diastolic function without any changes in A. Since the reported changes in left ventricular systolic and diastolic function after prolonged exercise mirror those produced with nitro-glycerine infusion that reduces left ventricular preload, we suggest that some of these changes previously reported may result from an altered sympathetic autonomic function with effects on the heart both directly and indirectly, as a consequence of changes in the peripheral circulation.

INTRODUCTION

In 1978 two runners developed acute pulmonary edema during the 90-km Comrades Marathon foot race in South Africa (17). The absence of cardiac disease, identifiable by either echocardiography or coronary and left ventricular angiography in either athlete and the rapidity with which these abnormalities regressed despite negligible therapy, suggested transient pulmonary edema of cardiac origin. No mechanism for this condition could be explained.

Subsequently, a number of echocardiographic studies have shown a variety of changes in left ventricular function after prolonged exercise (5, 6, 9, 12, 14, 15, 18, 19, 21, 22, 25, 27-29). This has given rise to the concept that prolonged exercise may result in a reversible "cardiac fatigue".

However it is now appreciated that prolonged exercise results in persistent reduction in total peripheral vascular resistance that can be sufficient to produce postural hypotension (11) and post-exercise collapse (10), perhaps as the result of a substantial reduction in right atrial pressure (1, 20). Since peripheral vascular resistance will influence left ventricular loading conditions, it follows that the evaluation of left ventricular function before exercise must anticipate any possible changes in order to ensure equivalent loading conditions before and after exercise (24).

If subjects are tested for cardiac dysfunction in the supine position before and after exercise, there may be a redistribution of the central blood volume that is sufficient to alter the right atrial pressure and hence the loading conditions of the heart after exercise. The study of Choong et al (1987) showed that changes in the peripheral circulation sufficient to affect the loading conditions of the heart alter measures of left ventricular function. Nitro-glycerine infusion, reduces the total peripheral vascular resistance in humans at rest in the supine position,

produced transmitral diastolic flow abnormalities similar to those measured in athletes with “cardiac fatigue” after prolonged exercise. In particular Choong et al (1987) showed that nitro-glycerine infusion reduced the early transmitral flow velocity (E) measured with echocardiography. However nitro-glycerine infusion did not alter the late transmitral flow velocity (A) measured echocardiographically. These studies may simply have identified the secondary effects on left ventricular function as a result of changes on peripheral vascular resistance after prolonged exercise.

The aim of this study was to identify any possible effects of peripheral vascular changes on left ventricular function after prolonged exercise. We hypothesised that the changes in peripheral vascular function could cause a reduction in central blood volume and hence reduce right atrial filling pressure after exercise. Echocardiographic tests were performed in the head down (Trendelenberg) position with the legs and pelvis elevated above the level of the heart. We assumed that this leg elevation before and after exercise would ensure equivalent left ventricular loading conditions before and after prolonged exercise.

Materials and Methods:

The 44 athletes in the study completed the Cape Town Ironman Triathlon competition comprising a 3.8km swim, 180km cycle and 42.2km run. All subjects signed an informed consent form prior to participation in this study after volunteering for the research study. Approval for this study was obtained from the Research and Ethics Committee of the Faculty of Health Sciences, University of Cape Town. Data were collected in the 2-5 days prior to the race and again immediately after the completion of the race. Data collection during the testing session comprised measurements of body mass (kg), systolic and diastolic blood pressures, echocardiography evaluation and venous blood collection for electrolyte and cardiac enzymology concentrations. A high-quality echocardiogram was obtained from each subject before the race and shortly after the athletes had completed the race. The interval between the race completion and recording of the echocardiographic data varied but was less than 30 minutes in all subjects.

Echocardiographic measurement:

All recordings were performed with the athletes in the left lateral decubitus position in the head-down (Trendelenberg) position before and after competition of the race. All subjects underwent 2 echocardiographic studies: a baseline study 2 – 5 days before the race and a second study, was performed immediately after completion of the race. Blood pressure was measured simultaneously with echocardiographic monitoring. A single experienced echocardiographer performed the measurements to prevent inter-observer variability (4). Two – dimensional echocardiograms were recorded from the apical four – chamber view using a 2.5 MHz probe from an Acuson Cypress Ultrasound machine (Siemens Medical Division, Plymouth Meeting, PA 19462 USA). Imaging location and gain settings were adjusted to yield optimal definition. M-mode images at the mitral valve tips were used to measure inter-ventricular septal wall thickness and left ventricular posterior free wall thickness during diastole and systole. The

apical four – chamber view was used for global volume and ejection fraction measurements using the modified Simpson’s rule (24). The calculation equations and measurements using the Modified Simpson method are as follows:

$$EDV = (LVLd/9) \times \{4 \times LVSAMVd + 2 \times LVSAPMd + (LVSAMVd \times LVSAPMd)^{1/2}\},$$

$$ESV = (LVLs/9) \times \{4 \times LVSAMVs + 2 \times LVSAPMs + (LVSAMVs \times LVSAPMs)^{1/2}\},$$

$$SV = EDV - ESV \text{ and Ejection fraction} = \text{Stroke volume/Diastolic volume multiply by } 100 (\%)$$

(24).

Doppler Recordings:

Two – dimensional guided continuous wave Doppler recordings of the left ventricle inflow tract at the level of the mitral valve annulus were obtained using an Acuson Cypress ultrasound machine (Siemens Medical Division, Plymouth Meeting, PA 19462 USA) equipped with a 2.5 MHz imaging and Doppler transducer. Recordings were obtained from the four – chamber view. Data from three to five cardiac cycles were combined to yield peak velocities of left ventricular inflow in early (E) and late diastole (A) and the ratio of E to A flow velocities.

Blood Measurements:

Venous blood from an ante – cubital vein was obtained for biochemical analysis before and after the race. The biochemical parameters measured included serum sodium and potassium concentrations, total creatine kinase activity including the proportion of the creatine kinase MB isoenzyme (CKMB). Four and a half millilitres of venous blood specimens were drawn up by venipuncture into lithium heparin vacutainer tubes. Blood was sampled at race registration and within 10 minutes of finishing the race for the analysis of pre-and post-race serum electrolyte, CK and CK-MB concentrations. The blood samples were centrifuged at 3000X g for 10 minutes at 4°C and stored at 20°C until further analysis. Plasma sodium and potassium concentrations were analysed using an EasyLyte PLUS Na/K/Cl analyser (Media Corporation, Bedford, MA). Serum CK activity and CK-MB activity were determined using an enzymatic

spectrophotometric assay with a commercial kit (Roche, Basel, Switzerland) and the Abbott IMX batch analyser with a commercial kit respectively.

