The assessment of Echocardiographic and tissue Doppler profiles of asymptomatic follow-up patients in a cardiology practice

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Declaration

Declaration with regard to independent work:

I, Johannes Joachim Steyn, identity number [redacted] and student number 8807735, do hereby declare that this research project submitted to the Central University of Technology, Free State, for the Degree: MAGISTER TECHNOLOGIAE: CLINICAL TECHNOLOGY, is my own independent work, and complies with the code of academic integrity, as well as other relevant policies, procedures, rules and regulations of the University; and has not been submitted before to any other institution by myself or any other person in fulfilment (or partial fulfillment) of the requirements for the attainment of any qualification.

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SIGNATURE OF STUDENT *DATE*

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List of Abbreviations

2-D	:	Two-dimensional Echocardiography
A’	:	Active Contraction Wave
ASE	:	American Society for Echocardiography
A-WAVE	:	Atrial Wave of the Mitral Flow
BP	:	Blood Pressure
BPM	:	Beats per Minute
BSA	:	Body Surface Area
CI	:	Cardiac Index
CO	:	Cardiac Output
CSA	:	Cross-Sectional Area
CW	:	Continuous Wave Doppler
D	:	Diameter
DT	:	Deceleration Time
E’	:	Early Muscle Wave
ECG	:	Electrocardiogram
E-WAVE	:	Early Wave of Mitral Flow
FVI	:	Flow Velocity Integral
HDL	:	High-Density Lipoprotein
IVRT	:	Isovolumetric Relaxation Time
IVS	:	Interventricular Septum
LA	:	Left Atrium
LDL	:	Low-Density Lipoprotein
LVED	:	Left Ventricle End-diastolic Diameter
LVEF	:	Left Ventricle Ejection Fraction
LVES	:	Left Ventricle End-systolic Diameter
LVH	:	Left Ventricle Hypertrophy
LVID	:	Left Ventricle internal dimension
LVOT	:	Left Ventricular Outflow Tract
LVPW	:	Posterior Wall
LVPW	:	Left Ventricular Posterior Wall
M-Mode	:	Motion Mode

MPI	:	Muscle Performance Index
PW	:	Pulse Wave Doppler
PWT	:	Posterior Wall Thickness
SF	:	Shortening Fraction
ST	:	Septal Thickness
SV	:	Stroke Volume
TDI	:	Tissue Doppler Imaging
VTI	:	Velocity Time Integral

Units of measure

circ/s	:	circumferences per second
cm	:	centimetres
cm/s	:	centimetres per second
cm^2	:	centimetres squared
dB	:	decibels
g	:	gram
g/m^2	:	grams per metre squared
Hz	:	Hertz
kg	:	kilogram
l/min	:	litres per minute
$l/min/m^2$	:	litres per minute per meter squared
m/s	:	meters per second
mm	:	millimetres
mm/s	:	millimetres per second
mmHg	:	millimetres of mercury
ms	:	milliseconds
b/min	:	beats per minute
ml	:	millilitres
Db	:	decibel

List of Definitions and Key Terms

Ejection fraction:	"The volume of blood ejected from the ventricle during each systole can be expressed as a percentage of the end-diastolic volume. This gives the ejection fraction of the heart. The normal range for the left ventricle ejection fraction is between 52% - 75 %." (Anderson *et al.*, 1993)
Fractional shortening:	"Represents the transverse diameter fractional shortening of the left ventricle at the level of the mitral valve and are generally considered as a very reliable index of left ventricle systolic performance." (Schmailzl *et al.*, 1994)
Left ventricle end-diastolic diameter:	"Left ventricle internal diameter at end-diastole." (D'Cruz, 1983)
Left ventricle end-systolic diameter:	"Left ventricle internal diameter at the end-systole." (D'Cruz, 1983)
M-mode Echocardiography:	"In the M-mode format, the B-mode line sweeps across the face of a cathode ray tube. Because of the persistence of the phosphor of the tube, the B-mode dots leave a trail as they move. This trail depicts the motion of intracardiac structure relative to time; also known as time-motion presentation." (Weyman, 1994)
E point:	"E-point reflects the maximal opening point of the mitral leaflet due to the early, rapid filling phase of the left ventricle," (Anderson, 2007)

Hemodynamic:	"Hemodynamic refers to the investigation of the physical principals of blood flow and the circulation." (Anderson, 2007)
Continuous wave:	"Continuous- wave Doppler refers to the continuous transmission of the Doppler signal towards the moving red blood cells and the continuous reception of the returning signals reflected from the moving red blood cells." (Anderson, 2007)
Pulsed-wave Doppler:	"With pulsed-wave Doppler, ultrasound signals are send out in short bursts or pulses." (Anderson, 2007)

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Summary

This main aim of this study was to assess patients in a general cardiology practice in order to determine the systolic and diastolic profiles of these patients. The aim was also to determine what effect life style and risk factors may have on the echocardiographic variables measured during such an examination. The specific aim of this study was the importance of not only examining the systolic function but the necessity to also examine the diastolic profile of patients. Life-style plays an important role, with the main culprit being obesity. Obesity was the single most important factor that affected the diastolic profile of patients seen in this study. With obesity a combination of other risk factors related to obesity was observed. Most abnormalities found due to these risk factors were associated with diastolic changes in the left ventricle.

Echocardiography is routinely used in daily practice, but the diagnostic value of this tool can be enhanced if proper analyses of the systolic as well as the diastolic profiles are determined. Many cardiologists only measure the systolic function of the heart as an indication of the well- being of the left ventricle, although in this study it was proven that systolic function did not alter with ageing or with changes in the risk profile.

Hundred-and-twelve patients, divided into three age groups, were evaluated in this study. Both systolic and diastolic variables were measured and analysed for abnormalities. None of these patients had systolic function abnormalities, although they had detectable anatomic changes due to ageing, obesity and hypertension. Several abnormalities were found on the diastolic profile of these patients.

Muscle thickness increased due to obesity and hypertension and even with ageing, but with no significant abnormalities in the systolic function of the heart. There was a slight increase in the circumferential shortening of the left ventricle and that both the septal and longitudinal functions decreased with ageing. It is noteworthy that even where the systolic function remained normal in ageing subjects, their diastolic profiles changed significantly.

Assessment of left ventricular function required a meticulous and systematic approach. In this study forty- one percent of patients visiting this general practice had abnormalities of their diastolic function although their systolic function was normal. It was found that with ageing, especially in the older age group, important abnormalities occur in their diastolic profile. The most common changes were that the E- peak velocity decreased and that the A- peak velocity of the trans-mitral flow increased. It seemed that passive filling decreased with ageing but that active filling increased simultaneously, causing the cardiac output to remain constant in older subjects. This is important to know because diseases affecting the atrium may have a profound effect on the cardiac output of older patients, even if they have normal systolic function, (due to the decreased passive filling they need their active filling or atrial contraction to support a normal cardiac output). An important marker will be to look at the ratio of the E/A- velocities in older patients to determine the ratio of active against passive filling.

Other than that, a relatively new tool in echocardiography called tissue Doppler was used to determine what happened to the muscle with ageing. Here it was demonstrated that the different layers of the left ventricle acted differently with ageing. Results showed that the longitudinal fibres weakened with ageing although the circumferential fibres remained unchanged or even strengthened with ageing.

It was apparent in this study that the traditional use of only systolic function may not be adequate when evaluating relative asymptomatic patients presenting at a general cardiology practice. It is important to also evaluate the diastolic profiles of these patients in order to scientifically quantify their heart health, even in asymptomatic patients. It is important to routinely evaluate the diastolic profile of patients so that early detection of these diastolic variables can be detected and timely consideration for its treatment can be given by their cardiologist. It is also important to take note of the significance of the obesity problem and the effect it has on the heart's health.

In conclusion, this study emphasizes the importance of the echocardiographic evaluation of diastolic cardiac function in addition to routine systolic evaluation in asymptomatic patients. This will enable the clinician to detect abnormalities early and tailor therapy accordingly. Lifestyle related risk factors, especially obesity, also have significant effects on diastolic cardiac function.

Opsomming

Die hoofdoel van hierdie studie was om pasiënte in 'n algemene kardiologiepraktyk te assesseer ten einde die sistoliese en diastoliese profiele van hierdie pasiënte te bepaal. Die doel was ook om te bepaal watter uitwerking leefstyl en risikofaktore mag hê op die eggo-kardiografiese veranderlikes wat tydens so 'n ondersoek gemeet word. Die spesifieke oogmerk van hierdie studie was die belangrikheid daarvan om nie alleen die sistoliese funksie te ondersoek nie, maar die noodsaak om ook die diastoliese profiel van pasiënte te ondersoek. Leefstyl speel 'n belangrike rol, met obesiteit as die vernaamste sondebok. Obesiteit was die enkel belangrikste faktor wat die diastoliese profiel beïnvloed het van pasiënte wat in hierdie studie ondersoek is. Tesame met obesiteit is 'n kombinasie van ander risikofaktore verwant aan obesiteit waargeneem. Die meeste abnormaliteite wat as gevolg van hierdie risikofaktore aangetref is, is geassosieer met diastoliese veranderinge in die linkerventrikel.

Eggo-kardiografie word roetinegewys in die daaglikse praktyk gebruik, maar die diagnostiese waarde van hierdie hulpmiddel kan verhoog word indien behoorlike analises van die sistoliese sowel as die diastoliese profiele gemaak word. Talle praktyke meet slegs die sistoliese funksie van die hart as aanduider van die welstand van die linkerventrikel, alhoewel dit in hierdie studie bewys is dat sistoliese funksie nie verander met veroudering of met veranderinge in die risikoprofiel nie.

Honderd-en-twaalf pasiënte, in drie ouderdomsgroepe ingedeel, is in hierdie studie geëvalueer. Sowel die sistoliese as die diastoliese veranderlikes is bepaal en geanaliseer vir abnormaliteite. Geeneen van hierdie pasiënte het abnormaliteite rakende sistoliese funksie getoon nie, alhoewel hulle sigbare anatomiese veranderinge as gevolg van veroudering, obesiteit en hipertensie getoon het. Talle abnormaliteite is aangetref op die diastoliese profiel van hierdie pasiënte.

Spierdikte het toegeneem as gevolg van obesiteit en hipertensie en selfs met veroudering, maar met geen betekenisvolle abnormaliteite in die sistoliese funksie van die hart nie. Dit het getoon dat daar 'n effense toename in die omtrek verkorting van die linkerventrikel was en dat beide die septale en lengte funksies afgeneem het met veroudering. Dit is belangrik om te

besef dat, selfs waar die sistoliese funksie normaal gebly het by ouer persone, hulle diastoliese profiele betekenisvol verander het.

Die assessering van linkerventrikulêre funksie vereis ŉ noukeurige en sistematiese benadering. In hierdie studie het een-en-veertig persent van die pasiënte wat hierdie algemene praktyk besoek het, abnormaliteite in hulle diastoliese funksie getoon, alhoewel hulle sistoliese funksie normaal was. Daar is bevind dat, met veroudering, veral in die ouer ouderdomsgroep, belangrike abnormaliteite in hulle diastoliese profiel voorkom. Die mees algemene veranderinge was dat die E-pieksnelheid afgeneem het en die A-pieksnelheid van die transmitrale vloei toegeneem het. Dit lyk asof passiewe vulling afneem met ŉ toename in ouderdom, maar dat aktiewe vulling tegelykertyd toeneem, wat veroorsaak dat die kardiale uitset dieselfde by ouer persone bly. Dit is belangrik om te weet, omdat siektes wat die atrium aantas ŉ groot invloed op die kardiale uitset van ouer pasiënte sal hê as gevolg van die verminderde passiewe vulling, dus verloor hulle hul aktiewe vulling of atriale kontraksie wat benodig word om ŉ normale kardiale uitset te ondersteun. ŉ Belangrike merker sal wees om na die ratio van die E/A-snelhede by ouer pasiënte te kyk om die ratio van aktiewe teenoor passiewe vulling te bepaal.

Hierbenewens is ŉ relatiewe nuwe hulpmiddel in eggo-kardiografie, genaamd weefsel-Doppler, gebruik om te bepaal wat by veroudering met die spier gebeur. Hierdeur is aangetoon dat die verskillende lae van die linkerventrikel anders optree by veroudering. Resultate het aangetoon dat die lengteweefsel verswak met ouderdom, alhoewel die omtrekweefsel onveranderd bly, of selfs sterker word met veroudering.

Dit was duidelik uit hierdie studie dat die tradisionele gebruik van slegs die sistoliese funksie nie toereikend is wanneer kardiologiepasiënte geëvalueer word nie. Dit is van die uiterste belang om ook die diastoliese profiele van hierdie pasiënte te evalueer ten einde op wetenskaplike wyse hulle hartgesondheid te verreken, selfs by asimptomatiese pasiënte. Dit is belangrik om roetinegewys die diastoliese profiel van pasiënte te evalueer sodat vroeë opsporing van hierdie diastoliese veranderlikes kan plaasvind en tydige oorweging vir die behandeling daarvan deur hulle kardioloog geskenk word. Dit is ook belangrik om kennis te neem van die belangrikheid van die probleme rakende obesiteit en die uitwerking wat dit op die hart se gesondheid het.

Ten slotte beklemtoon hierdie studie die belangrikheid van die eggo-kardiografiese evaluering van die diastoliese kardiale funksie bo en behalwe die roetine sistoliese evaluasie by asimptomatiese pasiënte.

Dit sal die klinikus in staat stel om vroegtydig abnormaliteite op te spoor en dienooreenkomstig terapie toe te pas. Veranderinge in leefstyl, veral wat obesiteit betref, het ook ’n betekenisvolle uitwerking op diastoliese kardiale funksie.

Chapter 1
Introduction

In the past decade it has become apparent that symptoms and prognoses of patients with congestive cardiac failure depend not only on left ventricular systolic function but also on left ventricular diastolic function (Pinamonti *et al.*, 1993; Xie *et al.*, 1994; Xie *et al.*, 1996).

Two-dimensional echocardiography and M-Mode is well suited for studies of left ventricular function, and Doppler echocardiography provides a non-invasive tool for the assessment of left ventricular diastolic function. Diastolic function of the left ventricle has been derived from flow velocities across the mitral valve. However, these measurements were influenced by load and age dependence, location of Doppler sample volume, rhythm and heart rate (Choong *et al.*, 1987; Downes *et al.*, 1990; Hurrell *et al.*, 1997; Mantero *et al.*, 1998; Nishimura *et al.*, 1989; Nishimura *et al.*, 1990; Stoddard *et al.*, 1989; Sztajzel *et al.*, 1993; Triulzi *et al.*, 1990).

Even though systolic and diastolic dysfunction often coexist, only a few Doppler echocardiographic variables combine measurements from systole and from diastole, but recently a new Doppler index of combined diastolic and systolic performance has been proposed (Tei *et al.*, 1995). The Tei index has proven to be a reliable method for the evaluation of global left ventricular performance, with clear advantages over older established indexes and prognostic value in many kinds of heart disease (Lakoumentas *et al.*, 2004).

It might be valuable to combine all these parameters in an echocardiographic study and use it in the decision-making process when treating patients. This study attempted to evaluate the changes in Doppler profiles during normal follow up of patients in a cardiology practice. Demographic data were taken into consideration as well as known disease processes and risk factors that can have an effect on these measurements.

This study is based on the hypothesis that routine Doppler systolic and diastolic evaluation is important even in asymptomatic patients and that routine evaluation of Doppler parameters should be considered during evaluation of patients at follow-up.

Chapter 2
Literature review

2.1 Introduction

The cardiovascular fetal system is the first system to reach a functional state in human development at age five weeks. The primitive heart is a tubular structure, which forms like a large blood vessel from mesenchymal cells in a region of embryonic tissue called the "cardiogenic area". The primitive heart tube is formed by the fusion of two thin-walled endocardial heart tubes and is located in the floor of the future pericardial cavity. The splanchnic mesenchyme adjacent to this tubular heart then condenses, forming the primordial myocardium and epicardium (Moore *et al*., 1988).

The heart is composed of three major types of cardiac muscle: atrial muscle, ventricular muscle, and specialised excitatory and conductive muscle fibres. The atrial and ventricular types of muscle contract in much the same way as skeletal muscle, except that the duration of contraction is much longer. On the other hand, the specialised excitatory and conductive fibres contract only feebly because they contain few contractile fibrils; instead, they exhibit rhythmicity and varying rates of conduction, providing an excitationary system of the heart (Guyton *et al.,* 1996).

The term "excitation-contraction coupling" indicates the mechanism by which the action potential causes the myofibrils of muscle to contract (Guyton *et al.,* 1996). When an action potential passes over the cardiac muscle membrane, the action potential also spreads to the anterior of the cardiac muscle fibre, along the membranes of the transverse (T) tubules. The T- tubule action potential in turn acts on the membranes of the longitudinal sarcoplasmic tubules to cause instantaneous release of calcium ions into the muscle sarcoplasm from the sarcoplasmic reticulum. In another few thousands of a second, these calcium ions diffuse into the myofibrils and catalyse the chemical reaction that promote sliding of the actin and myosin filaments along one another; this in turn produces the muscle contraction (Guyton *et al.,* 1996).

Any factor that increases venous return or slows the heart produces greater ventricular filling (preload) during the cardiac cycle's diastolic phase. An increase in end-diastolic volume

stretches myocardial fibres and initiates a powerful ejection stroke during contraction. This ejects the normal stroke volume plus any additional blood that entered the ventricles and stretched the myocardium (Mc Ardle *et al*., 2001). Two researchers, German physiologist Otto Frank (1865-1944) and British physiologist Ernest Starling (1866-1927) described the relationship between contractile force and the resting length of the heart's muscle fibres. This phenomenon, Starling's law of the heart, always operates during the cardiac cycle and applies to all of the heart's chambers (Mc-Ardle *et al*., 2001). This is termed cardiac systole. Doppler changes in cardiac systole and diastole are what this study aims to investigate.

2.2 Echocardiography

2.2.1 Introduction

Since Doppler's inception as a tool in clinical cardiology, echocardiography has been used to assess left ventricular systolic function. Doppler methodology determining intracardiac blood flow and tissue motion has evolved into a valuable technique for assessing the diastolic function (Feigenbaum *et al*., 2005).

Evaluation of ventricular systolic function is the most important application of echocardiography, so that even when evaluation of systolic function is not the focus of the examination, it plays an essential role in every study (Otto, 2004).

Assessment of systolic and/or diastolic function provides valuable prognostic information. In nearly all instances, an assessment of left ventricular systolic function should be an integral part of the routine examination (Feigenbaum *et al*., 2005). Both systolic and diastolic functions change as a disease processes, regresses or progresses. The treatment strategy for a patient's condition is affected by systolic and diastolic functions. Hence, echocardiography is especially useful for monitoring serial changes in systolic and diastolic functions in response to treatment and for following the progression of a patient's underlying cardiovascular disease (Oh *et al*., 1999).

2.2.2 Systolic function as part of the cardiac cycle

Systole typically is defined as the segment of the cardiac cycle from mitral valve closure to aortic valve closure. The onset of systole is defined by the electrocardiogram as ventricular depolarisation (onset of the QRS complex), with the end of systole occurring after repolarisation (end of T-wave). In terms of ventricular pressure and volume curves over time, systole begins when left ventricular diastolic pressure exceeds left atrial pressure, resulting in closure of the mitral valve (Otto, 2004).

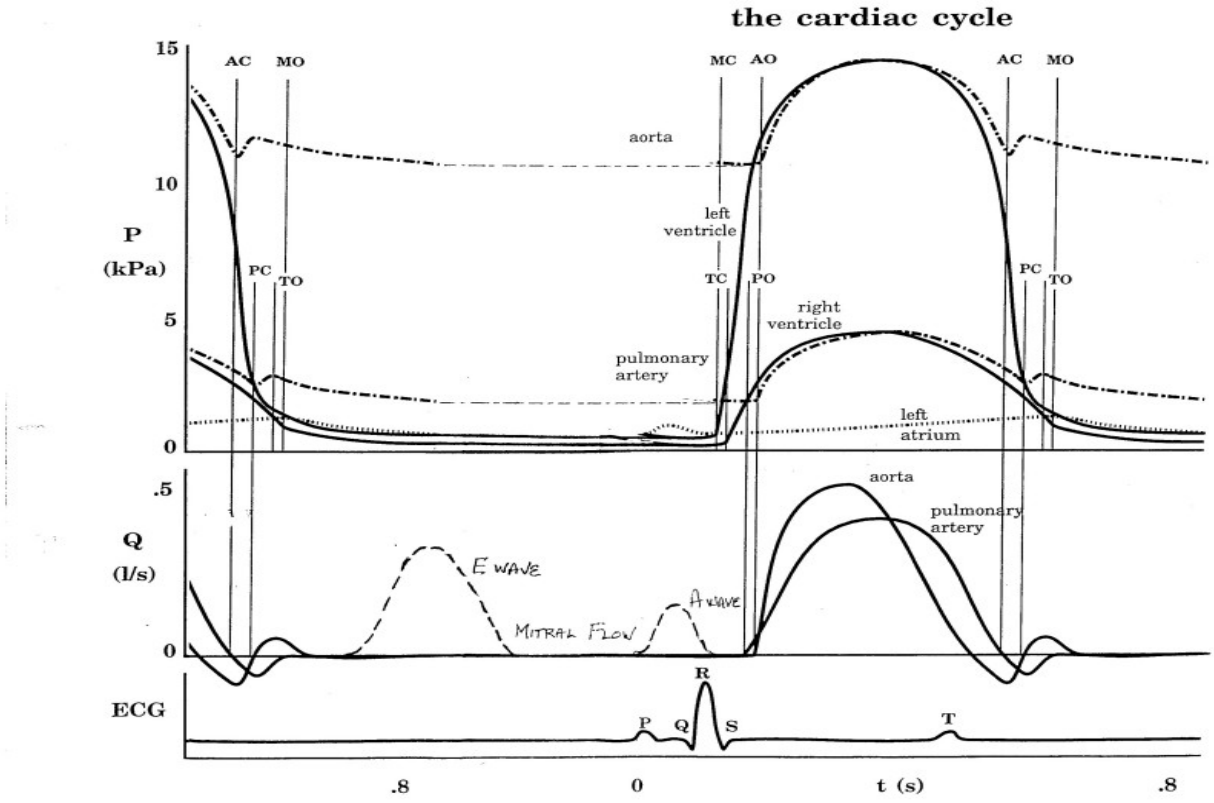

Fig 2.1 The cardiac cycle
(Adapted and modified from Nichols et al., 1998)

Mitral valve closure is followed by isovolumic contraction, during which the cardiac muscle depolarises, calcium influx and myosin-actin shortening occur, and ventricular pressure increases rapidly at a constant ventricular volume. When ventricular pressure exceeds aortic pressure, the aortic valve opens. During ejection, left ventricular volume falls rapidly as blood flows from the left ventricle to the aorta (See Fig 2.1).

"Systolic function" is affected by ventricular preload, ventricular afterload, intrinsic ventricular contractility, and heart rate. Asynchronous ventricular contraction secondary to coronary artery disease or a ventricular pacemaker may also affect systolic function.

Fundamentally, ventricular systolic function is best described by contractility: the ability of the myocardium to contract. However, contractility is affected by several physiologic parameters including, heart rate, coupling interval, metabolic factors and pharmacologic agents. In addition, for a given degree of contractility ventricular ejection performance can vary depending on preload and afterload (Otto, 2004).

Quantification of cardiac chamber size, ventricular mass, and function ranks among the clinically most important and most frequently requested tasks of echocardiography. Standardisation of chamber quantification has been an early concern in echocardiography and recommendations on how to measure such fundamental parameters are among the most frequently cited articles in the field (Sahn *et al*., 1978; Schiller *et al*., 1989).

According to Oh *et al*. (1999), the three variables used most frequently to express left ventricular global systolic function are:

A. Fractional shortening.
B. Ejection fraction.
C. Cardiac output.

Otto (2004) concluded that there are several other imaging parameters that provide a qualitative measurement of left ventricular systolic function, namely
M-Mode measurements:

- The separation between the maximum anterior motion of the mitral leaflet and the maximum posterior motion of the ventricular septum (E- point septal separation).
- The degree of anteroposterior motion of the aortic root.

Qualitative evaluation of overall systolic function is a simple and highly predictive index that is of great clinical utility e.g. pre-surgery evaluation. However, several factors can limit the usefulness of this evaluation (Otto, 2004). Ejection fraction is a global index of systolic function and one of the most commonly used markers of systolic function (Kerut *et al*.,

2004). This simple measurement has been found to be a strong predictor of clinical outcome in almost all major cardiac conditions and is used to select the optimal management strategy, including the implantation of intracardiac defibrillator or biventricular pacing (Otto, 2004).

The most commonly used assessment of left ventricular systolic function is the ejection fraction (Feigenbaum *et al.*, 2005; Roldan, 2005). The reason for this is that it is easy to do, it can be repeated regularly and is cost effective.

2.3 Fractional shortening

Fractional shortening can be described as the percentage change in the dimension of the left ventricle that occurs during systolic contraction (Oh *et al*., 1999).

It is a commonly used M-mode index of systolic performance and if no segmental left ventricle wall motion abnormalities are present, the fractional shortening and ejection fraction correlate well (Kerut *et al*., 2004).
Fractional shortening can be seen as a rough measurement of left ventricular systolic function (Otto, 2004) and alterations in preload and afterload can alter fractional shortening (Roldan, 2005).

Kerut *et al*. (2004) defined fractional shortening (FS) as follows:
FS% = 100 [(LVEDD)-(LVESD)]/ (LVEDD)
Where LVEDD is the left ventricle end-diastolic dimension and LVESD is left ventricle end-systolic dimension.

According to Otto (2004), the normal range is 25% to 45% (95% confidence limits).

2.4 Ejection fraction

Ejection fraction can be used as the global index of systolic function and one of the most commonly used markers of systolic function (Feigenbaum *et al.*, 2005; Kerut *et al.*, 2004; Roldan, 2005).

According to Kerut *et al.* (2004), the ejection fraction (EF) is the stroke volume (SV) divided by the end-diastolic volume (EDV):

EF = (SV/EDV) 100%

And since SV = (EDV-ESV) where ESV = end-systolic volume,

Therefore EF = [(EDV-ESV)/EDV] 100%.

According to Kerut and co-workers (2004), errors in estimating the ejection fraction may result from:

- Underestimation of ejection fraction because of endocardial echo dropout and the eyeball seeing mostly epicardial motion;
- Underestimation of ejection fraction when the left ventricle cavity is significantly enlarged. A large left ventricle can eject a large volume with less endocardial motion;
- Overestimation of ejection fraction in a normal left ventricle; and/or
- Significant left ventricle regional wall motion abnormalities.

Kerut *et al.* (2004) also concluded that quantitative methods to calculate ejection fraction are usually preferable. Left ventricle volume is obtained and from this the ejection fraction calculated. For an accurate ejection fraction calculation, one must be able to obtain proper positioned images along with good endocardial visualisation.

Otto (2004) stated that the following factors that can limit the usefulness of systolic function with ejection fraction measurement are:

- Firstly, the accuracy of the estimated ejection fraction is dependent on the experience of each observer.

- Secondly, inadequate endocardial definition can result in incorrect estimates of systolic function.
- Thirdly, integration of data from multiple tomographic images can be difficult when the pattern of contraction is asynchronous (with conduction defects, pacers, postoperative septal motion) or when the pattern of contraction is asymmetric (with prior myocardial infarction or with ischemia), especially when dyskinesis is present (See Fig 2.2).

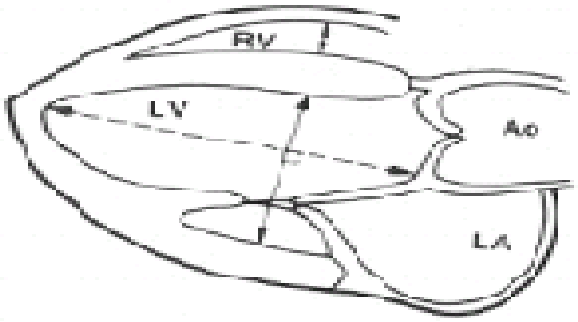

Fig 2.2 Schematic representation of a parasternal long axis view of the left ventricle.
(Adapted from Feigenbaum et al., 2005).

2.5 Cardiac output

Cardiac output provides the most significant indicator of the circulatory system's functional capacity to meet the demands for physical activity. As with any pump, the rate of pumping (heart rate) and quantity of blood ejected with each stroke (stroke volume) determine the heart's output of blood (McArdle *et al.*, 2000). McArdle *et al*. (2000) also concluded that blood flow from the heart increases in direct proportion to exercise intensity. From rest to steady-rate exercise, cardiac output increases rapidly, followed by a more gradual increase until it plateaus as blood flow matches exercise metabolic requirements. In sedentary, college-age men, cardiac output in strenuous exercise increases about four times the resting level to an average maximum of 22 l/min. Maximum heart rate for these young adults averages 195 b/min. Consequently, stroke volume averages 113 ml of blood per beat during maximal exercise (22 000 ml ÷ 195). In contrast, world-class endurance athletes generate maximum cardiac output of 35 l/min, with a similar or slightly lower maximum heart rate than untrained counterparts (McArdle *et al.*, 2000). The difference between maximum cardiac

outputs of aforementioned individuals relates solely to differences in stroke volume. The cardiac output of the Nordic Olympic medal winner in cross-country skiing increased eight times above rest to 40 l/min during a maximum exercise test. The accompanying stroke volume averaged 210 ml per beat, twice the volume of blood pumped per beat compared to the maximum stroke volume of a healthy, sedentary person of the same age (McArdle *et al*., 2000).

Otto (2004) concluded that the basic function of the heart is as a pump, so that measurements of cardiac output may thus be useful in routine day-to-day patient treatment. Cardiac output is the volume of blood pumped by the heart per minute, with stroke volume being the amount pumped during a single beat. While cardiac output can be derived from ventricular volumes as described above, a variety of other approaches to measurement are available, including indicator dilation methods (Fick, thermo-dilution), Doppler-velocity data, ventricular impedance, and radio nuclide methods.

Ventricular systolic function and cardiac output are dynamic, responding rapidly to the metabolic demands of the individual. Cardiac output increases from a mean of 6 l/min at rest to 18 l/min with exercise in young, healthy adults. Most of this increase in cardiac output is mediated by an increase of heart rate (McArdle *et al*., 2000).

With supine exercise there is only a minimal increase in stroke volume of approximately 10%, where as with upright exercise, the increase in stroke volume is approximately 20%-35%. With exercise, end-diastolic volume is unchanged or slightly decreased, but ejection fraction increases and end-systolic volume decreases (Otto, 2004). According to McArdle *et al.* (2000), two physiologic mechanisms regulate stroke volume and contribute in varying degrees to stroke volume increases during exercise.

The first mechanism, intrinsic to the myocardium, requires greater diastolic filling followed by a forceful systolic ejection. The second, governed by neurohormonal influences, involves normal ventricular filling followed by a forceful systolic ejection to cause systolic emptying (McArdle *et al*., 2000).

McArdle and co-workers (2000) found that greater ventricular filling during diastole in the cardiac cycle occurs due to any factor that increases venous return (preload), or slows heart

rate. An increase in end-diastolic volume stretches myocardial fibres, causing a powerful ejection stroke as the heart contracts. This expels the normal stroke volume plus the additional blood that entered the ventricles and stretched myocardium. The German physiologist Frank Otto (1865-1944) and a British colleague Ernest H. Starling (1886-1927) who experimented with animals in the early 1900s first described relationships between muscle force and the resting fibre length. Improved contractility of a stretched muscle (within a limited range) relates to a more optimum arrangement of intracellular myofilaments as the muscle stretches. Frank-Starling's law of the heart describes this phenomenon applied to the myocardium (McArdle *et al*., 2000).

McArdle *et al.* (2000) also concluded that physiologists taught the Frank-Starling mechanism as the "modus operandi" for all increases in stroke volume during exercise. They believed that enhanced venous return in exercise caused greater cardiac filling which in turn stretched the ventricles in diastole to produce a more forceful ejection. In all likelihood, this pattern describes the stroke volume response in transition from rest to exercise, or when a person moves from the upright to recumbent position. Enhanced diastolic filling probably also occurs in activities like swimming, in which the body's horizontal position optimises venous return and myocardial preload (McArdle *et al*., 2000).

Cardiac output and stroke volume reach the highest and most stable levels in the horizontal position. Near-maximal stroke volume occurs at rest in the horizontal position and increases only slightly during exercise. This postural effect becomes prominent when comparing circulatory dynamics at rest in the upright and supine positions. As upright exercise intensity increases, stroke volume also increases to approach the maximum value in the supine position McArdle *et al.* (2000).

In most forms of upright exercise, the heart does not fill to an extent that significantly increases cardiac volume to values observed in the recumbent position. The increase in stroke volume during exercise likely results from the combined effects of enhanced diastolic filling and more complete systolic emptying. In both recumbent and upright position, the heart's stroke volume increases in exercise despite resistance to flow-increased systolic pressure (afterload), McArdle *et al.* (2000).

At rest in the upright position, 40% to 50% of the total end-diastolic blood volume remains in the left ventricle after systole; this residual volume of the heart amounts to 50-70 ml of blood. The sympathetic hormones epinephrine and norepinephrine enhance myocardial stroke power and systolic emptying during exercise, which reduces the heart's residual volume. The time velocity integral (TVI), also called velocity time integral, is the area measured under the Doppler velocity envelope for one heartbeat. From the TVI the stroke volume (SV), and hence cardiac output (CO) and cardiac index (CI) may be calculated. The area (A) is obtained at the same level as the TVI measurement was made (Kerut *et al*., 2004). Left ventricular SV may be calculated as follows:

$SV = TVI_{OT} \text{ X } A_{OT}$

$SV = TVI_{OT} \text{ X } [D/2]^2 \text{ X } \pi$

$SV = TVI_{OT} \text{ X } D^2 \text{ X } 0.785$

Where D is the left ventricle outflow tract (LVOT) diameter in centimetres, TVI_{OT} is the TVI of the LVOT in centimeters, and A_{OT} is the calculated area of the LVOT. Kerut *et al.* (2004) also concluded that TVI and area measurement can be made at many sites, including the ascending aorta, aortic annulus, mitral inflow, tricuspid inflow, and pulmonary valve levels.

The aortic annulus is the most accurate of all the valves for stroke volume measurements. The aortic diameter is measured in the parasternal long axis in early mid systole, and the pulsed wave Doppler of aortic TVI obtained from the apical five-chamber view. The pulsed wave (PW) sample is placed at the same level as where the diameter measurement was made. SV measurement at the level of the tricuspid valve (TV) is generally not very accurate Kerut *et al*. (2004).

According to Kerut and co-workers (2004) this method of stoke volume determination makes the assumption that:

- The velocity profile is flat.
- The area of the profile is constant during the time obtaining the TVI.
- Flow is laminar (not turbulent).

2.6 Cardiac mass and index

Echocardiography was one of the first imaging modalities used clinically for determination of left ventricular mass. It has received widespread acceptance in epidemiologic studies of hypertension and valvular heart disease in which the presence of hypertrophy has been associated with worsened outcomes and its regression has been a goal of therapy (Feigenbaum *et al*., 2005). Left ventricular mass can be determined using a number of echocardiographic formulas and algorithms and has been shown to carry substantial prognostic importance in virtually all forms of heart disease.

Left ventricular mass can be estimated from M-mode dimensions of septal thickness (ST), posterior wall thickness (PWT), and the left ventricular internal dimension (LVID) at end-diastole. Note that the original description of this method by Reichek and Devereux used PENN convention measurements with the endocardial echoes included in wall thickness and excluded from chamber dimensions (rather than leading edge to leading edge) (Otto, 2004).

According to Feigenbaum *et al*. (2004) the earliest methodology for determining ventricular mass was based on M-mode measurement of septal and posterior wall thickness and the left ventricular internal dimension. M-mode calculation assumes a predefined ventricular geometry, and their accuracy will diminish in instances in which the left ventricular shape is abnormal.

One of the methods for determining left ventricular mass is the so-called cubed (Teicholtz) formula, which assumes that the left ventricle is a sphere. The diameter of this sphere is the interior dimension of the left ventricle and the sphere wall thickness is that of ventricular myocardium. The formula calculates the outer dimension of the sphere and then the inner dimension, the difference being the presumed left ventricular myocardial volume (Feigenbaum *et al.*, 2005).

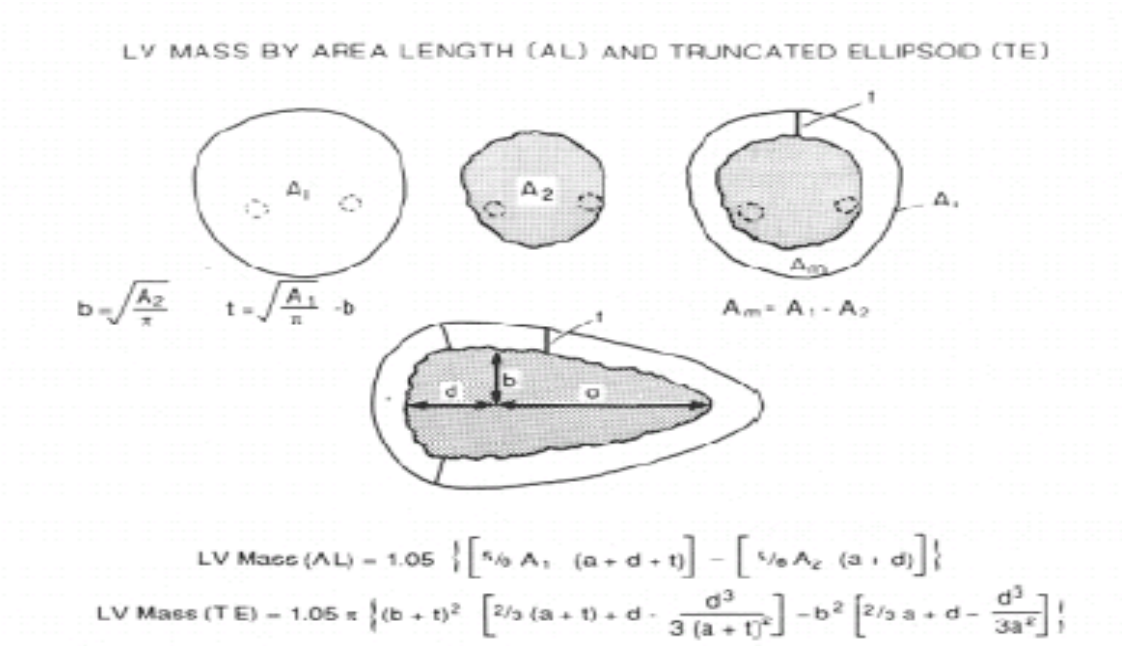

Fig. 2.3 . Methods for determining left ventricular mass using two-dimensional measurements (Adapted from Schiller et al., 1989.)

The cubed formula is expressed as left ventricular mass = (interventricular septum + left ventricular interior dimension + posterior wall)^3 - left ventricular interior dimension^3 (Feigenbaum *et al.,* 2004). The cubed methodology (Fig. 2.3) has been widely used, especially in serial evaluations, because for any given patient, the magnitude and direction of the error would be expected to remain constant and therefore the technique could be used for evaluating serial changes. A more accurate determination of left ventricular mass can be obtained with two-dimensional echocardiography.