Statistical analysis

Pre-race and post-race comparisons for cardiovascular parameters were made using an Analysis of Variance for Repeated Measures, adjusting for age and race time. Significance was taken at $P < 0.05$. All data are expressed as mean \pm standard deviation. Data analysis was completed using statistical computer software (Statistica).

RESULTS

The 44 athletes successfully completed the Ironman competition. Mean (\pm SD) race duration was 722.8 ± 100.3 minutes (swim= 67.1 ± 12.2 min, cycle= 376.2 ± 49.1 min, run= 267.5 ± 45.9 min).

Body mass fell significantly during the race (78.7 ± 9.1 vs. 75.3 ± 8.8 kg, $p < 0.0001$, Table 4.1).

Biochemical markers:

Serum sodium and potassium concentrations increased significantly during the race ($p=0.001$ and $p=0.000001$ respectively, table 4.1). Serum CK and CK-MB activity was significantly increased after race completion ($p=0.00001$ and $p=0.00000001$ respectively); however the CK-MB/Total CK ratio did not change significantly ($p= 0.09$, Table 4.1).

Cardiac measurements:

The heart rate measured immediately after the race was significantly higher than the pre-race value ($p < 0.01$), systolic blood pressure was unchanged ($p=0.09$) while diastolic blood pressure was significantly increased ($p=0.03$, Table 4.1).

Echocardiography data measured at rest:

The left ventricular septal and posterior free wall thicknesses measured at rest was $14.0\text{mm} \pm 2.4$ and $14.3\text{mm} \pm 3.0$ respectively (Table 4.2). These values are greater than those measured in sedentary subjects reported in other studies (Mean ventricular septal thickness = 9.1mm and posterior free wall thickness = 9.0mm of Non-athlete controls, 16). The athletes studied showed symmetric ventricular septal and posterior free wall thicknesses with normal septal/free wall ratios of $1.01 (<1.3)$ in keeping with previous studies (16). Other values at rest are reported in Table 4.2.

TABLE 4.2 Resting echocardiographic measurements of left ventricular dimensions in Ironman Triathletes before a 224 km Ironman triathlon

Echocardiography data at rest:	
Septum diameter (mm)	14.0 ± 2.4
LV posterior wall diameter (mm)	14.3 ± 3.0
Cardiac output (l/min)	4.88 ± 1.55
EDV (ml)	145±34
ESV (ml)	57±18
SV (ml)	88±24
EF (%)	61±8
E (m/s)	1.09±0.15
A (m/s)	0.65±0.12
E/A	1.72±0.27

Values are expressed as mean ± SD, LV = Left ventricle, EDV = End diastolic volume, ESV = End systolic volume, SV = Stroke volume, EF = Ejection fraction, E = Early transmitral flow velocity, A = Late transmitral flow velocity.

Echocardiography data after exercise:

There were no significant changes in EDV, ESV or SV after the race although the fall in ejection fraction (EF) approached significance (p=0.06, Table 4.3). The peak early (E) transmitral filling velocity decreased significantly (p=0.00002), while peak late (A) transmitral filling velocity remained unchanged (p=0.33). This resulted in a lower ratio of peak early to peak late transmitral filling (E/A) velocities after the race (p=0.04).

TABLE 4.3 Echocardiographic measurements of left ventricular function before and after a 224 km Ironman Triathlon

	Before race	Post race	P Value
<i>Systolic Function</i>			
EDV (ml)	145±34	149±33	0.50
ESV (ml)	57±18	64±21	0.08
SV (ml)	88±24	85±26	0.60
EF (%)	61±8	57±11	0.06
<i>Diastolic Function</i>			
E (m/s)	1.09±0.15	0.97±0.17*	0.00002
A (m/s)	0.65±0.12	0.62±0.12	0.33
E/A	1.72±0.27	1.59±0.31*	0.04

Values are expressed as mean ± SD, N = 44, * Significant different from pre-race (p < 0.05).

EDV = End diastolic volume, ESV = End systolic volume, SV = Stroke volume, EF = Ejection fraction, E = Early transmitral flow velocity, A = Late transmitral flow velocity.

DISCUSSION:

The aim of this study was to evaluate the possibility that changes in the peripheral vascular function might explain some of the alterations in left ventricular function reported after prolonged endurance exercise. The first important finding of this study was that the end diastolic volume (EDV) was the same before and after exercise in subjects studied in the head-down (Trendelenberg) position (Table 4.3).

Previous studies examined the effects of prolonged exercise on left ventricular function did not control for EDV which resulted in most of these studies (6, 14, 15, 18, 19, 25, 28, 29) showing a lower EDV after the exercise period. In only 3 previous studies (5, 12, 22) were the pre- and post-exercise EDV the same. One contributing factor for these discrepant findings might have been the timing of cardiac measurements during the recovery period since none of these studies evaluated subjects in the head-down position as we did. It is probable that the longer the recovery period, the less likely that the postulated peripheral vascular changes would still be present.

However the relevant point is that control of the EDV before and after exercise means that the left ventricular loading conditions in this study were likely to be similar before and after exercise than in those studies in which the EDV was reduced after exercise. Since preload reduction (3) causes abnormal changes in cardiac function similar to “cardiac fatigue” and since it is maintained in this study, any measured change in left ventricular function after exercise is less likely to be the result of a change in loading conditions before and after exercise. In this study maintenance of preload allows adequate ventricular filling with activation of the Frank Starling mechanism and this may assist in the maintenance of the blood pressure after exercise.

Our second and related finding was that systolic blood pressure was also the same before and after exercise. In only one other study (6) that measured left ventricular function after exercise has the blood pressure been the same both before and after exercise. Studies showed a reduction in systolic blood pressure after exercise (12, 14, 15, 18, 19, 22, 25, 28, 29). The left ventricular loading conditions in these studies were not the same before and after exercise since the afterload was likely lower after exercise since systolic blood pressure reflects changes in afterload.

Our third finding was the change in transmitral flow pattern after exercise that differed from previous studies (6, 14, 15, 28, 29). This study showed that early transmitral flow velocity decreased after exercise (Table 4.3) as also found in the previous studies (14, 28, 29). However, the late transmitral flow pattern was unchanged unlike the previous studies (6, 14, 28, 29) that reported a decrease in early transmitral flow velocity with an increase in the late transmitral flow velocity. Our findings were the same as when nitro-glycerine was infused. Subjects at rest showed a decrease in the early transmitral flow pattern without any change in the late transmitral flow pattern. This is similar to the abnormal Doppler flow pattern seen in studies that showed diastolic flow abnormalities after long endurance exercise (14, 28, 29).