When using two-dimensional echocardiography, geometric assumptions of the ventricular shape are typically still employed but the assumption is that of a bullet-shaped ventricle rather than a sphere (Feigenbaum *et al.,* 2004).

Additionally, mean left ventricular wall thickness is determined rather than wall thickness at only one point on the septum and posterior wall. Mean wall thickness can be calculated by determining the epicardial and endocardial areas of the short axis of the left ventricle at the mid-cavity level. The difference between these two areas then represents the myocardial area. The left ventricular area can then be calculated either by an area length method or by assuming a truncated ellipse geometry (Feigenbaum *et al*., 2004).

According to Kerut *et al.* (2004), M-mode echocardiography has been used for LV mass and volume calculations. LV-mass quantification using M-mode is based on the assumption that the LV is a prolate ellipsoid with a 2:1 long/short axis ratio. This assumption is fairly accurate for normally shaped ventricles, but for patients with LV segmental wall motion abnormalities or valvular regurgitation with altered LV geometry, this may not be accurate.

The well-validated cube formula for LV mass calculations using M-mode echo is:

$$\text{LV mass} = 0.8\{1.04[(IVS+LVID+PWT)^3-LVID^3]\}+0.6g$$

Where (ASE guidelines for measurements) IVS is diastolic interventricular septal thickness, LVID is diastolic LV internal dimension and PWT is diastolic posterior left ventricular wall thickness.

The PENN convention has also well described LV mass by another form of the cube formula:

$$\text{LV mass} = 1.04[(IVS+LVID+PWT)^3-(LVID)^3]-13.6g$$

Kerut and co-workers (2004) concluded when using this formula that normal mass values for males are $93\pm22 g/m^2$ and for females $76\pm18 g/m^2$.
Left ventricle volumes using M-mode, may be made using cube formula ($V=LVID^3$), but dilated ventricles will have an overestimated volume.
The Teichholz equation gives the best M-mode formula for estimating LV volume:

$$V_{diastole} = [7/ (2.4 +LVID)][LVID^3]$$

2.7 Diastolic dysfunction

2.7.1 Introduction

It has become widely recognised that virtually all forms of acquired organic heart disease are associated with a component of left ventricular diastolic dysfunction (Feigenbaum *et al.*, 2005).

There has been increasing recognition that diastolic ventricular function often plays an essential role in the clinical manifestation of disease in patients with a wide range of cardiac disorders. For example, many patients with clinical heart failure have normal systolic function with predominant diastolic dysfunction. Diastolic dysfunction may be an early sign of cardiac disease, often preceding clinical or echocardiographic evidence of systolic dysfunction (Otto, 2004).

Abnormalities of diastolic filling are increasingly recognised to play an important role in the symptomatology and prognosis of many forms of heart disease. It is well known that left ventricular diastolic dysfunction usually precedes systolic dysfunction and abnormal relaxation is observed at an early stage (Dougherty *et al.,* 1984; Grossman *et al.,* 1976; Ishida *et al.,* 1986).

Diastolic dysfunction with preserved ejection fraction accounts for 40% to 50% of heart failure cases in population-based studies. This observation has stimulated increased interest in the ability to characterize diastolic function non-invasively. The natural history of diastolic dysfunction is characterised by an initial and progressive impairment in the left ventricular relaxation followed by a superimposed decline in left ventricular compliance that results in the need for increased atrial pressures to maintain left ventricle filling and cardiac output.

2.7.2 Diastolic properties of the left ventricle

Diastole of the cardiac cycle has traditionally been divided into 4 phases: isovolemic relaxation, early rapid filling, diastases and atrial contraction.

The isovolumic relaxation time is a continuum of the systolic cardiac cycle and is, dependent on systolic function in addition to relaxation of the left ventricle. The early diastolic filling phase is dependent on both left ventricle relaxation and chamber compliance. The slow diastolic filling phase, or diastases, is dependent on heart rate and chamber compliance. The atrial contraction phase is dependent on the chamber compliance, left atrial function, and the electrical conduction system of the heart (Khouri *et al.*, 2004).

In addition to the 2 major determinants of diastolic function (ventricular relaxation and compliance), there are numerous independent factors that affect left ventricle properties and the filling of the left ventricle. Ventricular relaxation is a complex energy-dependant process during which the contractile elements are deactivated and the myofibrils returned to their original length. In other words, ventricular relaxation can be thought of as the duration of the decrease in left ventricle pressure after systolic contraction (Khouri *et al.*, 2004).

According to Otto (2004), there are several physiologic parameters that can be used to describe different aspects of diastolic function, but there is no single measure of overall diastolic function. The most clinically relevant parameters of diastolic function are:

- Ventricular relaxation;
- Myocardial or chamber compliance; and
- Filling pressures.

Additional parameters of interest include elastic recoil of the ventricle and the effect of pericardial constraint, but the importance of these factors in normal diastolic ventricular function remains controversial.

Assessment of left ventricle diastolic function requires a meticulous and systematic approach. The initial evaluation begins with echocardiographic observation of standard M-mode and 2-dimensional anatomic imaging. Anatomic evaluation of left atrium diameter and volume, left

ventricle mass, left ventricle relative wall thickness, and left ventricle systolic function should be the first step in the evaluation of diastolic dysfunction (Fig. 2.4) (Appleton *et al.*, 1993 and 2000).

Although several different definitions of diastole have been proposed, the most widely accepted clinical definition is the interval from aortic valve closure (end-systole) to mitral valve closure (end-diastole). The isovolumic contraction period, from mitral valve closure to aortic valve opening, typically is considered as part of systole (Otto, 2004).
Diastole can be divided into four phases:

- Isovolumic relaxation
- The early rapid filling phase
- Diastasis
- Late diastolic filling due to atrial contraction.

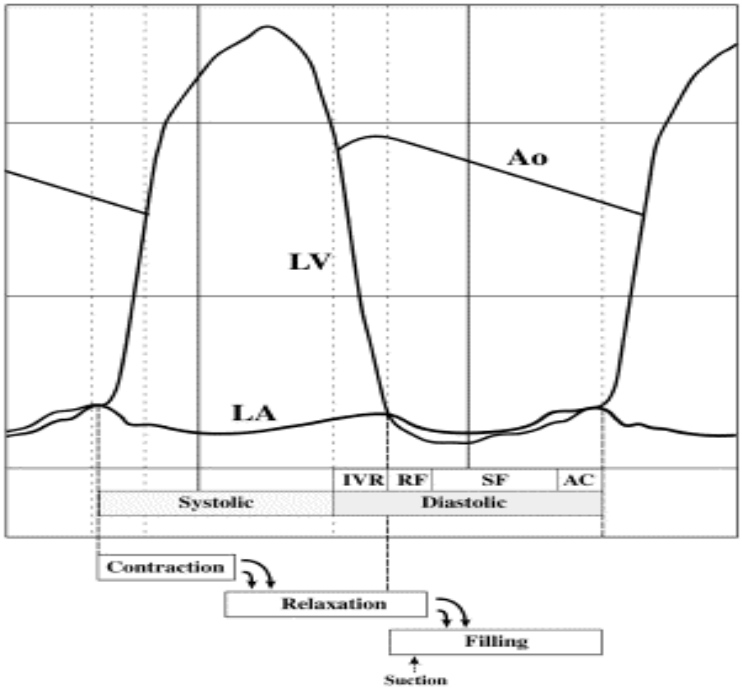

Fig. 2.4 *"Diastolic filling of left ventricle. Schematic representation of left ventricle, left atrial, and ascending aorta pressure. Cardiac cycle is classically divided into systole and 4 phases of diastole: isovolumetic relaxation, rapid filling, slow filling, and atrial contraction. Each phase is dependent on variables shown above. In a more practical and simplified system, cardiac cycle is divided into contraction, relaxation, and diastolic filling. Each of 3 phases is dependent on effects of preceding phase as shown above. Adapted with permission from The American College of Cardiology Foundation" (Adapted from Nishimura et al., 1997).*

It was not until the widespread availability of Doppler echocardiography that evaluation of diastolic function of the left ventricle became a viable clinical tool. There are a number of

Doppler approaches for determining diastolic function, including determination of mitral inflow patterns with pulsed Doppler imaging, evaluation of pulmonary vein flow, and the newer technique of tissue Doppler imaging (TDI), which can be used as a stand-alone technique or combined with mitral inflow patterns. A word of caution is advised when using Doppler parameters as markers of diastolic dysfunction. The accuracy and validity of Doppler markers of diastolic function are greatest in the presence of systolic dysfunction, and individual parameters may lose their validity in the presence of normal systolic function (Feigenbaum *et al*., 2005).

For evaluation of diastolic properties of the left ventricle, the mitral inflow pattern is evaluated from an apical transducer position with the sample volume placed at the tips of the mitral valve. Normal mitral inflow consists of biphasic flow from the left atrium into the left ventricle. In a healthy, disease-free individual, the early flow, coincident with the mitral E-wave, exceeds the later flow, which occurs with atrial systole both in velocity and volume. The magnitude of these flows, as well as their ratios, varies with age in the normal population. In healthy, young, disease-free individuals, the E-wave exceeds the A-wave, and therefore the E/A ratio is more than 1.0. In adolescents and young adults, there may be a disproportionate contribution of active ventricular relaxation to ventricular filling, which results in a markedly accentuated E-wave velocity. In this instance, the E/A ratio can exceed a value of 2.0 in a normal, disease-free individual. With advancing age, there is natural stiffening of the ventricle, which results in delayed relaxation. This results in a progressive decrease in E-wave velocity and an increase in A-wave velocity with age so that the anticipated E/A ratio in a disease-free individual older than the age of 60 is often less than 1.0. With pathologic degrees of stiffening of the left ventricular myocardium, a hierarchy of changes can be seen in the mitral inflow patterns (Feigenbaum *et al.*, 2005).

2.8 Grading of diastolic dysfunction

In most cardiac disease, the initial dysfunction is impaired relaxation (Fig. 2.5).

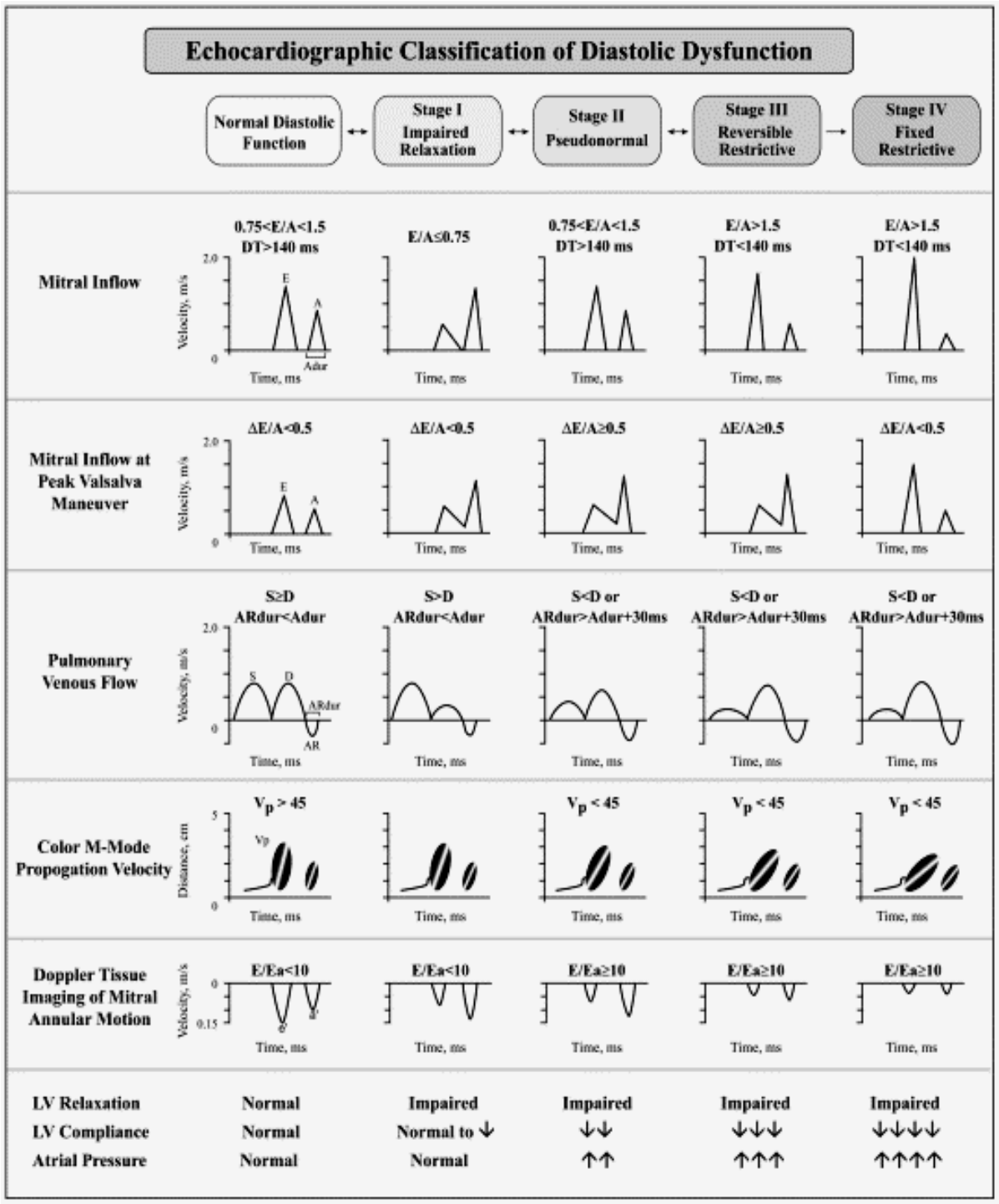

Fig. 2.5 *Echocardiographic classification of diastolic dysfunction. Adapted with permission from the American Medical Association. (Adapted from Redfield et al., 2003.)*

With further progression of the disease and a mild to moderate increase in LA pressure, the mitral inflow velocity pattern appears similar to a normal filling pattern (pseudo-normalised) (Oh *et al.*, 2006). After following a further decrease in LV compliance and increase in LA pressure, the diastolic filling becomes restrictive. Most patients with restrictive filling are symptomatic and have a poor prognosis unless the restrictive filling can be reversed by treatment (Capomolla *et al*., 2001).

Therefore, diastolic dysfunction can be graded as follows according to the diastolic filling pattern (Nishimura *et al*., 1997):

Grade 1 = impaired relaxation pattern with normal filling pressure

Grade 1a= impaired relaxation pattern with increased filling pressure

Grade 2 = pseudo-normalised pattern

Grade 3 = reversible restrictive pattern

Grade 4 = irreversible restrictive pattern

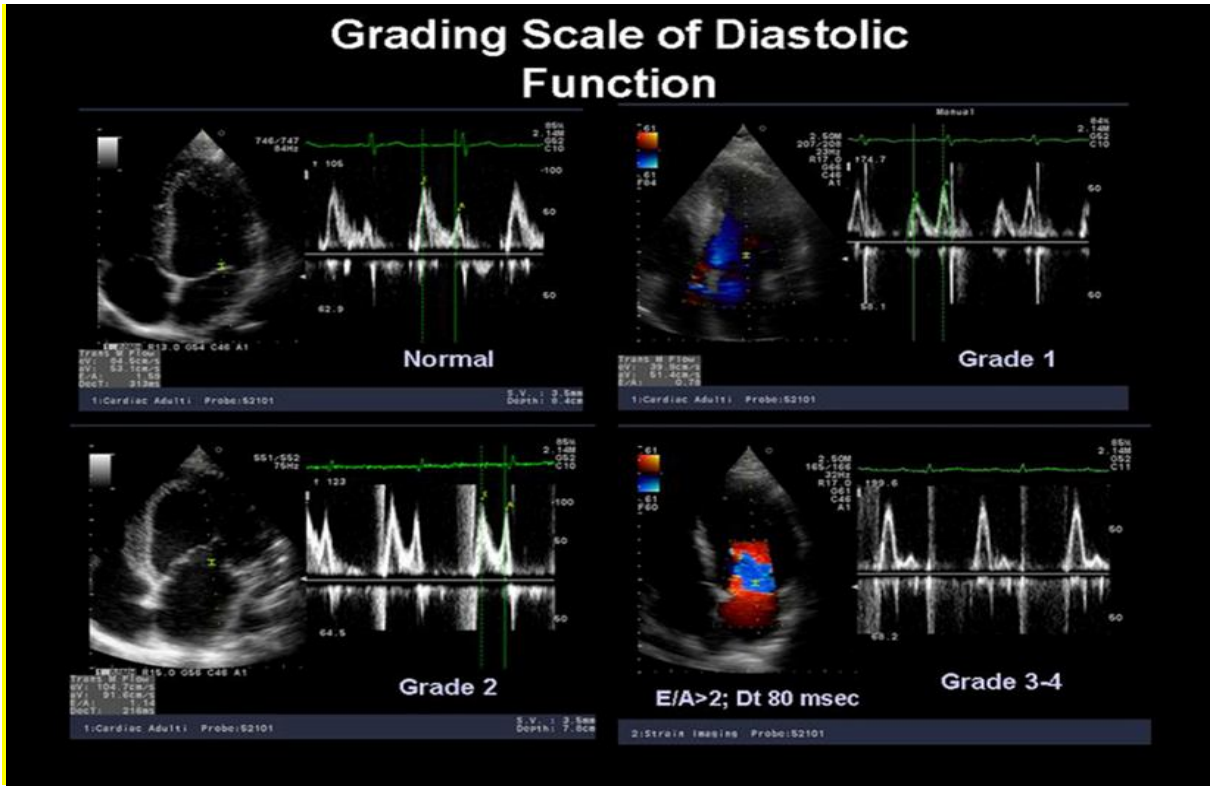

Fig. 2.6 *"Grading of diastolic dysfunction from normal to severe dysfunction (grade 3-4), evaluated by Pulse Wave (PW) Doppler of mitral inflow. Normal: DT 140-240 msec; E/A 0.75-1.5. Grade 1: DT> 220 msec, E/A <0.75. Grade 2: DT 140-220 msec, E/A 0.75-1.5. Grade 3-4: DT < 140 msec, E/A > 1.5; in grade 3, the E/A ratio is reversible, when compared to grade 4, with the pre-load changes". (Adopted from Scipione Carerj et al., 2009.)*

2.8.1 Grade 1

In nearly all types of cardiac disease, the initial abnormality of diastolic filling is slowed or impaired myocardial relaxation (Fig 2.5). The IVRT is prolonged. Mitral E velocity is decreased and A velocity increased, producing an E/A ratio less than 1 with prolonged DT (Fig 2.6). Whenever the E/A ratio is less than 1, impaired relaxation is usually present (Oh *et al*., 2006). E'(Passive myocardial relaxation) is also reduced, usually less than 7 cm/s (at the septal annulus).

Diastolic filling pressure is not increased and the E/E' is 8 or less (Ommen *et al*., 2000). In a subgroup of patients, E/E' is greater than 15, with E/A less than 1. This pattern has been designated grade 1a diastolic dysfunction in order to emphasise that the filling pressure is increased in the presence of a typical grade I mitral-inflow velocity pattern (Oh *et al.,* 2006). The "classic" pattern of mild left ventricular diastolic dysfunction is seen with left ventricular hypertrophy due to hypertension or to valvular aortic stenosis. The predominant abnormality is impaired relaxation, resulting in a pattern of reduced early diastolic filling and an enhanced atrial contribution to filling.

The Doppler velocity curve shows a prolonged IVRT, reduced acceleration to a reduced E velocity, prolonged early diastolic deceleration slope, an increased A velocity, and an E/A ratio <1. When left ventricular systolic dysfunction supervenes, the elevated left ventricular end-diastolic pressure and elevated left atrial pressure may result in "pseudo-normalisation" of this pattern with an enhanced E velocity and reduced A velocity. Coexisting mitral regurgitation also can lead to a "paradoxical" higher E velocity despite impaired ventricular relaxation (Otto, 2004).

Increased left ventricular mass decreases the rate of myocardial relaxation. In most of the patients with left ventricle hypertrophy, diastolic filling velocities consist of decreased E velocity with prolonged DT, increased A velocity, and E/A ration of less than 1 (Douglas *et al.,* 1989). As the myocardium becomes more fibrotic or stiff, the diastolic filling pattern evolves to a more pseudo-normal pattern and finally a restrictive ventricular filling can be seen in the setting of normal to hyperdynamic systolic function. However, in patients with hypertrophic cardiomyopathy, diastolic filling parameters appear to have a poorer correlation

with left ventricular pressure, most likely a result of more profound relaxation abnormalities in the presence of significant left ventricular hypertrophy (Symanski *et al.*, 1995).

2.8.2 Grade 2

As diastolic function deteriorates, the mitral inflow pattern goes through a phase that resembles a normal diastolic filling pattern, that is, the E/A ratio is 1 to 1.5 and DT is normal at 160 to 220 milliseconds. This is the result of a moderately increased LA pressure superimposed on a relaxation abnormality (Fig. 2.6). The best way to identify a pseudo-normalised pattern is to demonstrate impaired relaxation by E' less than 7 cm/s and increased filling pressure by E/E' greater than 15 (Oh *et al.*, 2006). Afterload of the left ventricle is defined as the resistance to ejection of blood from the ventricle to the systemic circulation. In other words, afterload represents the systemic vascular resistance.

Alteration of afterload can alter the diastolic profiles. Changes in afterload primarily affect the rate of left ventricular relaxation with subsequent changes in the transmitral inflow curve. An increase in afterload prolongs ventricular relaxation. Hence, the crossover of pressure between the left ventricle and left atrium occurs later. This results in a smaller initial driving pressure between the left ventricle and left atrium and a reduction in the peak mitral E wave velocity. Furthermore, there is also a decreased rate of fall in the gradient between the left atrium and left ventricle because of continued delayed myocardial relaxation, resulting in prolongation of the deceleration time. Finally, because there is less filling in early diastole, there will be greater filling with atrial contraction (increased A wave velocity).

Note that an increase in afterload produces the same effect as a decrease in preload (Anderson, 2004).

2.8.3 Grade 3 and 4

The term *restrictive diastolic filling*, or *restrictive physiology*, should be distinguished from restrictive cardiomyopathy. The increase in LA pressure results in earlier opening of the mitral valve, shortened IVRT, and an increase in early LV diastolic pressure, with rapid equalisation of the LV and LA pressures producing a shortened deceleration time DT. Atrial contraction increases LA pressure, but A velocity and duration are shortened because LV pressure increases even more rapidly. Therefore, restrictive physiology is characterised by

mitral flow velocities that show increased E velocity, decreased A velocity and shortened DT (< 160 msec) and IVRT (< 70 msec). Typically, the E/A ratio is more than 2.0 and occasionally increases to 5 (Fig. 2.6). Because myocardial relaxation is impaired in patients with a restrictive filling pattern, mitral annulus E' is reduced (< 7 cm/s and usually, < 5 cm/s).

The Valsalva manoeuvre may reverse a restrictive filling pattern to a grade 1 or 2 pattern, indicating the reversibility of high filling pressure (grade 3 diastolic filling). However, even if the restrictive filling pattern does not change with the Valsalva manoeuvres, reversibility cannot be adequate or filling pressure may be too high to be altered by the manoeuvres. Diastolic filling should be graded "irreversible restrictive" (grade 4) only when there is objective evidence of a persistent restrictive pattern with normal filling pressure (Oh *et al*., 2006).

2.9 Effects of age on diastolic function

With ageing, there is a gradual decrease in the rate of myocardial relaxation and elastic recoil and, therefore, the left ventricle pressure declines and filling becomes slower. With a normal left atrial pressure, the pressure crossover between the left ventricle and left atrium occurs later and the early transmitral pressure gradient is decreased. Hence, the isovolumetric relaxation time (IVRT) becomes longer and the mitral E velocity decreases with increasing age. Furthermore, the reduced filling in early diastole retards the equilibrium between the left ventricle and left atrium, resulting in prolongation of the deceleration time. Because early filling of the left ventricle is reduced, the contribution from atrial contraction becomes significant. These result in a gradual increase in the mitral A-velocity with ageing. Pulmonary venous flow velocities show similar changes with ageing. Since the pulmonary venous flow in diastole parallels the early mitral inflow, it follows the mitral E velocity that decreases with age, and consequently the pulmonary venous D velocity also decreases with advancing age. To compensate for this reduction in diastolic filling, systolic forward flow becomes more prominent. Note that the mitral inflow and pulmonary venous flow profiles in young individuals may be similar to that of the restrictive filling pattern. In these individuals, the mechanism producing this filling pattern is vigorous, normal relaxation rather than the high-driving pressure that occurs with restrictive physiology. Furthermore, the pulmonary venous D velocity may be greater than the pulmonary venous S velocity in normal young persons. In

addition, there may also be shortening of the mitral A-wave duration. However, when compared to the pulmonary venous atrial reversal duration, the mitral A-wave duration should be equal to or slightly longer than the pulmonary venous atrial reversal wave. In patients with restrictive physiology the reverse is true (the mitral A-wave duration is shorter than the pulmonary venous AR wave) (Anderson, 2004).

Age is an important variable which affects the interpretation of diastolic filling profiles. Abnormalities of left ventricle diastolic function have been described as part of the normal ageing process resulting from intrinsic myocardial changes and hypertrophy of the left ventricle. Due to these changes in myocardial relaxation and compliance with ageing, different diastolic filling patterns are expected for different age groups. In the normal, young individual, left ventricle elastic recoil is vigorous and myocardial relaxation is swift. As a result, approximately 85-95% of left ventricle filling occurs in early diastole and only a small proportion of filling occurs with atrial contraction (5-15%) (Anderson, 2004).

2.10 Diseases associated with diastolic dysfunction

The major causes of diastolic dysfunction include:

- Chronic hypertension
- Hypertrophic cardiomyopathy
- Aorta stenosis
- Coronary artery disease
- Restrictive cardiomyopathy eg. Amyloidosis.
- Ageing

However with regard to this study, the common confounding factors were limited to patients with clinical risk factors of alcohol consumption, smoking, hypertension, ischemia, cholesterol, diabetes and ageing affects as well as patients that are overweight and the researcher shall elaborate only on the above-mentioned risk factors in the literature review.

2.10.1 Alcohol

The long term consumption of alcohol is linked to the weakening of the heart muscle known as cardiomyopathy (Ettinger *et al.*, 1978). In a study done by "the Academy of Medical Science" in 2004 it was found that sporadic heavy drinking increases the risk of developing coronary heart disease, the most common form of heart disease (Ettinger *et al.*, 1978). They also found that men nearly double their chances of developing coronary heart disease when they drink more than eight units of alcohol per day. They also found that women have a 1,3 times greater risk in developing coronary artery disease if they consume more than 6 units of alcohol a day.

Drinking too much has the following effects on the heart:

Holiday heart syndrome: Ettinger and co-workers (1978) found that heavy alcohol consumption can cause a sudden irregular rhythm of the heart in apparently healthy people. This can result in shortness of breath, changes in blood pressure and an increase in the risk of a heart attack and even sudden death.

Increased risk of thrombosis: it was found by Mc Kee and Britton (1998) that alcohol can affect the levels if homocysteine in the blood. This in turn increases the risk of coronary artery disease.

Increase of blood pressure: According to the Department of National Health of Australia, men who regularly consume more than 8 units of alcohol a day have a four times higher risk of developing hypertension. Women who regularly consume more than 6 units of alcohol have double the risk of developing high blood pressure (Dept of Health, 2007).

Enlargement of the heart: Regular heavy drinking may lead to heart failure (British Heart Foundation and Disease).

2.10.2 Smoking

Research done by McGill and co-workers (1963) has confirmed that smoking can damage the blood vessels. Atherosclerosis begins in childhood and progresses from fatty streak to raised lesions in adolescence and young adulthood (McGill *et al.*, 1963; Stary, 1989; Strong *et al.*, 1963).

As individuals get older and enter middle age, raised lesions increase in size and continue to accumulate lipid and become susceptible to rupture of the fibromuscular cap and the overlying endothelium that can lead to occlusive thrombosis and ischemic injury to the brain or the heart (Constantinides, 1966; Fuster *et al*., 1992). They looked at the arteries of people 15-34 years of age who died from car accidents, suicide or murder and they looked for evidence of fatty built up in blood vessels, and measured the levels of cholesterol as well as thiocyanate which are markers of cigarette smoking. They found that the smokers showed more early signs of atherosclerosis than the people that have never smoked.

Ridolfe *et al*. (1998) found that smoking is one of the major risk factors for heart attack and the risk increases with length and intensity of exposure to cigarette smoke. They also found that in people less than 65 years of age it is estimated that 36% of men with coronary artery disease and 33% of women with coronary artery disease smoked.

Cigarette smoking is considered as one of the most important correctable risk factors for cardiac morbidity and mortality (Holbrook *et al.,* 1984; Zeiher *et al*., 1995). The immediate hazardous effects of smoking include, transient elevation of blood pressure and heart rate (Failla *et al*., 1997; Ijzerman *et al.,* 2003). In a study done by Alam and co-workers (2002) they found a smoking-related decrease in transmitral early velocity, an increase in late velocity, and a decrease in the ratio between early and late velocities immediately after smoking cigarettes, compared with baseline values before smoking.

2.10.3 Overweight

Since 1970 the prevalence of obesity among children between the ages 2 and 5 years has doubled and that of children and adolescents between the ages of 6 and 19 years has tripled. More than 17% or 9 million children and adolescents in America are now considered overweight (Hedley *et al*., 2004; Ogden *et al*., 2006).

An elevated body mass index is associated with several risk factors for heart disease including hypertension, dyslipidemia and diabetes (Freedman *et al*., 1999).

Freedman and co-workers (2005) found that overweight adolescents are likely to become obese adults.

Obesity is a chronic medical problem with increased prevalence in the world today and is now recognised as a global epidemic (Flegal *et al*., 2002). The risk of a premature death is doubled in obese people when compared to non-obese individuals and the risk of death from cardiovascular disease is 5 times higher (Echel *et al*., 2005; Isomaa *et al*., 2003).

Obesity is frequently associated with insulin resistance and is an independent risk factor for cardiovascular disease. Type 2 diabetes, hypertension and dyslipidemia are also found in association with insulin resistance. In a study done by Peverill *et al*. (2004) there were significant differences between septal E' and S' in their relationship to body size. The septal E' was negatively, rather than positively associated with body size. Secondly, the septal E' was not related to height but instead was associated with markers of fat-mass weight and BMI. Previous studies showed evidence that obesity is associated with abnormalities of diastolic function and that the effect of obesity may be independent of left ventricular mass (Chakko *et al*., 1991; Iacobellis *et al*., 2002).

2.10.4 Hypertension

Clinical and epidemiological studies have shown that a high proportion of patients with congestive heart failure have normal left ventricular ejection fraction (Devereux *et al*., 2000; Dougherty *et al*., 1984; O'Connor *et al*., 2000; Soufer *et al*., 1985).
These patients have a high prevalence of arterial hypertension in which the presence of congestive heart failure has widely been attributed to isolated diastolic dysfunction. These hypertensive patients have shown a high prevalence of diastolic dysfunction on echocardiographic studies done on them (Rusconi *et al*., 2001; Wachtell *et al*., 2000).
Commonly used parameters for measuring left ventricle systolic function are the ejection fraction and the shortening fraction; however, these parameters may have limitations as measurement of contractile properties of the left ventricle. The global assessment of left ventricle performance by means of ejection fraction does not take regional contractile function into consideration, and fractional shortening primarily reflects radial contraction of the left ventricle caused by the circular myocardial fibres (Poulsen *et al*., 2003).

Abnormal diastolic left ventricular filling is frequently found in patients with hypertension (Wahtell *et al*., 2000). Previous studies showed decreased left ventricle peak systolic

velocities in patients with hypertension and hypertrophy (Pela *et al.*, 2001; Vinereanu *et al.*, 2001).

2.10.5 Cholesterol

Cholesterol is one of the fats in the body that is used to make new cell membranes as well as vitamin D and hormones and without it our bodies will not function (McPherson *et al.*, 2006). There are two main types of cholesterol according to the Heart and Stroke Foundation.

Low-density lipoprotein (LDL) cholesterol – often called "bad" cholesterol because high levels of LDL-cholesterol in the blood promote the build-up of plaque in the artery walls.
High-density lipoprotein (HDL) cholesterol – often called "good" cholesterol because it helps carry LDL-cholesterol away from the artery walls.

Coronary artery disease is the most common form of heart disease and is caused by build-up of plaque, which is made up of cholesterol, fatty compounds, calcium and fibrin (Texas Heart Institute, 2005).

2.10.6 Ischemia

Coronary artery disease causes loss of myocardial contraction with subsequent systolic distension in the region being deprived of blood supply (Tennant *et al.*, 1935). This is reflected by abnormalities in the wall thickening and the motion of the wall demonstrated by echocardiography, which has become a clinically important method for detecting regional ischemia (Inoue *et al.*, 1971; Quinones *et al.*, 1974).

2.10.7 Diabetes

Diabetes mellitus is a major risk factor for increased cardiovascular risks in all patients and increases the morbidity and mortality rates (Stamler *et al.*, 1993). Diabetic cardiomyopathy was described as a disease entity in patients with insulin-dependent diabetes mellitus (Attali *et al.*, 1988; Galderisi *et al.*, 1991). Despite all known factors for cardiovascular disease and diabetes mellitus the prevalence of myocardial systolic and diastolic functional abnormalities

in asymptomatic patients with non-insulin-dependent diabetes mellitus is not well defined (Annonu *et al.*, 2001).

2.11 Tissue Doppler

2.11.1 Introduction

The development of tissue Doppler imaging rendered the echocardiographic evaluation of left ventricular function more comprehensive (Miyatake *et al*., 1995 Sutherland *et al.,* 1994). The study of the mitral valve annulus motion with echo-M-mode and tissue Doppler allows the detection of systolic and diastolic changes of the left ventricular long axis shortening (Gulati *et al.,* 1996), which had previously been poorly studied because of technical and methodological difficulties. Moreover, wall motion analysis by tissue Doppler is a promising method for evaluating left ventricular filling, which has been traditionally studied noninvasively by the transmitral Doppler flow. At present, studies evaluating left ventricular function by echo-tissue Doppler, either in healthy individuals or in patients with heart disease, are still incomplete (Garcia *et al*., 1996; Gulati *et al.,* 1996; ; Heinen *et al*., 1999; Miyatake *et al.,* 1995; ; Sohn *et al.*, 1997; Sutherland *et al.,* 1994; Zamorano *et al*., 1997).

Tissue Doppler imaging has evolved to become a useful noninvasive method that can complement other echocardiographic techniques in the assessment of left ventricular myocardial velocities in a variety of clinical conditions (Waggoner *et al*., 2001).

Conventional Doppler echocardiography permits the determination of the velocity and direction of blood flow through the heart and great vessels throughout the cardiac cycle as a function of time. Doppler tissue imaging (DTI), on the other hand, records systolic and diastolic Doppler velocities within the myocardium and at the corners of the mitral annulus (Anderson, 2004).

2.11.2 Physiology of tissue Doppler imaging

Mitral-inflow pulsed-wave Doppler is the standard echocardiographic method for assessment of left ventricular diastolic function. The technique measures intracavity gradients, which are dependent on left ventricular relaxation, preload, and end-systolic volume, and atrial and ventricular stiffness (Appleton *et al.,* 1988; Nishimura *et al.,* 1989). Doppler tissue imaging

(DTI) is a new technique that enhances low velocity, high-amplitude signals of myocardial motion and allows direct quantification of myocardial velocities (Donovan *et al.*, 1995; Palka *et al.*, 1995; Garcia *et al.*, 1996; Hada *et al.*, 1996) and assessment of regional myocardial systolic and diastolic function (Bach *et al.*, 1996; Derumeaux *et al.*, 1998).

Peak early myocardial diastolic velocity is relatively load-dependent and provides assessment of left ventricular filling pressure (Nagueh *et al.*, 1997). It correlates with the time constant of isovolumetric relaxation (Oki *et al.*, 1997; Oki *et al.*, 1998). Myocardial velocities provide additional value over mitral or pulmonary vein inflow indices and differentiate pseudo normal from a normal Doppler mitral inflow pattern (Farias *et al.*, 1999; Sohn *et al.*, 1997).
Firstly, conventional Doppler echocardiography sets filters to detect signals within the range of intracardiac blood flow velocities (15 to 100 cm/s). Secondly, the amplitude of signals arising from moving blood cells is fairly low (0 to 15 dB).

However, myocardial Doppler signals have important acoustic differences compared with blood. Firstly, myocardial wall motion velocity is much slower than blood flow velocity (usually less than 10 cm/s). Secondly, the Doppler signal intensity of wall motion is much greater than that of the Doppler signals arising from red blood cells (greater than 40 dB). For these reasons, adjustments must be made to record low-velocity, high-intensity myocardial signals (Azevedo *et al.*, 1997).

Myocardial DTI E/A wave ratio is helpful in the early assessment of diastolic dysfunction in patients with hypertension (Azevedo *et al.*, 1997), in transplantation rejection (Puleo *et al.*, 1998), and in diagnosis of restrictive cardiomyopathy (Garcia *et al.*, 1996). Besides decreased amplitude of diastolic myocardial motion, left ventricular hypertrophy leads to delay in onset and slowing of left ventricle diastolic relaxation (Nishimura *et al.*, 1989; Appleton *et al.*, 1998). The influence of left ventricular hypertrophy with preserved systolic function on the duration of myocardial diastolic velocities has not been determined (Tasneem *et al.*, 2001).

Doppler assessment of left ventricular filling and more recently pulmonary venous flow have been used to estimate different parameters of left ventricular diastolic function, including left ventricular filling pressure, relaxation, and stiffness (Appleton *et al.*, 1988; ; Hoit *et al.*, 1994; Labovitz *et al.*, 1987; Nishimura *et al.*, 1989). Analytical models, animal experimentation, and human studies have demonstrated that not only the rate of isovolumic ventricular

relaxation but also preload, end-diastolic volume, and atrial and ventricular stiffness are determinants of standard pulsed Doppler filling indexes (Appleton *et al.*, 1993; Choong *et al*., 1987; Choong *et al.*, 1988; Thomas *et al.*, 1991). Impairment of left ventricular relaxation results in prolongation of the isovolumic relaxation time, reduction in early transmitral flow velocity (E) with prolongation of the E-wave deceleration time, increased atrial contraction velocity, and increased systolic (S) pulmonary venous flow (Basnight *et al*., 1991; Nishimura *et al*., 1997).

In contrast, increasing filling pressure shortens isovolumic relaxation time, increasing early transmitral gradient and transmitral flow velocities, and reducing early flow deceleration time, atrial contraction velocity and pulmonary vein systolic flow. Hence, all the standard pulsed Doppler filling indexes change in a typical parabolic or U-shaped pattern during the progression from normal to severe diastolic dysfunction (Appleton *et al.*, 1988; Little *et al.*, 1995). Determining whether a specific Doppler pattern corresponds to a patient in "left" versus the "right" limb of the parabola is often difficult unless other relevant clinical and/or invasive information is available (Appleton *et al*., 1992; Choong *et al.*, 1988; Colan *et al*., 1985; Ishida *et al*., 1986).