Brutsaert et al (1984) postulated that elevations in either pre-or afterload delay the onset of relaxation. The maintenance of end diastolic volume and systolic blood pressure after exercise by leg elevation in our study ensured adequate filling of the heart early in the diastolic period. The A wave remained unchanged after exercise due to adequate left ventricular filling. This contrasts with the abnormal filling patterns found in the pathological conditions such as left ventricular hypertrophy, myocardial ischaemia or hypertrophic cardiomyopathy where the A wave is increased (16).

The only variable for which we could not control adequately in this study, was altered sympathetic B-stimulation with impaired response to sympathetic vasoconstriction after exercise. Long-term exposure of adrenergic receptors to increased concentrations of catecholamines result in a decreased chronotropic response (7, 8) due to the altered B-adrenergic responsiveness to prolonged exercise (7). The same phenomenon is present in the pathogenesis of heart failure where there is an altered adrenergic responsiveness to the elevated catecholamines. Despite the altered cardiac responsiveness to catecholamines after prolonged exercise, in our study the ejection fraction was maintained and the cardiac output was elevated after the race.

Our fourth incidental finding was that none of our subjects developed postural hypotension after exercise. The systolic blood pressure was the same before and after exercise (Table 4.1) which contrasts with the findings after less demanding ultra-endurance exercise in which subjects were studied in the horizontal but not the Trendelenberg position (10, 11). This would seem to indicate that the degree of atrial stretch may influence the regulation of the post-exercise blood pressure, as it seems to when atrial pressure falls to very low levels (1).

In summary, this study shows that some of the changes in left ventricular function measured after prolonged exercise may be due to peripheral circulatory changes. The evidence for this is the following:

The technique of leg elevation used in this study equalised EDV and systolic blood pressure before and after exercise thereby preventing the development of any degree of post-exercise postural hypotension. As a result, the loading conditions on the heart were likely the same before and after exercise. Despite these similar loading conditions, some changes in left ventricular function were evident indicating that prolonged exercise does have some direct

effects on left ventricular function. Specifically, there was a decrease in early transmitral flow velocity during diastole without any change in the late transmitral velocity flow pattern. This change mimics the effects of an altered loading condition on transmitral flow pattern at rest as shown in previous studies (3).

Finally it is relevant to note that previous studies (9, 21, 27) examining cardiac function during exercise failed to demonstrate the development of cardiac systolic dysfunction during exercise. Notably systolic BP increased significantly during the exercise period in all of these studies and the ejection fraction was either maintained (9) or increased (21, 27). If “cardiac fatigue” is a real phenomenon, it should also be evident during exercise. These findings suggest that at least some features of cardiac fatigue, such as the late the transmitral flow velocity and ejection fraction, are the result of peripheral vascular changes, consequently to stopping exercise.

Changes in left ventricular function after prolonged exercise may reflect, in part, changes in the left ventricular loading at the end of prolonged exercise. The lack of standardization of study design to maintain preload and afterload in the recovery period in previous studies (5,6,12,13,14,15,18,19,21,22,25,28,29) do not exclude the possibility that the “cardiac fatigue” measured in those studies was the result of changes in peripheral vascular function induced by prolonged exercise. Paradoxically it is expected that cardiac fatigue should manifest during exercise when the expected cardiac demands are higher due to the higher workload as a result of the higher rate-pressure product and peripheral demands and not during the recovery period. But such “cardiac fatigue” has not been shown during exercise (9, 21,27).

A study to confirm our hypothesis would be to evaluate LV function both before and after exercise with and without leg elevation. The echocardiographic measurements will be taken

before and after exercise with the control group being the athletes measured in the horizontal position. The findings of this study suggest that such a study is necessary to confirm or refute our new hypothesis.

TABLE 4.1 Body mass, cardiovascular measures, serum electrolyte concentrations and creatine kinase activities before and after a 224 km Ironman Triathlon

	Pre-race	Post-race	P Value	N
Mass (kg)	78.7 ± 9.1	75.3 ± 8.8	0.0001	41
Heart rate (beats/min)	58 ± 11	78±13*	0.0001	44
Systolic BP (mmHg)	121 ± 13	116± 18	0.09	44
Diastolic BP (mmHg)	58 ± 9	63± 12*	0.03	44
Sodium (mmol/l)	140.2±1.7	141.9±2.9*	0.001	41
Potassium (mmol/l)	4.2±0.40	4.8±0.60*	0.000001	41
Total CK (mmol/l)	65±26	896±873*	0.000001	28
CK-MB (ng/l)	2.6±2.7	42.6±41.9*	0.0000001	28
CK-MB/Total CK (%)	4.5±3.5	5.3±3.7	0.09	28

Values are expressed as mean ± SD, N = Sample number

BP = Blood pressure

CK = Creatine kinase activity

CK-MB = Creatine kinase MB isoenzyme activity

* Significant different from pre-race (p < 0.05)

TABLE 4.2 Resting echocardiographic measurements of left ventricular dimensions in Ironman Triathletes before a 224 km Ironman triathlon

Echocardiography data at rest:	
Septum diameter (mm)	14.0 ± 2.4
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ESV (ml)	57±18
SV (ml)	88±24
EF (%)	61±8
E (m/s)	1.09±0.15
A (m/s)	0.65±0.12
E/A	1.72±0.27

Values are expressed as mean ± SD

LV = Left ventricle

EDV = End diastolic volume

ESV = End systolic volume

SV = Stroke volume

EF = Ejection fraction

E = Early transmitral flow velocity

A = Late transmitral flow velocity.

TABLE 4.3 Echocardiographic measurements of left ventricular function before and after a 224 km Ironman Triathlon

	Before race	Post race	P Value
<i>Systolic Function</i>			
EDV (ml)	145±34	149±33	0.50
ESV (ml)	57±18	64±21	0.08
SV (ml)	88±24	85±26	0.60
EF (%)	61±8	57±11	0.06
<i>Diastolic Function</i>			
E (m/s)	1.09±0.15	0.97±0.17*	0.00002
A (m/s)	0.65±0.12	0.62±0.12	0.33
E/A	1.72±0.27	1.59±0.31*	0.04

Values are expressed as mean ± SD; N = 44.

EDV = End diastolic volume

ESV = End systolic volume

SV = Stroke volume

EF = Ejection fraction

E = Early transmitral flow velocity

A = Late transmitral flow velocity.