Doppler tissue echocardiography is a recent Doppler application that allows direct measurement of myocardial velocities. In one approach, the velocities of left ventricular motion in its axial plane are obtained by interrogating the basal myocardial segment near the mitral annular region from the apical acoustic window (Garcia *et al.*, 1996; Isaaz *et al*., 1993;). Peak early diastolic myocardial velocity has been shown to correlate well with the time constant of isovolumic relaxation (Oki *et al.*, 1997) and appears to be relatively independent of preload (Sohn *et al*., 1997).

Doppler myocardial velocities have been found to be clinically useful in differentiating patients with restrictive cardiomyopathy from those with constrictive pericarditis in whom left ventricular relaxation is normal (Garcia *et al.*, 1996). Movement and velocities of cardiac structures are related to underlying systolic and diastolic function of the heart. Tissue Doppler provides a means for measuring and displaying cardiac wall motion velocities. Tissue velocities are lower (5 to 20 cm/s) than blood-flow velocities. Although tissue velocities with low frequency are filtered during conventional Doppler recording of blood-flow velocities, tissue Doppler rejects high frequencies to measure wall motion velocities.

Tissue Doppler velocities can be recorded directly or can be auto correlated to a colour scheme (Oh *et al.,* 1999). Isaaz *et al.* (1989) were able to obtain a pulsed Doppler profile of the left ventricle posterior wall, and this concept was expanded by McDicken *et al.* (1992), who developed a prototype of colour Doppler velocity display of myocardial wall dynamics. Since these reports, tissue Doppler imaging of normal and abnormal wall motion has been reported. Several investigators have used tissue Doppler to evaluate regional and global diastolic function in the setting of acute ischemia and diastolic heart failure (Fernandez *et al.,* 1998), and it has been noted that mitral annulus velocity measured by tissue Doppler is an indicator of myocardial relaxation, relatively unaffected by preload or afterload. This property of mitral annulus velocity appears to be useful in estimating left atrial pressure in conjunction with mitral inflow E velocity (Oh *et al.,* 1999).

Doppler tissue imaging or tissue Doppler has been applied to evaluate diastolic function by measuring mitral annulus velocity during diastole. The mitral annulus velocity profile during diastole reflects the rate of changes in the long-axis dimension and in left ventricle volume. When myocardial relaxation is abnormal, the ratio of mitral annulus motion during atrial systole to the total diastolic annular motion is increased (Oh *et al.,* 1999). Sohn *et al.* (1997) demonstrated that mitral annulus velocity determined by DTI is relatively preload-dependent and is useful in differentiating pseudo normal (grade 2 diastolic dysfunction) from normal mitral inflow velocity pattern. Mitral annulus velocities are markedly decreased in patients with restrictive cardiomyopathy, which is clinically useful in distinguishing it from constrictive pericarditis, which has a preserved mitral annulus velocity (Garcia *et al.,* 1996).

Using the early diastolic velocity of the mitral annulus (E') as pre-independent index of left ventricle relaxation, E/E' has been found to correlate well with mean pulmonary capillary wedge pressure (Nagueh *et al.,* 1997). Tissue Doppler echocardiography allows for quantitative measurement of myocardial motion. Mitral annulus velocity in diastole is reflective of changes in velocity for the left ventricle long axis. In normal hearts, the long axis and circumferential motion are approximately the same. By recording mitral annulus motion from the apex, the effect of myocardial translation is minimised. A typical spectral pattern will demonstrate a single systolic velocity towards the left ventricle centroid (Sm) and two signals away from the centroid during early (Em) and late (Am) diastole.
This method appears to be relatively insensitive to preload; therefore it may help differentiate normal from pseudo normal filling. With abnormal active relaxation, mitral annulus motion

during diastole (atrial systole) is increased. Mitral annulus velocity is markedly reduced with restrictive cardiomyopathy, but with constrictive pericarditis, the velocities are preserved.

With ageing the Em:Am (Fig 2.7) ratio decreases. For mitral annulus spectral recordings the pulse-wave sample box should be 3-7 mm, the TDI function activated, Doppler gain reduced and wall filters minimised. At the mitral annulus the sample box may be placed in the septum, lateral, anterior of inferior aspects to help differentiate pseudo-normal from normal filling. For the young, normal Em is greater than 10 cm/s, and for adults normal Em is greater than 8 cm/s. For abnormal relaxation, pseudo-normal and restriction to filling Em should be less than 8 cm/s (Kerut *et al.*, 2004).

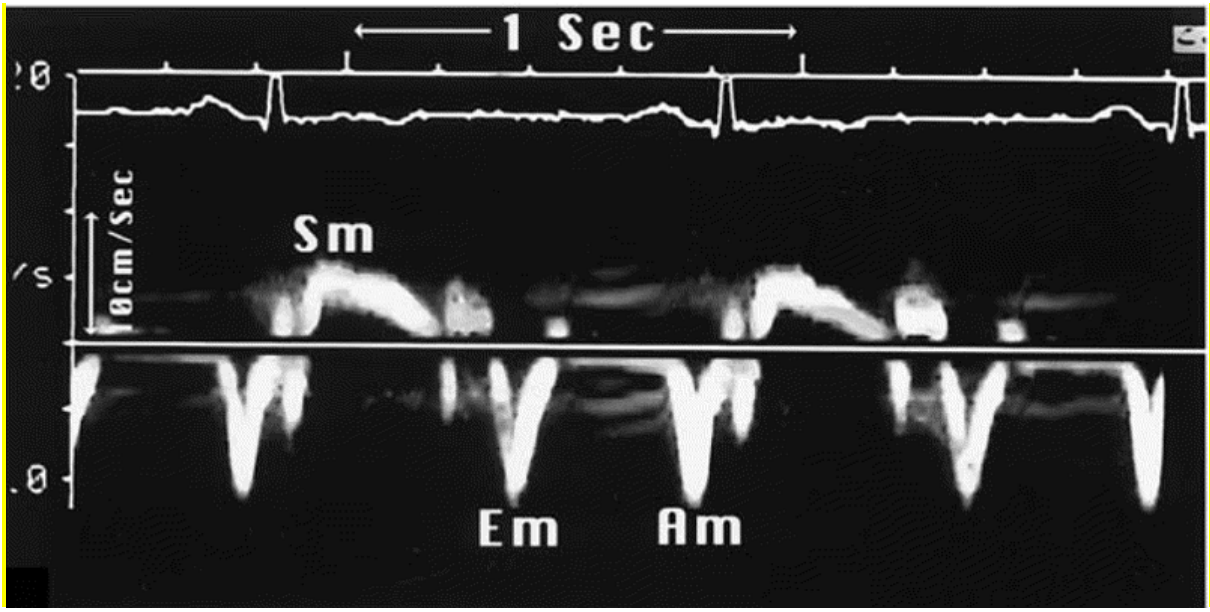

Fig. 2.7 *Myocardial velocities recorded from apical view include apically directed systolic velocity (Sm wave), atrially directed early myocardial lengthening velocity (Em wave), and atrially directed late myocardial lengthening velocity (Am wave). Less prominent biphasic velocities were seen during isovloumic contraction and relaxation phases as well.*

2.11.3 Methods for obtaining tissue Doppler images

Current DTI settings measure velocities in a range of 0.2-40 cm/s and detect amplitudes of greater than 20 dB.

DTI velocities may be displayed as either spectral PW Doppler velocities or colour-encoded M-mode or 2-D mode. However, for the purpose of diastolic function assessment, DTI velocities are best displayed as spectral PW Doppler velocities because this modality provides high temporal and velocity range resolution as well as displaying quantitative velocity information. Myocardial velocities can be recorded by placing the PW Doppler sample volume at the lateral corner of the mitral annulus from the apical four-chamber view. Myocardial velocities may also be recorded from the septal side of the mitral annulus manner. When recorded from the apical views, the myocardial velocities are composed of three components. These components include:

- An apically directed systolic myocardial velocity (Sm):
- An early diastolic atrially directed myocardial velocity (Em): and
- A late diastolic atrially directed myocardial velocity (Am).

In addition to these three distinct velocities (Fig. 2.7), less prominent biphasic velocities can be seen between the Sm and Em waves during left ventricular isovolumic relaxation period and between Am and Sm waves during the isovolumic contraction period. Since the velocity of annular motion reflects shortening and lengthening of the myocardial fibres along a longitudinal plane, it has been suggested that the early diastolic velocity recorded at the septal or lateral corner of the mitral annulus can provide an index of left ventricular relaxation which is not affected by the LA pressure (Anderson, 2004). In particular, it has been suggested that the Em can be used in the differentiation between normal and pseudo-normal filling profiles (Farias *et al.*, 1999; Nagueh *et al.*, 1997).

Table 2.1 Normal values for the mitral annulus velocities derived by DTI

Author (year)	PT NO.	Sampling site	Em velocity (cm/s)	Am velocity(cm/s)
Sohn *et al.,* 1997	59	Septal side	10.0 ± 1.5	9.5±1.5
Nagueh *et al.*, 1997	34	Lateral side	12 ± 2.8	8.4 ± 2.4
Farias *et al.,* 1999	27	average	16.0 ± 3.8	11.0 ± 2.1

PT (Patient numbers); Em (initial muscle relaxation); Am (atrial contraction muscle relaxation)

Table 2.2 Values of the mitral Em velocity (initial muscle relaxation) derived by DTI separating abnormal relaxation, pseudonormal, and restrictive physiology from the normal

Author (Year)	Normal	Abnormal relaxation	Pseudonormal	Restrictive physiology
Nagueh *et al.*, 1997	12 ± 2.8	5.8 ± 1.5	5.2 ± 1.4	_
Farias *et al.*, 1999	16.0± 3.8	7.5 ± 2.2	7.6 ± 2.2	8.1 ± 3.5

Isaaz *et al.* (1989) first reported the use of TDI in the evaluation of left ventricular function with pulsed Doppler recordings of intramyocardial velocities in the posterior wall. The use of colour TDI, including M-mode and 2-dimensional instrumentation, was subsequently reported by Sutherland *et al.* (1994). Tissue Doppler imaging methods have required modifications in signal processing of the returned Doppler signals. The high-pass wall filters, which are used to eliminate the low-velocity and high-amplitude signals of myocardial walls for detection of blood flow velocities in conventional Doppler/colour-flow modalities, are bypassed for TDI. In addition, gain amplification is used to enhance low-velocity myocardial signals and eliminate the blood flow signals within the cardiac chambers (Sutherland *et al.*, 1999).

When pulsed-wave TDI is performed, spectral gain settings often must be reduced to optimally record the low-velocity and high-intensity signals from the myocardial walls. Because the myocardial velocities are low (<25 cm/s), an appropriate scale must also be incorporated to obtain proper display and accurate measurements (Waggoner *et al*., 2001). When colour TDI is used, the 2-dimentional imaging gain must be reduced for optimal colour display of myocardial velocities. To display myocardial velocities, colour TDI employs autocorrelation methods, similar to those used for conventional colour-flow imaging (Waggoner *et al*., 2001).

Preset TDI controls are present on some ultrasonographic systems and should be used for proper acquisition of myocardial velocities. It is particularly important that the system is optimised to filter out the high-velocity signals of blood flow within the cardiac chambers and display only the low-velocity and high-amplitude signals of the wall motion velocities. A 2.5 to 4 MHz transducer should be used for imaging (Waggoner *et al*., 2005). When using colour TDI, the colour sample window can be placed within a specific wall segment to be analysed or placed to encompass the entire area of the left ventricle image. After image acquisition and digital storage, further analysis can be completed off-line by novel software programmes (Waggoner *et al.*, 2001).

Pulsed TDI, as opposed to colour TDI, offers improved temporal resolution and the ability to quantify peak rather than mean myocardial velocities. It does not require off-line analysis, and it provides instantaneous display of the Doppler spectral information. A small sample volume (2 mm axial length) is used for accurate placement in the myocardium within the boundaries of the endocardium and epicardium. The sample gate can be placed at any site within the 2-dimensional image in either parasternal or apical windows. Pulsed TDI has limitations because only regional quantification of myocardial velocities can be done at selected sites, and sampling cannot be localised to the endocardial or epicardial layers (Sutherland *et al.*, 1994).

When using pulsed TDI, the preset function should be employed if it is available on the ultrasonographic system. The myocardial area of interest to be assessed should be placed in the centre of the ultrasound beam for parallel alignment of the sample cursor. The Nyquist limit should range from 20 to 30 cm/s, with a minimum gain and low wall filter settings. The monitor sweep speed should be set at 50 to 100 mm/s to optimise the spectral display of

myocardial velocities (Pellerin *et al.*, 1999; Uematsu *et al*., 1995). Colour or pulsed TDI performed in parasternal long-or short-axis views enables assessment of the anteroseptal or inferoposterior left ventricle wall velocities with pulsed Doppler, colour TDI, or colour M-mode echocardiography.

Colour TDI is visually appealing and discloses differential velocities between the subendocardial and subepicardial layers during systole and diastole (Uematsu *et al*., 1995; Pellerin *et al.*, 1999) (Table 2.1). Colour M-mode TDI can be superior to 2-dimensional colour TDI for the temporal display of these velocity differences, but it is limited because of the M-mode cursor orientation in most systems. With colour TDI, a higher velocity of shortening and relaxation can be observed in the endocardium compared with the epicardium, and it can be quantified as a myocardial velocity gradient (Pellerin *et al.*, 1999; Uematsu *et al*., 1995). Myofibre orientation in the anteroseptal and posterior myocardial regions in the parasternal long-axis view is perpendicular to interrogation with TDI methods. As such, the quantification of myocardial velocities may be influenced by angle, excessive motion of the heart anterior in the chest, and cardiac translation (Pellerin *et al.*, 1999; Uematsu *et al*., 1995).

An alternative approach includes the use of pulsed TDI in the apical views. The apical imaging approach is feasible in most patients and provides a method for the assessment of left ventricle long-axis shortening and lengthening. Typically, pulsed Doppler sampling is performed in the basal regions of the left ventricle, adjacent to the mitral annulus, for assessment of regional systolic and diastolic myocardial velocities in the lateral, septal, anterior, and inferior walls and the anteroseptal and posterior segments (Azevedo *et al.*, 1996; Gulati *et al.*, 1996; Rodriguez *et al.*, 1996). Recent investigators have reported that pulsed TDI measurement of myocardial velocities also can be obtained in the mid and apical regions of the left ventricle. Adequate myocardial velocities signals are sometimes difficult to obtain in these segments, particularly in the apex (Galiuto *et al*., 1998; Pai *et al.*, 1998).

The motion of the mitral annulus can be assessed with TDI for determination of global left ventricular systolic function, similar to the manner in which conventional 2–dimensional or M-mode imaging provide measurements of the descent of the base (Pai *et al*., 1991; Simonson *et al*.,1989).

Myocardial velocities recorded with pulsed TDI have 3 main components. These include systolic, early diastolic and late diastolic velocities. Directionality of the TDI velocity display

is dependent on location of the pulsed Doppler sample volume relative to the myocardial site. The systolic myocardial velocity (Sm) may show 2 components in some patients, representing isovolumic contraction and the systolic ejection phase. The diastolic component is very similar in appearance and timing to mitral flow velocities obtained with conventional pulsed Doppler: an early diastolic myocardial velocity (Em) at the time of atrial contraction.

Both Em and Am are present in sinus rhythm, but during atrial fibrillation or tachycardia, Am may not be evident. In addition, an isovolumic relaxation velocity can be seen. Measurements include Sm, Em and Am and the ratio of Em/Am (Table 2.2). Time intervals of isovolumic contraction and relaxation may have application for regional function. Pulsed TDI may be influenced by cardiac translation, but the effect is lessened with the use of apical windows (Waggoner *et al*., 2001).

Otto (2004) also explained that on 2D echocardiography, the mitral annulus moves towards the ventricular apex in systole, with the magnitude of this motion proportional to the extent of shortening in the ventricular length, a useful measure of overall left ventricular systolic function. Normal subjects have motion of the mitral annulus toward the apex equal or greater than 8mm, with a mean value of round and about 12 (2) mm in both four and two chamber views.

The sensitivity of mitral annulus motion < 8 mm is 98% with a specificity of 82% for identification of an ejection fraction < 50% (Otto, 2004).

2.12 Muscle Performance Index

2.12.1 Introduction

An index of myocardial performance has been devised to incorporate both systolic and diastolic time intervals in expressing global ventricular performance (Tei *et al.*, 1995). The index of myocardial performance incorporates both systolic and diastolic time intervals for evaluation of global ventricular performance. Whereas systolic dysfunction will result in a prolonged isovolumic contraction time and a shortened ejection time, both systolic and diastolic dysfunction results in a prolonged isovolumic relaxation time (Kerut *et al*., 2004).

Myocardial performance index is a noninvasive, quantitative, Doppler-based measure of global cardiac function, which integrates systolic and diastolic function (Dandel *et al.*, 2004; Tei *et al.*, 1995). Muscle performance index is a ratio derived by the sum of isovolumic contraction time and isovolumic relaxation time divided by left ventricle ejection time (Fig. 2.8). The normal value for this parameter has been determined to be 0.39 ± 0.05 (Tei *et al.*, 1995).

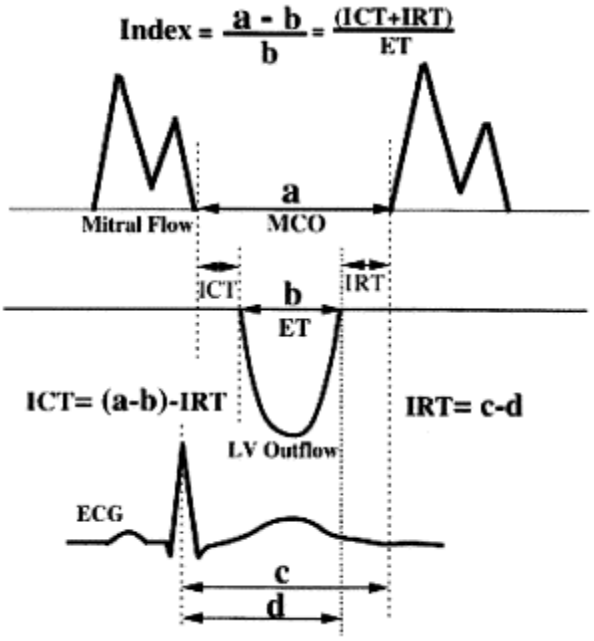

Fig 2.8 *Method used for calculating left ventricular index of myocardial performance, defined as (a-b)/b, whereas A is interval between cessation and onset of mitral inflow, and b is ejection time (ET) of LV outflow. Isovolumic relaxation time (IRT) is measured by subtracting interval between R wave and onset of mitral flow. Isovolumetric contraction time (ICT) is obtained by subtracting IRT from (a-b). Reproduced with permission (Adapted from Tei et al., 1996)*

2.12.2 Importance of muscle performance index

In one third of patients with congestive heart failure, signs and symptoms of heart failure have been attributed to isolated diastolic dysfunction (Grossman *et al.*, 1991). In these patients, the prevalence and annual mortality differ from those of patients with other forms of cardiac failure (European Study Group *et al.*, 1998; Nishimura *et al.*, 1997; Zile *et al.*, 1999). Consequently, diastolic heart failure has emerged as a separate clinical entity within the last 15 years (European Study Group *et al.*, 1998; Nishimura *et al.*, 1997; Zile *et al.*, 1999). Published criteria for diastolic heart failure are the presence of signs or symptoms of heart failure, evidence of abnormal relaxation or filling, and an ejection fraction of at least

45% (European Study Group *et al.*, 1998). The Tei index (or muscle performance index) has been found to be a valuable quantitative echocardiographic index of ventricular function by incorporating both systolic and diastolic performance of the right and left ventricles (Tei *et al.*, 1997).