* Significant different from pre-race (p < 0.05)

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CHAPTER FIVE

CARDIAC SYMPATHETIC STIMULATION DURING EXERCISE / B-RECEPTOR RESPONSE

CHAPTER 5

Sympathetic stimulation during exercise

In our study we showed that the loading conditions on the heart were similar before and after the Ironman Triathlon. This was achieved by ensuring that the venous return to the heart was maximized by studying subjects in the head down (Trendelenberg) position. However we did find that the size of the E wave which measures early transmitral flow velocity decreased after exercise and this may not have been due to altered loading conditions. Thus other possibilities must be considered. One possibility is that the altered responsiveness to sympathetic stimulation (Friedman et al 1986, Eysmann et al 1996) may have caused the changes in the early transmitral Doppler flow velocity since this flow velocity is affected by changes in sympathetic stimulation (Udelson et al 1990, Schulman et al 1992, Cheng et al 1992). These studies show that decreased sympathetic stimulation causes a decrease in the size of the E wave, of the type found in this research study (Table 4.3). Post exercise beta-receptor desensitisation could not be controlled for in this study. This Chapter reviews the role of the sympathetic autonomic nervous system and receptor response to exercise to understand how this mechanism might have contributed to the findings reported in Chapter 4.

Receptor:

Cardiac nerve stimulation leads to the release of chemical transmitters that modify cell function. Sympathetic (catecholamine) nerve stimulation of the heart acts mainly on the beta-adrenergic receptors, although alpha-adrenergic receptors are also present. Most of the cardiac beta-adrenergic receptors are of the B1-subtype. Parasympathetic (muscarinic) receptors mediate parasympathetic influences on the heart and consist of the M2-subtype.

Desensitization:

Beta-receptor function may be modified by persistent stimulation of the receptor by agonist binding. The B-adrenergic receptors may lose their ability to generate a response when the

neurotransmitter norepinephrine is continually delivered to the heart, a phenomenon called desensitization. When the sympathetic system becomes chronically overactive as occurs with heart failure, the receptors similarly become desensitized to the agonist. Resensitization is the opposite of desensitization and occurs when a receptor becomes more responsive to an agonist after a period of decreased agonist binding to the receptor. An example of this principle is shown when patients with congestive cardiac failure are treated with low dose beta-blockers. Beta-blocker medication is contraindicated in heart failure due to the negative inotropic effect on the heart, however low dose therapy increases the cardiac inotropic response by increasing the receptor sensitivity to circulating catecholamines.

B-adrenergic receptor:

(A) Cellular actions of B-adrenergic receptors

The cellular actions of catecholamine function on the heart is attributed to the predominant cardiac receptor, the B1-AR subtype. B1-AR subtype couples to the stimulatory GTP regulatory protein (Gs) with adenylyl cyclase (AC) activation and accumulation of cAMP. The cAMP is the secondary messenger that increases calcium entry into the cytosol which then increases cardiac contractility and rates of relaxation. Cytosolic cAMP concentrations are regulated by the balance between the rates of production from adenylyl cyclase, which synthesise cAMP, and rates of degradation by phosphodiesterase that hydrolyses cAMP to AMP. The cAMP levels are regulated by feedback loops. The phosphorylation of B-receptors by the cAMP-dependent protein kinase results in B-receptor desensitization after prolonged exposure to the B-adrenergic receptor agonist, norepinephrine. Cytosolic calcium concentrations also regulate cAMP concentration by inhibiting adenylyl cyclase and activating phosphodiesterase activity.

B-Receptor response to agonist binding

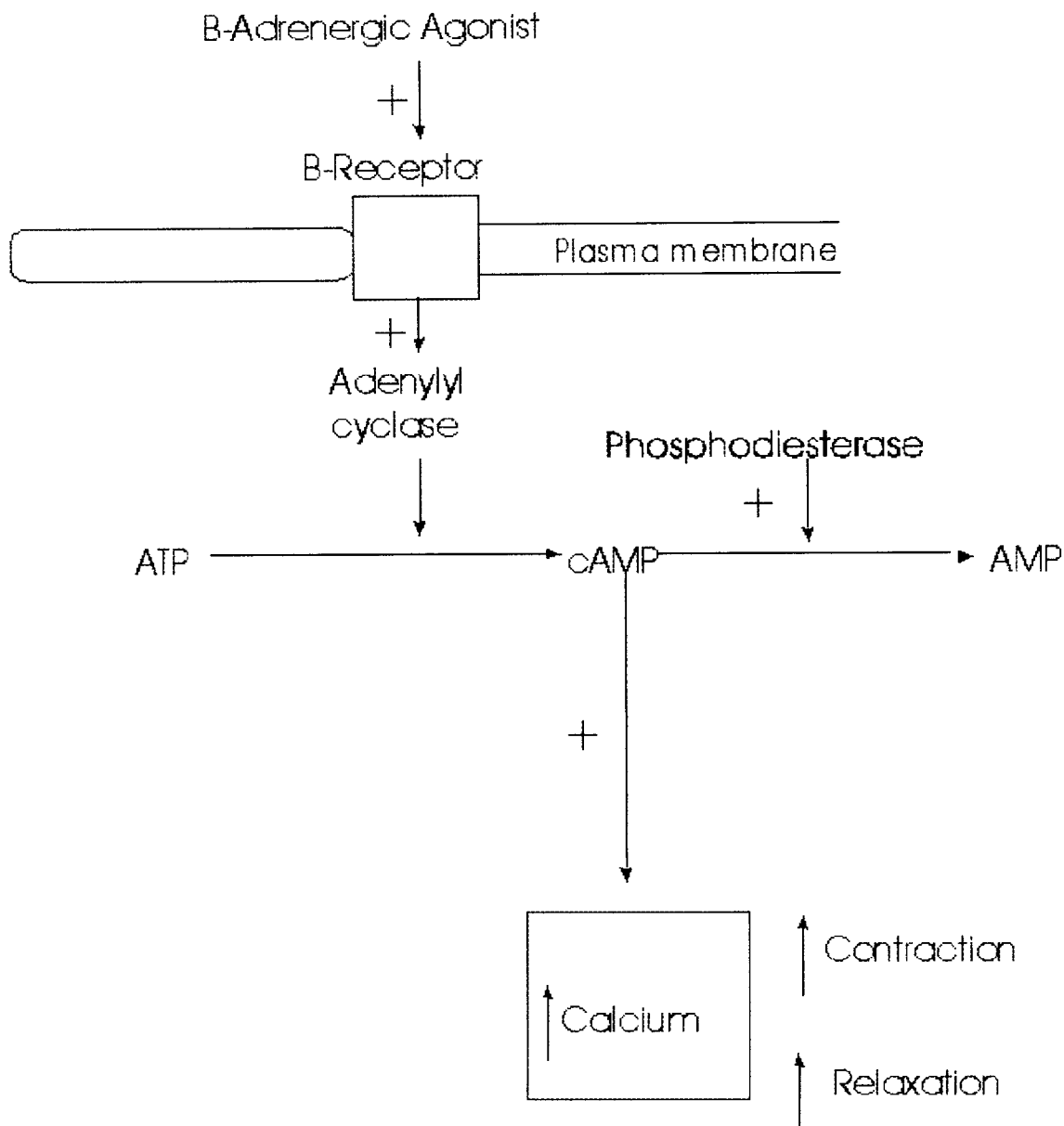


Figure 5.1. Cardiac beta-receptor response to agonist receptor binding. The agonist norepinephrine (NE) binds to the B-receptor to activate adenylyl cyclase. Adenylyl cyclase stimulates cAMP production. cAMP is broken down by phosphodiesterase which hydrolyses cAMP to AMP. The resulting increase in the intra-cellular calcium concentration causes an increase in the force of contraction and in the rate of relaxation.

(B) Exercise and B-adrenergic receptor response

B-adrenergic receptors of many tissues demonstrate desensitisation after agonist exposure. Friedman et al (1986) studied the effect of a single bout of acute dynamic exercise of 60 minutes duration and demonstrated a transient diminution of the chronotropic response to B-adrenergic stimulation. Eysmann et al (1996) showed that prolonged exercise similarly causes a reduced cardiac chronotropic response to sympathetic stimulation in normal sedentary individuals.

The cAMP dependent protein kinase phosphorylation of the B-receptors is dependent on the prevailing agonist concentration and the duration of stimulation. The B-receptor desensitisation with diminished inotropic response after exercise may therefore cause an ineffective cardiac response to the development of hypotension during the recovery period after prolonged exercise especially in the heat.

Summary:

It is apparent that prolonged exercise causes B-receptor phosphorylation with the desensitisation of the receptor to continued sympathetic stimulation. The reduced chronotropic and inotropic cardiac response after prolonged exercise may influence the cardiac response to the possible reduced loading conditions following prolonged exercise (Holtzhausen et al 1995) and which are due to the reduction in the total peripheral vascular resistance. The altered loading conditions together with the reduced cardiac response may be misinterpreted as “cardiac fatigue”. In an attempt to reduce the effects of venous pooling in the peripheral circulation the research study was conducted in the head down position to increase venous return. However we could not control for a decreased B-receptor response following prolonged exercise.

Prolonged exercise causes a 'dose-dependent' change in the B-receptor response to sympathetic stimulation due to the time-dependent B-receptor phosphorylation after agonist binding.

Prolonged exercise causes a reduced sympathetic response (Friedman et al 1986, Eysmann et al 1996) that affects the early transmitral flow pattern by altering the "diastolic suction" mechanism (Udelson et al 1990, Schulman et al 1992, Cheng et al 1992), causing a reduction in the size of the E wave as shown in our research study.

Effects of prolonged exercise on B-receptor

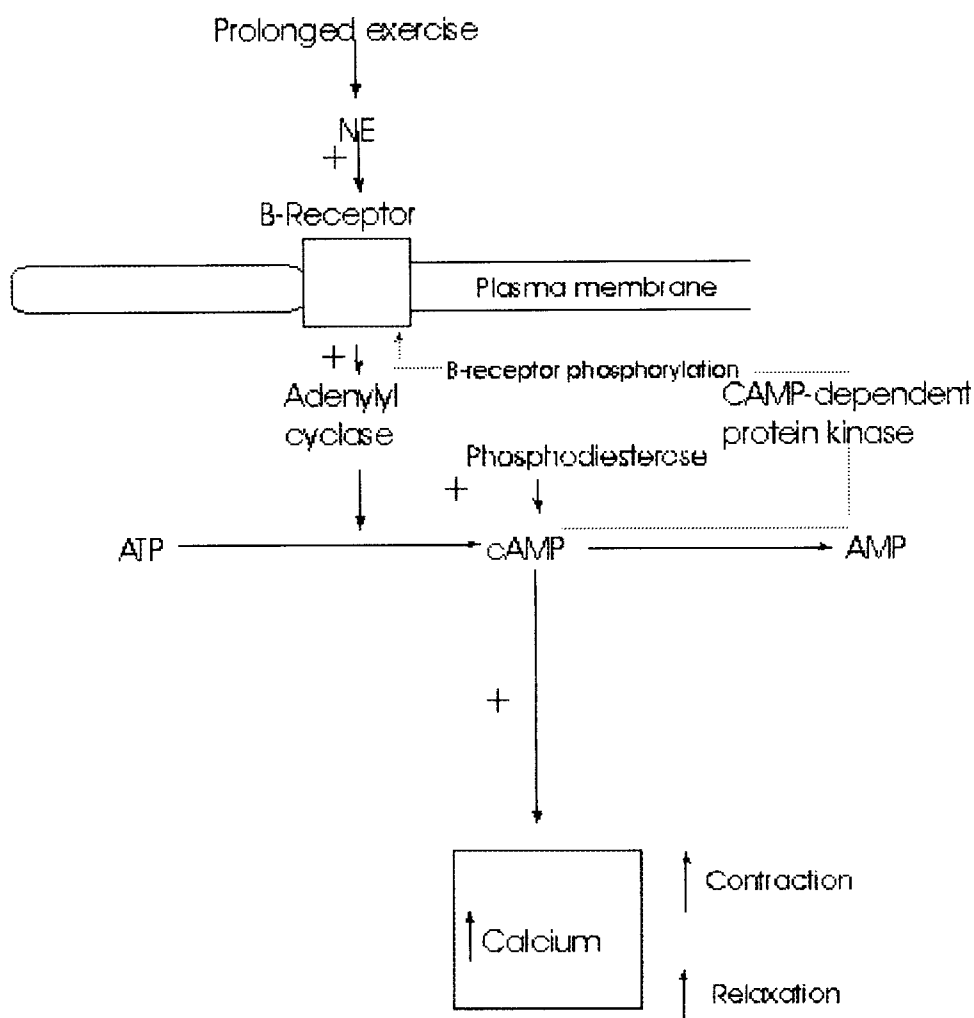


Figure 5.2. Cardiac beta-receptor response to prolonged exercise. Prolonged B-receptor agonist binding stimulates B-receptor phosphorylation by cAMP dependent protein kinase activity. The effect of this is to reduce the B-receptor sensitivity to agonist binding. This effect is dependent on the duration of stimulation and the agonist (norepinephrine) concentrations during exercise.