It is defined as the sum of isovolumic contraction and relaxation times divided by the ejection time, which requires measurement of the time interval between the end and onset of mitral or tricuspid inflow and the ejection time of the left ventricle or right ventricle outflow. Currently employed measurements of systolic function are dependent on preload, such as ejection fraction, and non-invasive measurements of diastolic function are still being established. Nonetheless, the Tei index is easy to perform, reproducible, and independent of heart rate and blood pressure (Harada *et al.*, 1998; Harjai *et al.*, 2002). It is relatively independent of age and also has a low degree of interobserver and intraobserver variability (Harjai *et al.*, 2002). In adults, the Tei index correlates well with invasive measures of left ventricular systolic and diastolic function (Harada *et al.*, 1998; Eidem *et al.*, 2001; Harjai *et al.*, 2002). It is also a sensitive indicator of overall cardiac dysfunction in patients with mild to moderate congestive heart failure. The Tei index is particularly useful in congenital heart disease, where the anatomy may not be suitable for conventional methods of assessing ventricular function (Eidem *et al.*, 1998; Williams *et al.*, 2000).

2.12.3 Information on the subject

Small population-based studies have shown that muscle performance index (MPI) independently predicts mortality after myocardial infarction (Poulsen *et al.*, 2000; Moller *et al.*, 2001; Symanski *et al.*, 2002; Moller *et al.*, 2003; Sasao *et al.*, 2004; Yuasa *et al.*, 2005).
Systematic evaluation of the influence of heart rate, changes in preload or afterload, and alterations in contractility on MPI have not been performed in the normal or dysfunctional left ventricle. More often, previous studies (Bruch *et al.*, 2000) have correlated ambient heart rate with MPI for groups of patients with normal and abnormal function. Despite this limitation, heart rate had little effect on both normal and abnormal left ventricle function. Similarly, the effects of preload were assessed by tilt test in theatre, which was confirmed in a study done by Lavine *et al.* (2005). Increasing the preload resulted in an increase in echocardiographic left ventricular size with a decline in index of myocardial performance. The components of the index of myocardial performance were not addressed in this study.

Lavine *et al.* (2005) also noted a reduction in the index of myocardial performance but with acute shortened IVRT and chronic left ventricle dysfunction (prolonged left ventricle ejection time).

Chapter 3

3.1 Aim of the study

The study examined the presence or frequency of systolic and diastolic changes in a cardiology practice and secondly it examined the effects that certain clinical risk factors may have on their systolic and diastolic profiles, if any.

3.2 Study Objectives

The objectives of this study were:

- To determine the occurrence of systolic changes in a specific cardiology practice;
- To determine the occurrence of diastolic changes in a specific cardiology practice;
- To determine the effects of age and body composition on the systolic and diastolic parameters; and
- To determine the influence of certain clinical risk factors on the systolic and diastolic parameters.

Chapter 4
Methodology

4.1 Study design

The study design is cross-sectional descriptive study. Variants of analysis were used.

4.2 Study lay-out diagram

See below the study lay-out of the research project (fig. 4.1).

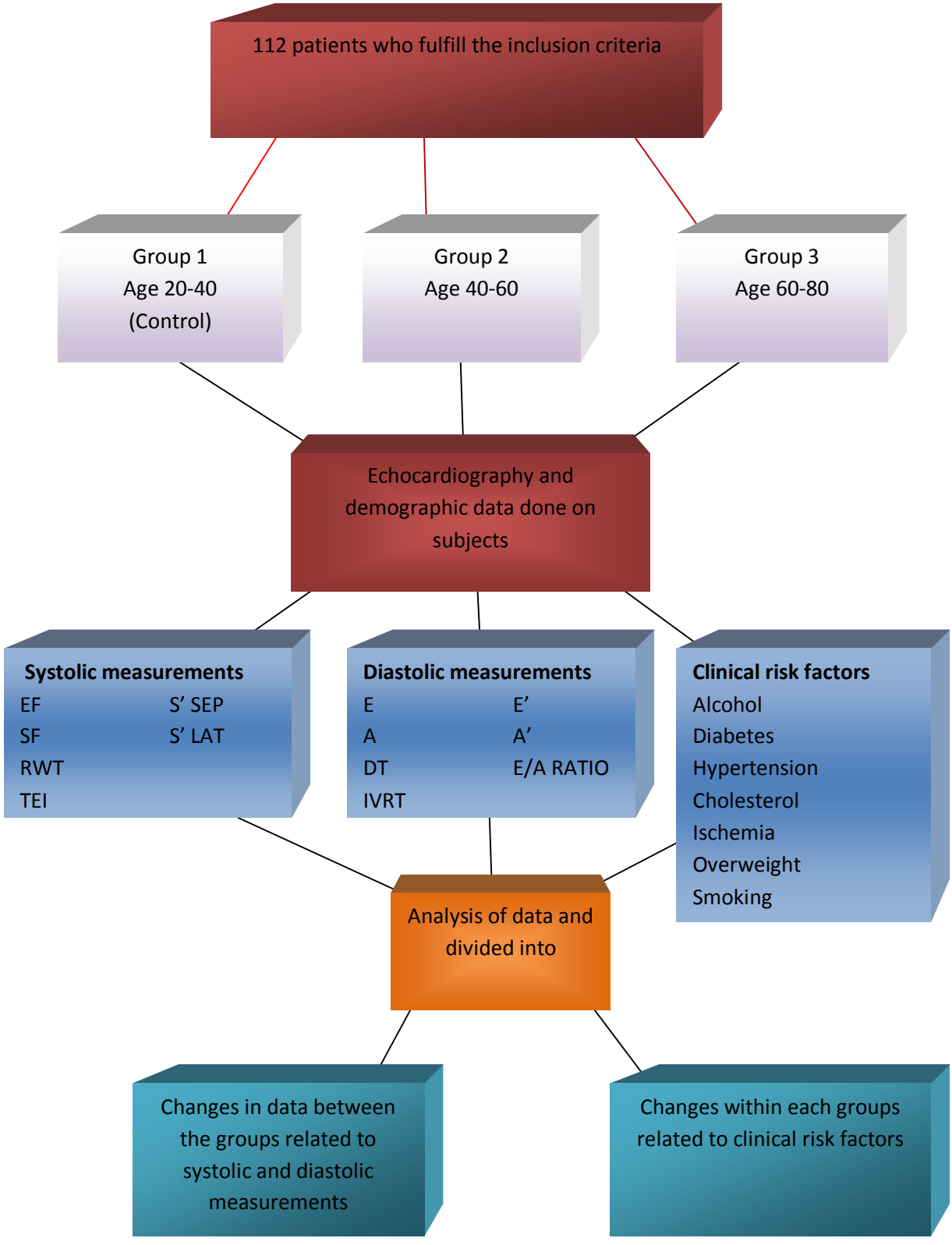

Fig. 4.1 Study lay-out of the research study

4.3 Study plan

The study was conducted at a Cardiology private practice at Medi-Clinic in Bloemfontein. The study was carried out on 112 patients who gave informed consent and fit the inclusive criteria during period July-October 2007. An Echocardiogram was done once off on all patients with an ECG connected. A patient data sheet was completed and analysed.

4.4 Study Population

4.4.1 Sample size

It was expected that 60 % of the total study population would have systolic or diastolic abnormalities. The study population was divided into 3 age groups:

Group 1: Patients with an age range between 20 and 40 years old. (Younger)

Group 2: Patients with an age range between 41 and 60 years old. (Middle age)

Group 3: Patients with an age range between 61 and 80 years old. (Elderly)

Group 1 was considered as the control group because they were recruited students from the local university and was not seen as patients in the cardiology practice, the reason for this being to test changes in the older group against variables in the younger group as reference when analysing the effect of ageing.

4.4.2 Inclusion criteria

- South Africans citizens
- Male and female patients were evaluated
- Their age between 20 and 80 years.
- Patients that are in sinus rhythm.
- Patients must have a technically adequate echocardiogram.
- No evidence of infarction or infarction areas on the echocardiogram.
- No conduction abnormalities or ventricular ectopy.
- No patients with other diseases that may influence the study parameters.
- Only patients that consented to participate in the study were used.

4.4.3 Exclusion criteria

- Technically inadequate images.
- Poor quality echocardiogram.
- Patients who do not give consent.
- Patients with regional wall motion abnormalities.
- Patients with acute infarction.
- Patients with lung disease.
- Patients with valve disease.
- Pregnant patients.
- Patients who are on beta-blockers.
- Patients with a conduction delay abnormality on the ECG.
- Patients in atrial fibrillation.
- Patients with previous bypass operation.
- Patients with an implanted pacemaker.
- Patients that take any medication that may influence the measurements to be done.

4.4.4 Justification for inclusion and exclusion criteria

- For ethical and confidential reasons all the patients gave their consent to participate in this study.
- Patients must be in sinus rhythm because an abnormal rhythm influences the measurements of systole and diastole.
- The patients should have adequate images because the importance of accurate measurements.
- They should use no medication because that can influence diastolic parameters.
- No conduction abnormalities or previous infarction was included because that influenced measurement of the diastolic or systolic parameters.
- Patients with lung disease were not included in the study because of its influence on the diastolic measurements.
- Valve disease patients were excluded because it changed the diastolic components of the cardiac cycle.
- No pregnant patients were included due to overexposure of ultrasound.
- No patients with previous bypass or pacemaker operations were included because of segmental changes on the heart muscle.

4.4.5 Withdrawal criteria

The patients could withdraw from this study at any stage. The patient's withdrawal will not be held against him/her and treatment at the Cardiologist will continue as if he/she had never enrolled in this study. No patients withdrew from the study and no dropouts were recorded during the study period.

4.4.6 Subject identification

The study subjects were identified using the same code that is usually used to file the echocardiograms in this practice, namely by using the first three letters of the subject's surname, the first initial and the year of birth. For the purpose of the study, an extra number was added that fits the consent form's number.

4.5 Study variables

The research study is very safe. There are no adverse affects from doing an echocardiogram on a patient. The information obtained from the tests done on the patients was kept strictly confidential and were available only to the researcher and the cardiologist treating the patient.

4.6 Financial implications

There was no financial implication for the study subjects other than their normal consultation fee. There were no financial implications for the private practice where the echocardiography was done because no new equipment needed to be bought and the necessary equipment was already available in the practice. The normal consultation examination was followed, but for the study additional measurements were done. There were no financial implications for the patients. The patient or his/her medical aid was only liable for the normal consultation fee to the cardiologist.

4.6 Premature discontinuation of the study

The study was not discontinued prematurely. Neither the researcher nor any other of the study leaders felt that a patient's confidentiality was breached and no unethical procedures occurred.

4.8 Methods used for data collection

- During the routine consultation an echocardiogram was performed on the patient as part of the normal cardiological examination. An ECG was connected to the patient's chest.
- This test was done by the researcher, who is a senior clinical technologist in cardiology and echocardiographer.
- The patient's height and weight were measured on a scale with height measure band and the body mass index was calculated.
- An ECG was connected as part of the echocardiography examination and used in the measurements of systolic and diastolic function.
- All the above-mentioned data were recorded and written down on the data sheet (Appendix C).
- Left ventricular ejection fraction was measured as well as the shortening fraction and all the systolic flow velocities using the Doppler echocardiography and tissue Doppler echocardiography.
- Left ventricle diastolic measurement was done using Doppler echocardiography and tissue Doppler echocardiography.
- The left ventricular mass was measured according to the recommendations of the American Society of Echocardiography (2005).
- The appropriate method for measuring mitral valve inflow is to use a two-dimensionally directed pulsed sample volume placed at the tips of the mitral valve. This is the point at which the mitral flow velocities are maximal.
- The ultrasound beam needs to be parallel with the direction of blood flow and the lowest possible filter settings were used to ensure that a full and complete Doppler flow signal was obtained
- To measure left ventricle isovolumic relaxation time the interval from aortic valve closure to mitral valve opening, a 3-4 mm size sample volume was placed in the area of the mitral leaflet tips.
- The patient was asked to exhale and keep his/her breath for a while during which the diastolic measurement was taken.
- Three beats were analysed and the mean value was taken of each of the separate values.
- All the above data were collected and included on the data sheet (See Appendix C). The patient's age was determined and also included into the data sheet.

- All the above-mentioned patients were weighed against the inclusion and exclusion criteria. Those who qualify were asked to give their written consent.
- All data on the echocardiography datasheets (Appendix C) were then processed and analysed.
- The data were analysed with the help of the Department of Biostatistics at the University of the Free State.

4.9 Apparatus

A Toshiba Powerplus 6000 echocardiographic machine with a 2.5-3.7 MHz transducer and adult package software was used in the measurements of all the parameters of systolic and diastolic function and the measurement of the index of myocardial performance. The machine also has the following facilities available:

- The measurement of tissue Doppler images.
- An ECG was connected to the patient so that gated measurements can be done.
- Have measurement analysis packages to analyse all the parameters.

All the other data were analysed afterwards using a commercially available, scientific calculator.

4.10 Special investigation (echocardiogram)

The researcher conducted all the measurements and did the echocardiogram.
The standard positioning of the patient in the partial left decubitus position with the head of the bed elevated by 30 degrees was used.

An ECG was connected by the researcher himself to determine if it matched any excluding criteria regarding any arrhythmia or conduction abnormalities. The ECG is also of importance when measurement for this study is done.

Normal echocardiography was done on all subjects. They underwent normal M-Mode and 2D and colour sonography to determine normal anatomical and physiological parameters.
Left ventricular measurements were taken just below the mitral valve tips. Measurements of the left ventricular mass using the recommendations of the American Society of Echocardiography (Sahn *et al.*, 1978) were performed. Measurements of the interventricular

septum and the internal dimension and the posterior wall thickness of the left ventricle at end-diastole according to the ECG was conducted and written down on the data sheet.

Doppler echocardiography (Oh *et al*., 1997) was conducted, placing the sample volume at the tips of the mitral valve opening at the narrowest point in a four chamber view. The patient was asked to stop breathing and measurements of the trans-mitral inflow were taken. Measurements of the E wave, deceleration time, isovolumetric relaxation time, and the A wave were performed and included on the data sheet.
Tissue Doppler imaging of the annular septum and posterior wall was conducted and measurements of the Em velocity, Am velocity and the Sm velocity were performed and included on the patient's data sheet.

In this study the use of different systolic and diastolic measurements were conducted on the patients and the researcher analysed those changes in a statistical manner to also determine the individual changes of those specific parameters and the effects they had on the muscle performance index. The measurement of the muscle performance index was conducted according to a standardized formula (See Fig. 2.8).

All measurements of this index were included in the patient data sheet (Appendix C).
The left ventricle ejection fraction was measured by using the Teicholtz formula (Teicholtz *et al*., 1976).

4.11 Statistics

A multi-variant analysis was done on the data. The data obtained from this study were analysed by an independent Biostatistician of the University of the Free State. Numerical variables were summarised by means, standard deviations or percentiles, depending on the data distribution. Categorical variables were summarised by frequencies and percentages. Differences between the groups were summarised using 95% confidence intervals for differences in means, medians or percentages.

4.12 Ethics

4.12.1 Ethical approval

Ethical approval for the research project was obtained from the Ethics Committee of the University of the Free State (ETOVS nr 95/07).

4.12.2 Consent form

Consent was needed from the physician to use the patients in his practice. A consent form had to be signed by all research subjects to be included in the study. All the patients were informed about the purpose of the study, and that there would be no extra financial burden on them, as well as that there would be no adverse effects and that this study will not have any implication on their normal treatment regime.

The researcher explained the consent form to the patients in English and Afrikaans. The patients decided in which language he/she wanted to sign the form. An information sheet in Afrikaans and English were available to all the study subjects. An example of the information sheet and the consent form are included in Appendix A and B.

4.12.3 Confidentiality

The confidentiality of this study was very important. None of the information obtained during this study was made public and would only be available to the researcher and the cardiologist treating the patient.

4.12.4 Safety of the research project

The research is very safe and the procedure that was used is a normal cardiological procedure that is used in normal practice for cardiology patients. The use of ultrasound has no adverse effect on the body and thus is safe for use on the research patients.

Chapter 5
Results

5.1 Patient demographic data

Hundred-and-fifty patients' systolic and diastolic variables were measured with echocardiography in this study. Hundred-and-twelve of these patients met the inclusion criteria. They consisted mainly of asymptomatic follow-up patients who had a history of previous heart disease or presented for routine precautionary evaluation due to the presence of certain risk factors. Group 1 was recruited as normal controls.

The study group was classified according to age: 20-40 years of age (group 1), 40-60 years of age (group 2) and from 60- 80 years of age (group 3) (See Fig. 5.1). Eighty nine percent of the patients were male and only 23 % were female.