CHAPTER SIX

ALTERATIONS IN SERUM ACTIVITIES OF THE CARDIAC ENZYMES AFTER PROLONGED EXERCISE

CHAPTER 6

Alterations in serum activity of the “cardiac” enzymes after prolonged exercise:

Introduction:

The CK-MB isoenzyme has been considered a diagnostic hallmark for assessing myocardial infarction (Grande et al 1980, Puleo et al 1994). However, CK is only released from the heart if there is irreversible myocardial injury (Ishikawa et al 1997). Increased serum concentrations of cardiac troponin T is a more sensitive indicator of myocardial cell injury than is serum CK-MB activity since it is cardiac specific in origin and its detection in the circulation may be used as a prognostic indicator in patients with unstable angina pectoris (Hamm et al 1992). False positive results have however been reported in patients with conditions such as polymyositis, dermatomyositis, Duchenne muscular dystrophy (Kobayashi et al 1992) and in renal failure (Hafner et al 1994). The usefulness and reliability of serum enzyme markers of reversible and irreversible myocardial ischaemia is therefore questionable in the studies that have used these measurements when assessing the effect of prolonged endurance exercise on cardiac function since false positive results have been reported in conditions where concomitant muscle injury occurs (Kobayashi et al 1992, Hafner et al 1994, Laslett et al 1996, Muller-Bardorff et al 1997, Bodor et al 1997). The purpose of this chapter is therefore to review the significance and reliability of using myocardial enzyme markers as a diagnostic and prognostic indicator when assessing myocardial injury during or after prolonged exercise when concomitant muscle injury occurs.

The creatine kinase (CK) isoenzymes MM and MB are located primary in the cell cytosol of the skeletal muscle and cardiac muscle respectively. Despite the presence of CK MB isoenzyme in skeletal muscle, this isoenzyme has been used as a marker of myocardial infarction. The

clinical manifestations of chest pain with ECG changes have been interpreted to indicate myocardial ischaemia when there is also an elevated serum CK MB activity. However, the CK MB isoenzyme is released from the cytosol or mitochondria only when there has been irreversible myocardial injury (Hamm et al 1992, Bakker et al 1993, Ishikawa et al 1997). Other markers of cardiac injury include the appearance of cardiac troponin T and I. The cardiac isoform of troponin T (TnT) is believed to be specific for cardiac muscle since skeletal TnT subunits have amino acid sequences different from those of cardiac TnT.

Cardiac troponin T (cTnT):

Troponin T (TnT) is the tropomyosin-binding subunit of the troponin complex that is involved in the calcium-dependent regulation of striated skeletal muscle (Ebashi et al 1973). Cardiac and skeletal muscle TnT is derived from different genes and from differential RNA splicing (Gahlmann et al 1987). Cardiac troponin T (cTnT) is expressed in foetal and neonatal skeletal muscle in humans but is suppressed in healthy adult skeletal muscle.

Cardiac TnT can be released from the heart during attacks of unstable angina before irreversible damage has occurred. Reports in the literature have however documented elevated levels of cardiac TnT in the absence of cardiac damage in conditions such as polymyositis, Duchenne muscular dystrophy and in renal patients on dialysis (Kobayashi et al 1992, Hafner et al 1994). Bodor et al (1995) has shown that cardiac TnT is not 100% cardiac specific but is also expressed by regenerating as well as by non-regenerating (normal) skeletal muscle.

False positive results:

Kobayashi et al (1992) observed increased plasma concentration of cTnT in the absence of myocardial involvement in patients with polymyositis. Saggin et al (1990) demonstrated that cTnT is re-expressed in response to skeletal muscle injury in rats.

The first generation of troponin T Elisa tests reported a higher rate of false positive results in patients with severe skeletal muscle injury (Muller-Bardorff et al 1997) than the newer

generation troponin T assays. Muller-Bardorff et al (1997) proposed that false-positive results previously reported might be explained by an unspecific binding of skeletal muscle troponin T to the wall of the test tube sample that could be detected by the cross-reactive enzyme-labelled antibody used in the troponin I assay. In their study to assess troponin T assay specificity, they replaced the cross-reactive antibody with a cardiac specific monoclonal antibody and reported a reduction in the incidence of false positive results. However, 5 of the 40 patients with renal failure and 4 of the 20 patients with muscular dystrophy reported false positive results.

Whether the false positive results are the result of re-expression of cTnT in regenerating rat or human skeletal muscle (Saggin et al 1990) or lack of testing specificity is unclear and requires further investigation. It has however been found that in complex clinical situations where specificity is required, cardiac troponin I (cTnI) appears to be highly specific (Bodor et al 1995, Apple et al 1997, Shave et al 2002) since the absence of false positive recordings of myocardial ischaemia has been documented in patients with acute or chronic muscle disease or renal failure.

It has also been shown that the elevated levels of cardiac troponin T and I concentrations after prolonged exercise do not correlate with the depressed ejection fraction in athletes showing “cardiac fatigue” (Rifai et al 1999).

Since the sensitivity of Troponin I is comparable to that of CK-MB to assess for myocardial damage and it does not appear to be a superior marker that should replace CK-MB (Polanczyk et al 1999), CK-MB was used as a screening measurement during our research study to assess for post exercise myocardial damage. In the research study the CK-MB fraction showed no change after prolonged exercise and subsequently no further investigations were done on the blood samples.

Pathophysiology of serum cardiac troponin concentrations after myocardial injury.

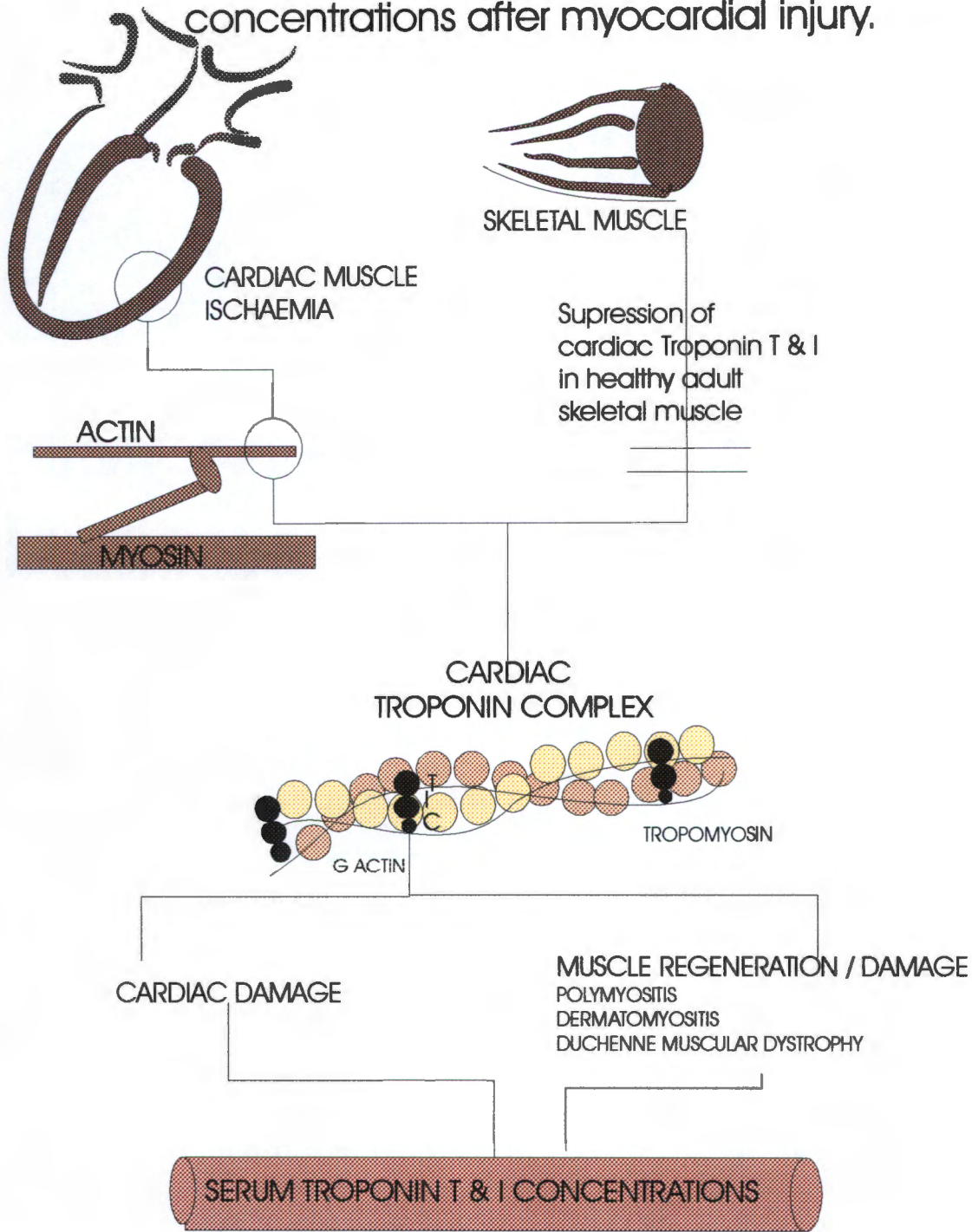


Figure 6.1 The mechanism whereby troponin markers of myocardial ischaemia enter into the circulation. The production of cardiac Troponin T and I are suppressed in skeletal muscle under normal circumstances. Cardiac Troponin T and I are produced in cardiac muscle and released into the circulation in the presence of cardiac ischaemia. The cardiac Troponin complexes are however also released in certain muscular disorders such as Polymyositis, Dermatomyositis and Duchenne Muscular dystrophy.

Studies assessing cardiac enzyme activities after prolonged exercise

Studies (Niemelä et al 1984, Douglas et al 1987, Lucia et al 1999, Whyte et al 2000) have measured cardiac enzyme activity after prolonged exercise. All of these studies showed a significant increase in total CK and in the CK-MB activities after exercise. The percentage of CK-MB was within normal limits (<5%) in all of these studies. In addition to the measurements of serum CK activity, Lucia et al (1999) and Whyte et al (2000) assessed more specific enzyme markers of myocardial damage such as troponin I and troponin T respectively. Whyte et al (2000) measured an increase in troponin T concentrations immediately after prolonged exercise. Concentrations returned to normal after 48hrs. Lucia et al (1999) reported no change in serum troponin I concentrations after a 42 km footrace.

Table 6.1 Table showing the studies that have measured markers of myocardial damage (CK, CK-MB, Troponin T and I) after prolonged exercise.

Study	CK activity		CK-MB activity		CK-MB %		TnT concentration		TnI concentration
	After exercise	Recovery	After exercise	Recovery	After exercise	Recovery	After exercise	Recovery	After exercise
Niemela et al 1984	↑	↑	↑	↑	↔				
Douglas et al 1987	↑	↑	↑	↑	↔	↔			
Lucia et al 1999	↑		↑		↔		↔		↔
Whyte et al 2000 Half triathlon	↑	↑	↑	↑	↔		↑	↔	
Whyte et al 2000 Full triathlon	↑	↑	↑	↑	↔		↑	↔	
Hassan et al 2003	↑		↑		↔				

Summary:

The sensitivity of CK-MB for detecting myocardial damage is comparable with the highly specific troponin T and troponin I (Polanczyk et al 1999). Accordingly serum concentrations of CK and CK-MB were measured in this study to assess for biochemical evidence of myocardial ischaemia. The possibility of false positive tests when using cardiac enzyme markers such as the first and second generation Troponin T assays (Shave et al 2002) due to lack of assay specificity or due to muscle damage and regeneration, requires further investigation.

Conclusion:

It is therefore apparent that increased serum CK-MB activity is a useful screening parameter when assessing for myocardial infarction or damage after prolonged exercise. However, CK-MB activity may not detect reversible myocardial ischaemia. The cardiac troponin T is as sensitive as CK-MB, however it is more specific and may detect reversible ischaemia. False positive results of myocardial damage may occur in conditions in which regeneration of skeletal muscle occurs. Since prolonged endurance exercise may produce muscle damage during the exercise period, reported studies assessing myocardial injury with these markers during or following prolonged exercise may have measured an artefact of degenerating and regenerating skeletal muscle.

Alternatively, it may be the result of non-specificity of the assays used to test for myocardial ischaemia in the latter conditions. Since most of the studies that assessed for cardiac fatigue after prolonged exercise have not used the more specific Troponin I enzyme activity and since one study (Lucia et al 1999) that used this measurement did not show any change in serum

Troponin I concentrations, the reliability of those studies that did not include the measurements of Troponin I for their interpretation of “cardiac fatigue” remains questionable.

Furthermore, it has been shown that the elevated levels of troponin concentrations after prolonged exercise do not correlate with changes in the reduced ejection fractions that have implied cardiac dysfunction (Rifai et al 1999).

CHAPTER SEVEN

SUMMARY AND CONCLUSION

CHAPTER 7

SUMMARY:

The cardiac response to prolonged exercise assessed with echocardiography after the termination of exercise is likely to be influenced by the prevailing loading conditions. Preload reduction due to peripheral vascular changes that includes a persistent reduction in total peripheral vascular resistance can be sufficient to produce postural hypotension (Holtzhausen et al 1995) and post-exercise collapse (Holtzhausen et al 1994, Noakes 2003). This is exacerbated when exercising in the heat, when the end diastolic volume is reduced and hence a reduced activation of the Frank-Starling mechanism.

This cardiac response when exercise is completed is further influenced by the beta-receptor desensitisation after exercise (Friedman et al 1986, Eysmann et al 1996). Prolonged exercise reduces the B-adrenergic responsiveness in healthy sedentary humans (Friedman et al 1986, Eysmann et al 1996) so that the altered loading conditions after exercise combined with a blunted cardiac response to B-stimulation could then be misinterpreted as “cardiac fatigue”.