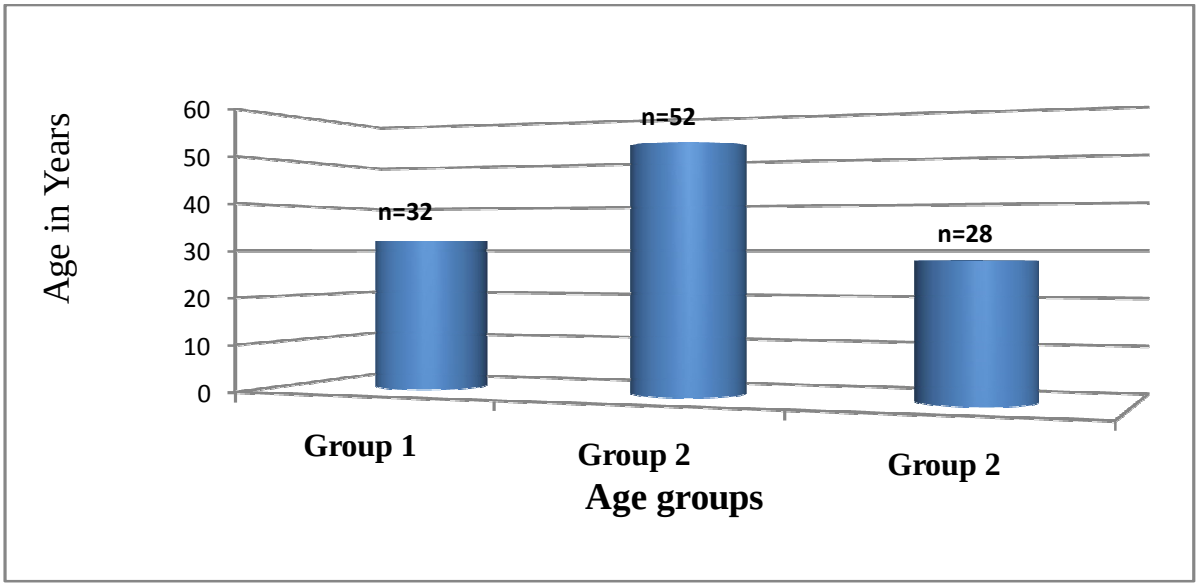

Fig 5.1 Group distribution according to age

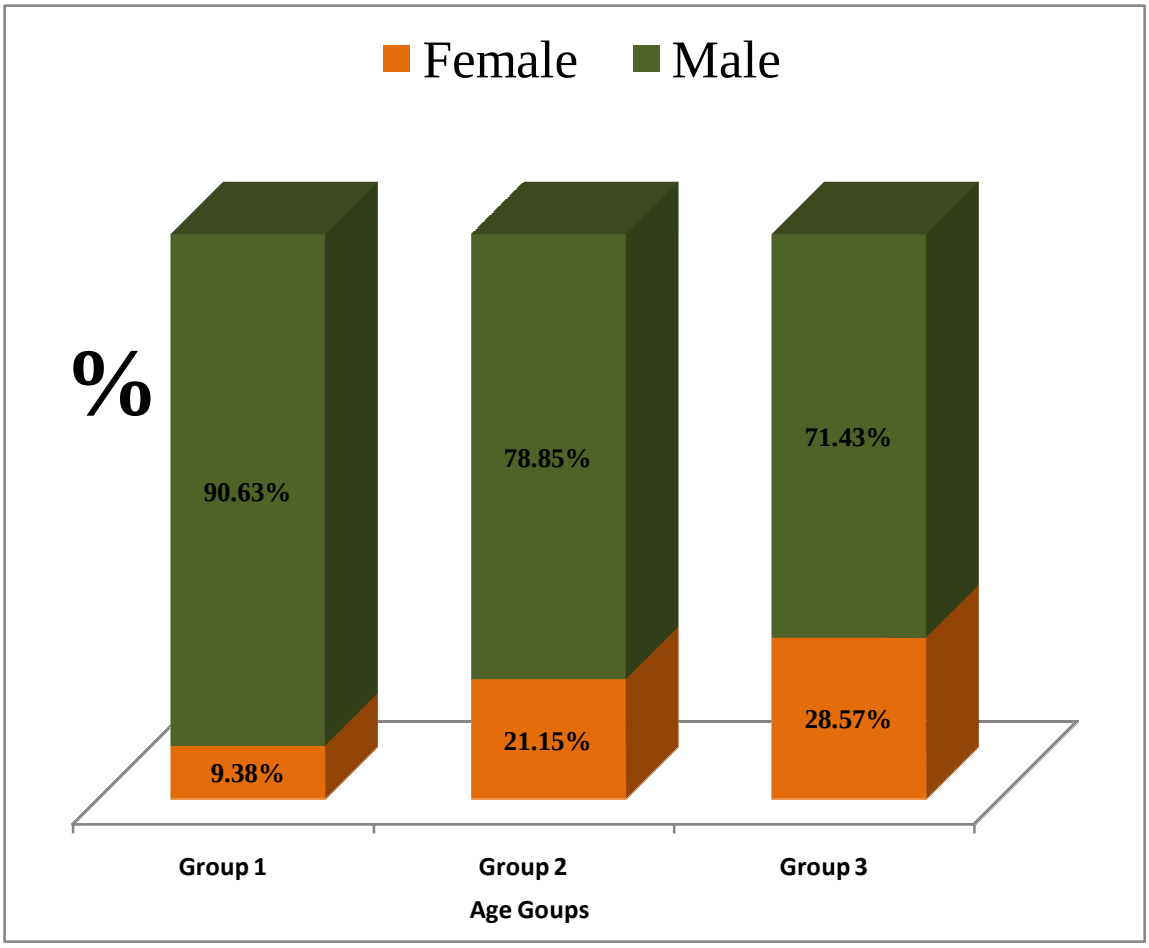

Fig 5.2 Gender distribution of the study population according to age

The gender differences were large in all the different age groups. Group 1 has the largest male percentage (90.63%) in the study group and group 3 the smallest (71.43%). Marked gender differences were present in all groups with males dominant (Fig. 5.2).

Table 5.1 Body composition of the study population according to age

	Group 1 (n=32)	Group 2 (n=52)	Group 3 (n=28)	Comparison between groups	p-value	95% CI
weight (kg)				**1-2**	*0.195*	
mean	*80.2*	*84*	*76*			
std.	*(14)*	*(15)*	*(12)*	**1-3**	*0.202*	
				2-3	*0.008*	0.42;16.6
length (cm)				**1-2**	*0.043*	-0.85;8.7
mean	*179*	*175*	*170*			
std.	*(8.1)*	*(9.1)*	*(9.2)*	**1-3**	*0.002*	3.60;14.61
				2-3	*0.020*	0.06;10.40
BSA (cm^2)				**1-2**	*#*	
mean	*1.98*	*2*	*1.9*			
std.	*(0.19)*	*(0.21)*	*(0.17)*	**1-3**	*#*	
				2-3	*#*	
BMI				**1-2**	*0.003*	-4.5;-0.47
mean	*24.9*	*27.4*	*26.6*			
stdev.	*(3.4)*	*(3.8)*	*(3.2)*	**1-3**	*0.056*	-3.79;0.45
				2-3	*0.312*	

No data available.
$p \leq 0.05$ is significant.
In Table 5.1 only data with a significant p-value (in yellow), 95% confidence interval values were indicated.

Significant differences were present between the groups with regard to weight, height and BMI (Table 5.1). A one-way Anova test in table 5.1 represents the whole study population as well as the different age groups.

The average BMI for the total group was 26.58. Group 2 had a higher BMI than the study population average. In all three age groups the male population had a higher BMI average than the female population.

The BMI was divided in 3 categories according to Laquatra (2000) classification for nutrition and weight management (Table 5.2).

Table 5.2 BMI and BSA variables in the different age and BMI groups

				BMI CATEGORIES			
Group Distribution	n	Average BSA (cm^2)	Average BMI	Underweight (< 18.50 %)	Normal weight (18.50-24.99 %)	Overweight (25.0-30.0%)	Obese (>30.0%)
Total group	112	1.96	26.58	n=1 (1%)	n=43 (38%)	n=47 (42%)	n=21 (19%)
				Group 1			
Total	32	1.98	24.9	1 (3%)	n=18 (56%)	n=10 (31%)	n=3 (10%)
Male (91%)	29	2.02	25.2	0	n=17 (59%)	n=9 (31%)	n=3 (10%)
Female (9%)	3	1.6	22.7	1 (34%)	n=1 (33%)	n=1 (33%)	n=1(33%)
				Group 2			
Total	54	1.99	27.54	0	n=16 (30%)	n=24 (44%)	n=14 (26%)
Male (78%)	42	2.07	28.28	0	n=11 (26%)	n=18 (43%)	n=13 (31%)
Female (22%)	12	1.71	24.93	0	n=5 (42%)	n=5 (50%)	n=1 (8%)
				Group 3			
Total	28	1.88	26.61	0	n=9 (32%)	n=14 (50%)	n=5 (18%)
Male (71%)	20	1.96	26.87	0	n=6 (30%)	n=10 (50%)	n=4 (20%)
Female (29%)	8	1.68	25.96	0	n=3 (32%)	n=4 (50%)	n=1 (13%)

Thirty-eight percent of the study population were classified as normal; 56% of group 1, 30% in group 2 and 32% in group 3 had a normal weight. Sixty-one percent of the total study population were overweight with 41 % in group 1, 70% in group 2 and 68% in group 3. Nineteen percent of the total study population were obese (Table 5.2).

The average body surface area (BSA) for the total study population was 1, 96 cm^2. Group 1 and 2 were almost similar to the study population average. BSA increased in groups 2 and 3 (p=0.029). The male population had on average a higher BSA in all 3 age groups. Group 3 showed a below average BSA with both the male and female groups averages below the group average height.

5.2 Left heart dimensions

The left ventricular mass was measured and indexed with the body surface area of the patients to determine if left ventricle hypertrophy was present.

Table 5.3 Left heart dimensions according to age and weight

	Age groups			BMI categories		
	Group 1 (n=32)	Group 2 (n=52)	Group 3 (n=28)	Normal (n=44)	Overweight (n=47)	Obese (n=21)
LV mass (g)						
mean	206	240	253	216	247	244
std.	(58.18)	(71.90)	(81.44)	(62.02)	(79.74)	(79.68)
LV Mass Index (g/cm^2)						
mean	100	120	130	106	122	130
std.	(23.66)	(32.14)	(35.30)	(25.76)	(34.65)	(36.82)
LV Internal dimension diastole(mm)						
mean	51	50	48	52	49	49
std.	(4.23)	(6.76)	(6.42)	(4.88)	(6.27)	(6.50)
LV Internal dimension systole(mm)						
mean	32	32	30	32	31	30
std.	(3.64)	(6.08)	(5.98)	(4.48)	(5.68)	(5.81)
Relative wall thickness (%)						
mean	0.40	0.45	0.5	0.39	0.47	0.49
std.	(0.08)	(0.12)	(0.13)	(0.07)	(0.13)	(0.03)
Left atrium internal dimension(mm)						
mean	34	37	40	34	37	40
std.	(7.20)	(7.71)	(4.89)	(6.97)	(7.56)	(5.35)

5.2.1 Muscle thickness

Table 5.3 shows a 26% increase in mass index from the normal weight group to the obese group. The left ventricle mass increased with ageing (p=0.029) with the most significant changes observed between group 1 and group 3 (p<0.005). With regards to left ventricle mass index, the largest difference were observed between group 1 and group 3 (p<0.001).

5.2.2 Left ventricle internal dimensions

Changes occurred in the internal dimension of systole and diastole with ageing. There was a 5.9 % decrease in the diastolic dimension of the left ventricle with ageing and a 6, 25% decrease in the systolic internal dimension of the left ventricle. Internal dimension was compared according to the BMI categories and no difference were detected (Table 5.3). A 5,8% decrease in internal diastolic dimension and a decrease of only 3,1 % for the systolic dimension were observed (Table 5.3).

5.2.3 Relative wall thickness

The relative wall thickness increased with 28% during ageing from group 1 to group 3 (Table 5.3). Significant differences were detected in the relative wall thickness between the different age groups: between group 1 and 2 (p=0.011), group 2 and 3 (p=0.101) and group 1 and group 3 (p=0.001). When the relative wall thickness is compared according to the BMI categories almost the same scenario is demonstrated (Table 5.3). The obese group showed a 26 % change in relative wall thickness from the normal weight group to the obese group (p=0.331).

5.2.4 Left atrium

In Table 5.3 the LA size increased 18% with ageing (p=0.007). The mean value for atrial size for the whole study population was 37 mm with only group 3 above study average (40 mm). Differences were significant for group 1 and 3 (p=0.001) and between group 2 and 3 (p=0.022) but not for group 1 and 2 (p=0.139).

5.3 Hemodynamic variables

Hemodynamic variables of the study population are indicated in Table 5.4.

Table 5.4 Mean hemodynamic variables for the study population (n=112)

	n	Heart rate (Bpm)	Stroke volume (ml)	Stroke volume index (ml/cm^2)	Cardiac output (l/min)	Cardiac output index ($l/min/cm^2$)
Total group	112					
mean		71	104	53	7.4	3.8
std.		(12.47)	(22.53)	(11.90)	(1.85)	(1.01)
Group 1	32					
mean		69	95	48	6.6	3.3
std.		(12.44)	(29.47)	(9.05)	(1.98)	(0.83)
Group 2	52					
mean		72	107	54	7.7	3.9
std.		(13.01)	(23.00)	(12.28)	(1.67)	(0.95)
Group 3	28					
mean		68	110	59	7.5	4.0
std.		(12.23)	(22.15)	(12.56)	(1.80)	(1.02)

The mean heart rate of the study population was 71 beats per minute and it more or less remained the same with ageing (p=0.230). As illustrated in Table 5.4, the stroke volume (p=0.019) and stroke volume index (p=0.002), the cardiac output (p=0.008) and the cardiac output index (p=0.001) demonstrated an increased value with ageing. The average cardiac output of group 3 was less than group 2, but correlated with a lower stroke volume in that group as well. Only group 1 showed a lower value than the study population average.

The stroke volume between groups 1 and 2 increased significantly (p=0.012) as well as between groups 1 and 3 (p=0.011) (Table 5.4). Differences in stroke volume index between group 1 and 2 (p= 0.011), group 1 and 3 (p=0.004) and group 2 and 3 (p=0.093) were present.

The cardiac output indexed to BSA increased significantly between group 1 and 2 (p=0.007) and group 1 and 3 (p=005) but no significance difference was detected between group 2 and 3 (p=0.463).

5.4 Systolic data

All relevant data for systolic variables can be viewed in Table 5.5.

Table 5.5 Systolic measurements of the left ventricle

	n	Ejection fraction (%)	Shortening fraction (%)	Ejection time (m/s)	Mean circumferential shortening (circ/s)	S' septum (cm/s)	S' lateral (cm/s)
Total group	112						
mean		67	37	283	1.3	8.5	10
std.		(7.88)	(6.05)	(23.09)	(0.23)	(1.53)	(2.35)
group 1	32						
mean		68	38	272	1.4	9.5	12
std.		(5.60)	(4.42)	(18.83)	(0.16)	(1.65)	(2.1)
group 2	52						
mean		66	37	283	1.3	8.4	10
std.		(8.38)	(6.34)	(26.02)	(0.26)	(1.43)	(2.08)
group 3	28						
mean		68	38	294	1.3	7.9	9
std.		(9.51)	(7.36)	(25.93)	(0.27)	(1.24)	(2.02)

The ejection fraction (p=0.527), shortening fraction (p= 0.594) and the mean circumferential shortening (p=0.279) did not change significantly with ageing (Table 5.5). With ageing the ejection time prolonged but not always significant between group 1 and 2 (p=0.138), group 1 and 3 (p=0.003) and between group 2 and 3 (p=0.074).

The systolic prime (S') of the tissue velocity of the septum ($p<0.001$) and the lateral wall ($p<0.001$) also decreased with ageing. S' septum ($p<0.001$) and S' lateral ($p<0.001$) demonstrated a decrease between group 1 and group 3. Between group 2 and 3 no significance ($p=0.061$) was detected in the S' of the septum, although the S' lateral of the same groups did show significant decrease ($p=0.0103$) (Table 5.5). The Tei index demonstrated normal values in all the groups but was lower in the overweight subjects of group 1 ($p=0.040$). Also, a significant lower value of the Tei index were found in group 3 with ischemic risk factors versus those without ischemia ($p=0.010$). Subjects in group 2 with diabetes had a significantly lower Tei index compared to those without diabetes ($p=0.040$).

5.5 Diastolic data

The trans-mitral E peak showed a decline with ageing ($p=0.001$). The A peak increased with ageing ($p<0.001$). The ratio measurement between the groups also decreased in value with ageing (See Table 5.6).

The isovolumetric relaxation time increased significantly ($p=0.009$) with ageing (group 1 to 3) as well as the deceleration time of the left ventricle ($p=0.001$). The ratios of the E and A peaks also changed with ageing ($p<0.001$) (Table 5.6).

Muscle velocity measurements were not affected by volume loading of the left ventricle. A decrease in the velocity of the E' of the septal aspects ($p<0.001$), as well as the lateral aspects ($p<0.001$) of the annulus, was detected. The A' showed a significant increase in velocity over the septal ($p=0.004$) and lateral annulus ($p=0.001$) (Table 5.6).

The E'/A' ratio of the septum decreased with ageing ($p=0.043$) and a significant decrease in ratio were apparent on the lateral wall ($p<0.001$).

Table 5.6 Diastolic data according to age and BMI categories.

		Age groups			BMI categories		
Variables with Mean and Std.	Total study group	Group 1	Group 2	Group 3	Normal weight	Over-weight	Obese
	(n=112)	(n=32)	(n=52)	(n=28)	(n=43)	(n=46)	(n=23)
E (cm/s)	73 (17.00)	83 (15.95)	70 (16.66)	68 (14.69)	80 (15.76)	67 (16.86)	70 14.54)
A (cm/s)	64 (18.00)	47 (11.14)	65 (12.72)	80 (16.03)	52 (15.76)	65 (16.86)	84 (14.55)
E/A	1.3 (0.52)	1.8 (0.52)	1.1 (0.33)	0.9 (0.16)	1.6 (0.55)	1.1 (0.33)	0.8 (0.15)
IVRT (ms)	100 (21.00)	92 (18.29)	101 (22.36)	107 (18.40)	173 (18.63)	193 (21.67)	238 (20.48)
DT (ms)	195 (56.63)	171 (31.71)	189 (47.03)	233 (74.05)	94 (32.50)	102 (50.40)	109 (81.92)
E' Septum (cm/s)	10 (3.02)	13 (2.25)	9 (2.13)	7 (1.43)	12 (2.60)	8 (2.20)	7 (1,37)
A' Septum (cm/s)	10 (2.22)	9 (2.01)	11 (2.31)	11 (1.66)	9 (2.17)	11 (2.19)	11 (1.65)
E'/A' Septum	1.1 (1.22)	1.5 (0.41)	1 (1.71)	0.7 (0.17)	1.3 (0.44)	1 (1.80)	0.7 (0.14)
E' Lateral (cm/s)	13 (4.44)	18 (3.88)	12 (2.70)	11 (2.93)	16 (4.02)	11 (3.03)	9 (2.92)
A' Lateral (cm/s)	12 (3.00)	9 (2.50)	12 (2.82)	13 (2.33)	10 (2.65)	12 (2.98)	13 (2.12)
E'/A' Lateral	1.2 (0.70)	2 (0.74)	1 (0.34)	0.8 (0.24)	1.7 (0.75)	1 (0.35)	0.7 (0.24)

The p- values between the different age groups are illustrated in Table 5.7

In Table 5.6 diastolic measurements mean values, associated with different BMI groups are illustrated.

The E peak decreased with increased BMI although there was a small increase from group 2 in the obese group. The A peaks also increased with abnormal BMI as it did with ageing. The deceleration time and isovolumetric relaxation time increased with increased BMI even more compared to ageing. The measurements of tissue Doppler between the BMI groups showed a similar profile as with ageing, but the E' lateral velocity decreased more with advancing BMI than with age (Table 5.6).

The p-values between the different age groups are illustrated in Table 5.7.