The post exercise period is associated with a redistribution of blood volume from the general circulation to the splanchnic and renal circulation. The reduced muscle pump system due to venodilatation, especially when exercising in the heat, and the peripheral vascular changes may cause a temporary reduction in the central blood volume while the necessary re-adjustments of fluid distribution takes place after exercise. The reduced sympathetic nervous system response due to the B-receptor desensitisation will result in an inadequate compensatory response to the prevailing loading conditions (Friedman et al 1986, Eysmann et al 1996).

Since the peripheral vascular changes may influence the LV loading conditions, it follows that the evaluation of LV function before and after exercise must anticipate any possible change in fluid distribution in order to ensure equivalent loading conditions before and after exercise. Previous studies assessing the effects of prolonged exercise on LV function did not attempted to control for the loading conditions (Chapter3), by maintaining the preload and afterload conditions in the post exercise period.

Studies showed that the cardiac loading conditions affect diastolic flow characteristics, which can be misinterpreted as diastolic dysfunction. Choong et al (1987) showed that nitro-glycerine infusion at rest causes transmitral flow patterns similar to diastolic abnormalities of hypertrophic cardiomyopathy (Takenaka et al 1986), hypertrophy secondary to hypertension (Inouye et al 1984, Snider et al 1985) and obesity (Chakko et al 1991), ischaemic heart disease (Wind et al 1987) and valvular heart disease (Otto et al 1989).

Since the peripheral vascular changes will influence the left ventricular loading conditions, it follows that the evaluation of the left ventricular function before and after exercise must anticipate any possible changes in central blood volume in order to ensure equivalent loading conditions before and after exercise. Previous studies (Niemelä et al 1984, Perrault et al 1986, Douglas et al 1987, Niemelä et al 1987, Seals et al 1988, Douglas et al 1990, Vanoverschelde et al 1991, Manier et al 1991, Ketelhut et al 1992, Lucia et al 1999, Whyte et al 2000) that assessed the effects of prolonged exercise on left ventricular function did not control for the loading conditions and as a result all of these studies did not maintained both the preload and afterload after exercise.

The aim of our research study was to identify any possible effects of these peripheral changes on left ventricular function after prolonged exercise by using leg elevation before and after exercise to ensure equivalent loading conditions before and after prolonged exercise. The outcome of the research study showed that when the loading conditions were chosen to maximize venous return before and after exercise in 44 athletes who completed a 224 km Ironman Triathlon there was no evidence for cardiac systolic dysfunction. Evidence for diastolic dysfunction was shown by the decrease in peak early transmitral flow velocity. However the absence of any changes in the late transmitral flow pattern shows that the left atrium was contracting adequately and that there was no evidence of left ventricular relaxation abnormalities, unlike pathological conditions such as myocardial ischaemia, aortic stenosis and hypertrophic cardiomyopathy.

Studies of serum cardiac enzyme activities after exercise provided inconclusive evidence of myocardial ischaemia. The CK-MB percentage has been consistently normal in the studies (Niemelä et al 1984, Douglas et al 1987, Lucia et al 1999, Whyte et al 2000) that measured cardiac enzyme activities as a potential marker of cardiac damage. Furthermore the validity of the studies that used the earlier assays of troponin T as a marker of myocardial damage after prolonged exercise remain questionable as shown by the false positive results that occur in conditions in which concurrent muscle damage occurs (Bodor et al 1997, Kobayashi et al 1992, Hafner et al 1994). The only definitive measurement to diagnose reversible myocardial ischaemia in the presence of concomitant muscle injury is the troponin I concentration and one of the only studies (Lucia et al 1999) that used this measurement reported normal blood concentrations after prolonged exercise.

Alterations in the sympathoadrenergic function are known to affect cardiac function as seen in congestive cardiac failure where it forms the cornerstone of the pathophysiology. Neurohumeral control of diastolic and systolic function is apparent as sympathetic drive may modulate LV diastolic function. Thus B-blockade in hypertensive patients resulted in an additional reduction in the rate of left ventricular filling when blood pressure was unchanged (Fouad et al 1983). The reduced cardiac beta-receptor response that occurs after prolonged exercise (Friedman et al 1986, Eysmann et al 1996) may similarly cause a change in the left ventricular filling pattern that may be misinterpreted as cardiac dysfunction.

Finally, it is relevant to note that previous studies (Upton et al 1980, Palatini et al 1994, Goodman et al 2001) failed to demonstrate the development of cardiac systolic dysfunction during exercise. In all of these studies, the ejection fraction was either maintained (Goodman et al 2001) or increased during exercise (Upton et al 1980, Palatini et al 1994). If real “cardiac fatigue” is present after exercise, then it should be present also during exercise when the cardiac demands are at its maximum.

Conclusion:

Previous studies did not control the left ventricular loading conditions when cardiac function is measured after exercise. The phenomenon of “cardiac fatigue” may be an artefact of inappropriate left ventricular loading conditions combined with an inappropriate cardiac response due to the cardiac B-receptor desensitisation that develops during prolonged exercise.

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Appendix 1

Informed consent

Post exercise cardiac fatigue.

I _____ have been fully informed of the nature of this research project and hereby give my consent to act as a subject for the test.

I am fully aware of the procedures involved:

History taking Questionnaire

Medical examination

Echocardiographic examination – screening assessment before and after exercise

Blood will be drawn for screening before and after exercise for cardiac enzyme analysis

I am aware of the potential risks and complications.

I understand that the data collected may be used for scientific purposes and publication in a confidential manner.

I understand the implications of my informed consent and any questions I may have, had been answered to my satisfaction.

Name: _____ Signed: _____ Date

Researcher: Dr M Y Hassan Signed _____ Date

Supervisor: Professor T.D. Noakes

Witness: _____ Signed _____ Date

Appendix 2

Medical Assessment Form

Surname:

Date:

Name:

Date of Birth:

Occupation:

Medical History, Cardiovascular System (CVS) :

Examination:

Height =

Weight =

CVS:

Auscultation:

Aortic

Pulmonary:

Mitral:

Left Sternal Border

Screening:

Data before Ironman Triathlon:

Time	Date	Pulse	BP	Echocardiographic Data (Recordings taken according to the American College of Cardiology)										
				EDV	ESV	SV	EF	IVDd	IVDs	LVPWd	LVPWs	E	A	E/A

Data after Ironman Triathlon:

Time	Date	Pulse	BP	Echocardiographic Data (Recordings taken according to the American College of Cardiology)										
				EDV	ESV	SV	EF	IVDd	IVDs	LVPWd	LVPWs	E	A	E/A

KEY: BP = Blood pressure, EDV= End diastolic volume, ESV = end systolic volume, SV = Stroke volume, EF = Ejection Fraction, IVD= Septal diameter, d = diastole, s = systole, LVPW = left ventricle posterior wall, E = Early transmitral flow velocity, A = Late transmitral flow velocity