Table 5.7 t-test comparison between the groups of the diastolic data

	t-test comparison between groups for diastolic data			
	group 1	group 2	group 3	
E	<0.01			*
	<0.01			*
		>0.05		
A	<0.001			*
	<0.001			*
		<0.001		*
E/A	<0.001			*
	<0.001			*
		<0.01		*
IVRT	>0.05			
	<0.05			*
		>0.05		
DT	>0.05			
	<0.001			*
		<0.001		*
E' Septum	<0.001			*
	<0.001			*
		<0.01		*
A' Septum	<0.01			*
	<0.05			*
		<0.05		
E'/A' Septum	>0.05			
	<0.05			*
		>0.05		
E' Lateral	<0.001			*
	<0.001			*
		< 0.01		*
A' Lateral	<0.001			*
	<0.001			*
		>0.05		
E'/A' Lateral	<0.001			*
	<0.001			*
		>0.05		

*Significant p-values

p=value between group 1 and group 2

p=value between group 1 and group 3

p=value between group 2 and group 3

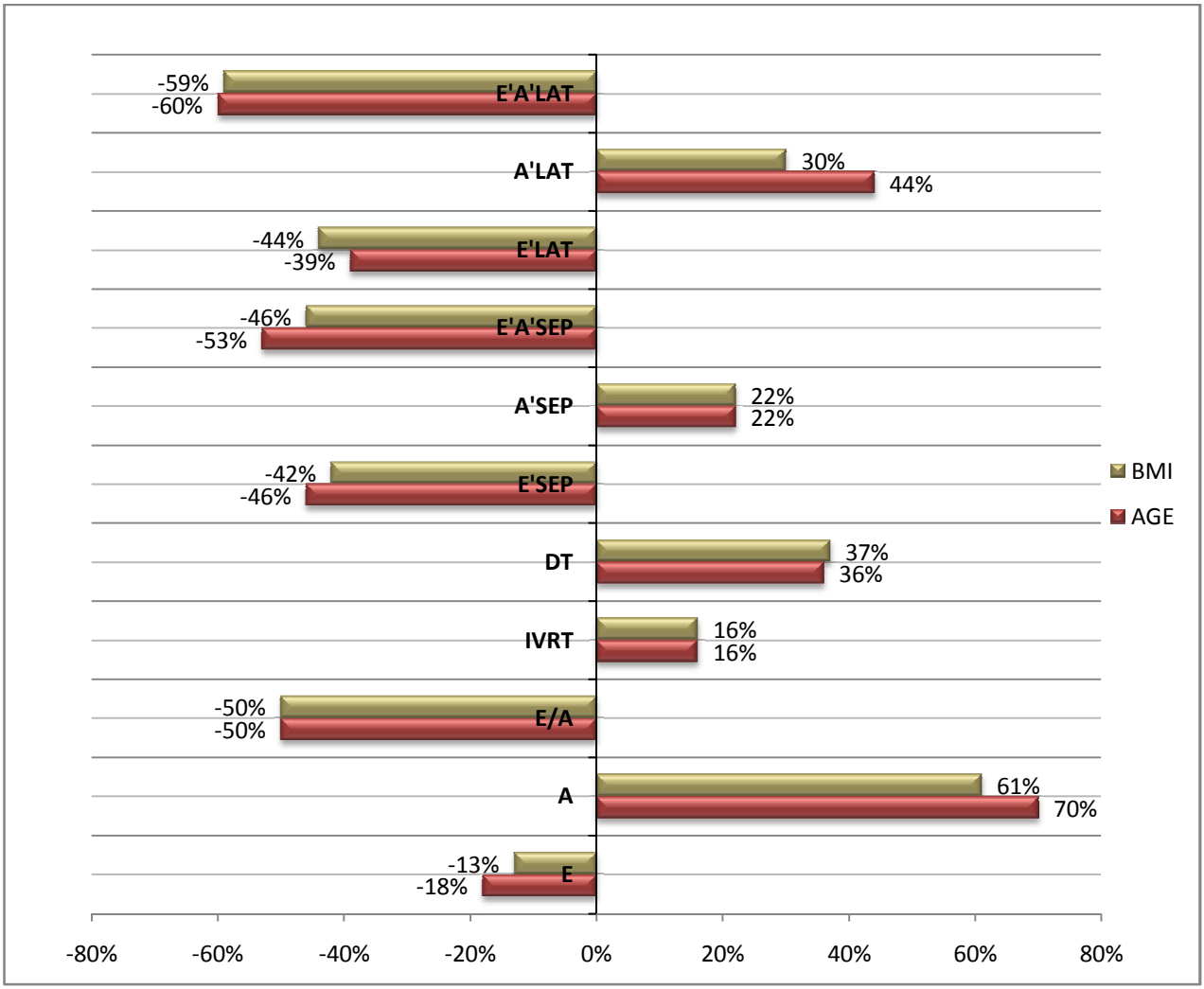

Fig. 5.3 Percentage differences of diastolic variables between ageing and BMI categories.

In Fig. 5.3 the differences in diastolic measurements were compared with the BMI and the age groups. A prominent change on the diastolic variables was detected on the A' lateral TDI. The A peak of the trans-mitral inflow also differed between the groups. From the E/A ratios the E'/A' of the septum showed the largest percentage difference amongst the two groups. The E' lateral velocity showed a 44% decrease from the normal weight group to the obese group and a 39% change from the younger group to the older group. Age appears to have a greater effect on the lateral E' parameter than the BMI (Fig. 5.3).

5.6 Clinical risk factors

Table 5.8 indicates the incidence of risk factors between the different age groups. The most prevalent risk factors are highlighted in red.

Table 5.8 Incidence of risk factors among the age groups

	Group 1 (n=32)	**Group 2** (n=52)	**Group 3** (n=28)
Alcohol (n=29)	17(53%)	11(21%)	1(4%)
Smokers (n=42)	21(65%)	15(29%)	6(21%)
Overweight (n=70)	13(41%)	38(71%)	19(71%)
Hypertension (n=47)	2(6%)	24(46%)	21(75%)
Cholesterol (n=36)	2(6%)	27(52%)	7(25%)
Ischemia (n=42)	0(0%)	21(40%)	21(75%)
Diabetes (n=7)	0(0%)	4(8%)	3(11%)

According to Table 5.8 it appears that obesity was the most dominant risk factor observed between the age groups. Group 2 and 3 had all the risk factors associated with them but group 1 did not have ischemia or diabetes as a risk factor. Group 2 had the most risk factors of all the groups.

5.6.1 Group 1

Fig. 5.4 represents the frequency of combinations of different risk factors. Each colour represents the number patients per combination of risk factors. For instance, in patients who only had one risk factor (blue bar), cholesterol was found in only one, two were overweight, four were smokers and three were alcohol consumers. In patients who had 2 risk factors (green bar), one was overweight, seven were smokers and six consumed alcohol. The group with a combination of three risk factors (red bar) nine were overweight, nine were smoking and seven consumed alcohol. With a combination of four risk factors (black bar) only one smoked, one had high cholesterol, one consumed alcohol and one was overweight.

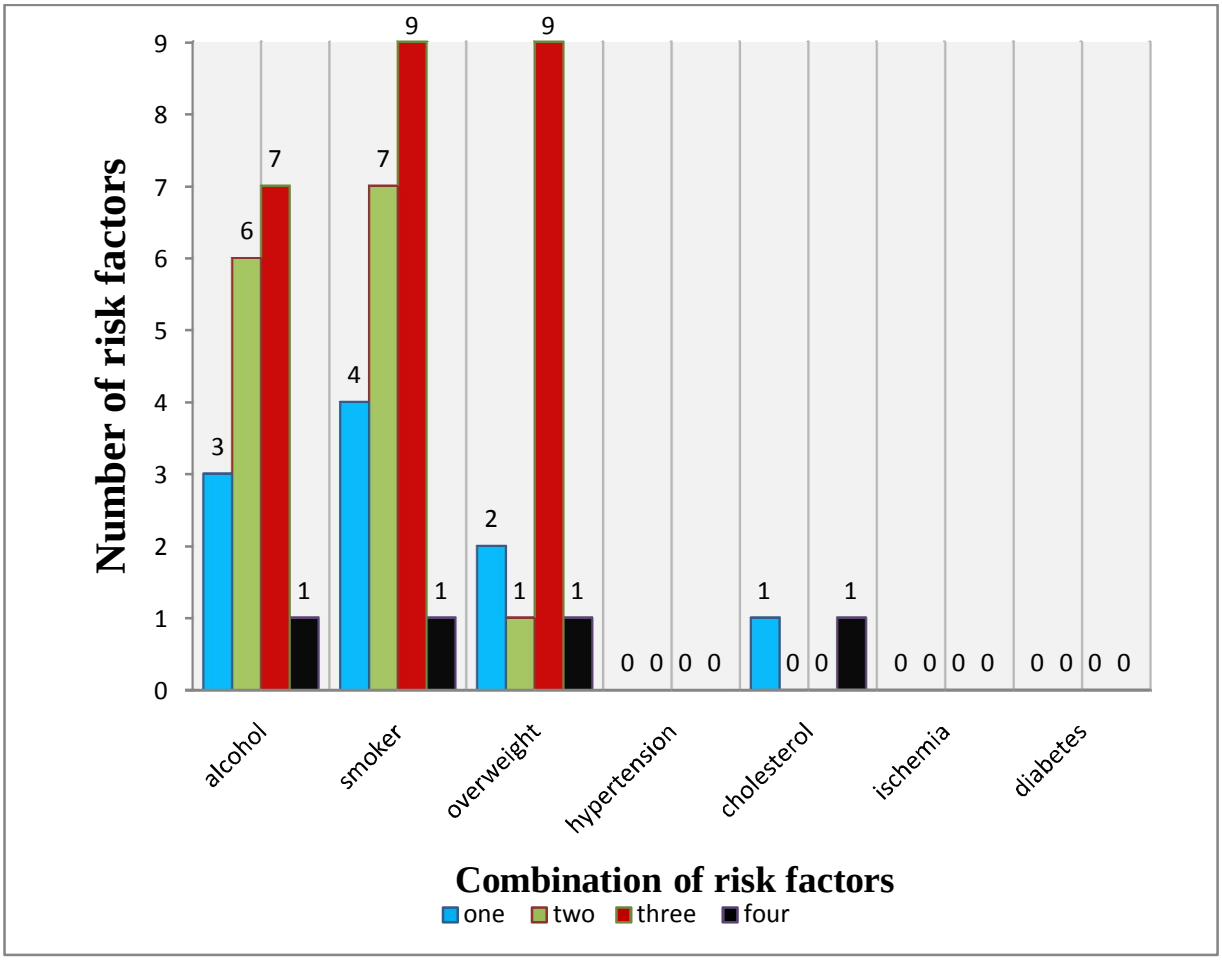

Fig 5.4 Frequency of risk factor combination in group 1

5.6.2 Group 2

Group 2 had the most combinations and also the highest frequency of risk factors in comparison to the other groups. With a combination of 3 risk factors, having cholesterol and being overweight had the highest frequency. In the combination of 4 risk factors, being overweight was the most common risk factor, with ischemia and hypertension also very prominent. Groups with 5 risk factors had all the risks associated with them. Only one patient had six risk factors associated with him. Cholesterol and being overweight had the highest frequency in this age group (Fig. 5.5).

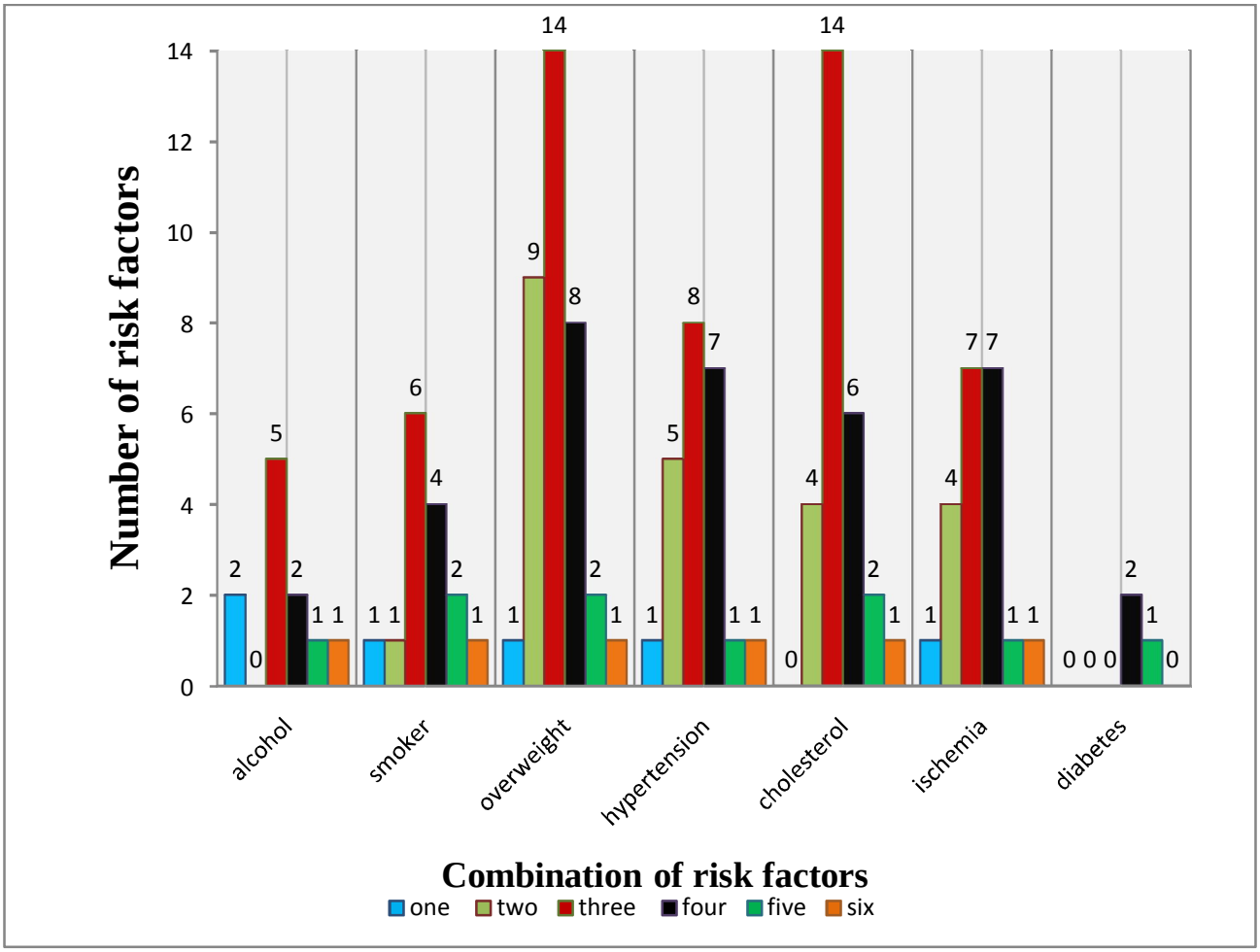

Fig 5.5 Frequency of risk factor combination in group 2

5.6.3 Group 3

In this age group the patients with only one risk factor were divided between ischemia and being overweight. The most frequent risk factor of being overweight occurred in the patients with a combination of four risk factors. Other prevalent risk factors in this group were hypertension, cholesterol and ischemia (Fig. 5.6).

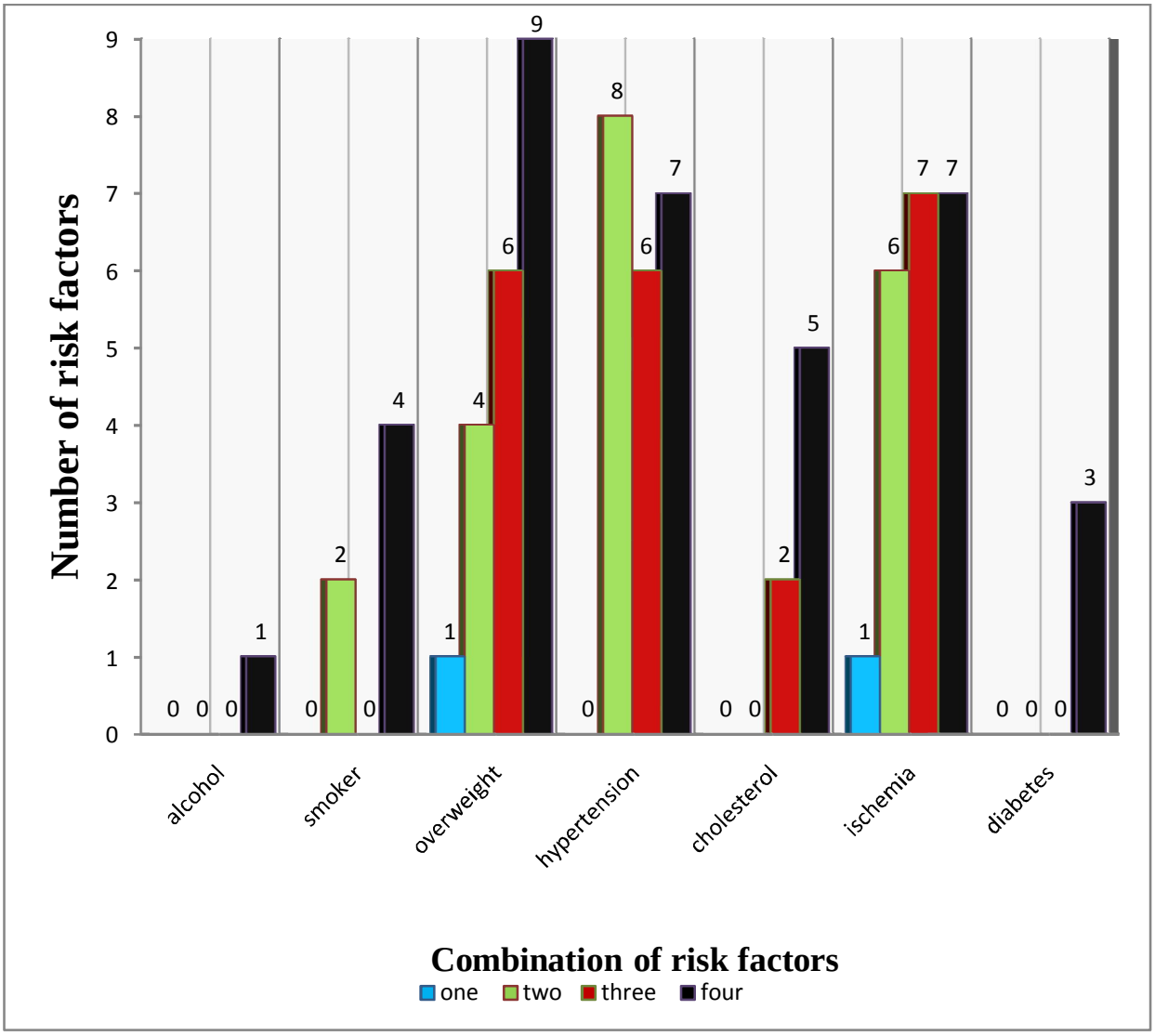

Fig. 5.6 Frequency of risk factor combination in group 3

5.7 Clinical risk factors

Table 5.9 Diastolic variables for overweight as risk factor

		Group 1 (n=19) mean (std)	**Group 2** (n=15) mean (std)	**Group 3** (n=8) mean (std)
	Normal weight / Overweight	(n=13)	(n=37)	(n=20)
RWT	Normal weight	0.38 (0.05)	0.43 (0.08)	0.51 (0.14)
	Overweight	0.41(0.11)	0.46 (0.13)	0.49 (0.12)
Mass (g)	Normal weight	189.84 (34.73)	218 (72.70)	229.13 (69.76)
	Overweight	230.46 (76.64)	248.93 (70.76)	262.85 (85.38)
Mass Index (g/cm^2)	Normal weight	98.84 (15.24)	114.67 (32.07)	123.38 (34.31)
	Overweight	109.31 (32.06	119.35 (32.51)	136.05 (35.89)
E (cm/s)	Normal weight	80.58(16.60)	74.26 (16.09)	64.75 (14.09)
	Overweight	85.85 (15.02)	68.65 (16.83)	68.8 (15.11)
A (cm/s)	Normal weight	42.74 (9.44)	59.66 (12.35)	78.62 (13.16)
	Overweight	54.23 (9.71)	65.83 (12.59)	81.15 (17.30)
E/A ratio	Normal weight	1.96 (0.59)	1.28 (0.35)	0.83 (0.14)
	Overweight	1.60 (0.30)	1.07 (0.30)	0.86 (0.17)
E'/A' ratio sep	Normal weight	1.59 (0.47)	1.76 (3.12)	0.70 (0.16)
	Overweight	1.27 (0.21)	0.76 (0.21)	0.67 (0.17)
E'A' ratio lat	Normal weight	2.22 (0.81)	1.2 (0.40)	0.88 (0.31)
	Overweight	1.62 (0.45)	0.94 (0.27)	0.71 (0.18)
S' sep (cm/s)	Normal weight	9.26 (1.41)	8.43 (1.64)	8.37 91.06)
	Overweight	9.85 (1.95)	8.43 (1.36)	7.65 (1.26)
S' lat (cm/s)	Normal weight	11.37 (1.95)	10.13 (2.35)	9.62 (3.11)
	Overweight	11.77 (2.39)	10.32 (1.98)	8.75 (1.40)
TEI	Normal weight	0.43 (0.13)	0.45 (0.09)	0.45 (0.09)
	Overweight	0.34 (0.09)	0.43 (0.13)	0.44 (0.16)

Measurement of the diastolic variables in group 1 with overweight risk factor revealed significant changes occurred in the trans-mitral A wave (p=003) 95% confidence interval(CI) (-18.63;-4.36), E/A ratio (p=0.030)95% CI(-0.01;0.72), E'/A' ratio septum (p=0.013) 95%

CI(0.04;0.60),E'/A' ratio lateral (p=0.013) 95%CI (0.08;1.11), S' lateral (p=0.030) 95% CI (-1.97;1.17) and the Tei index (p=0.040) 95% CI (0.01;0.17).

Group 2 only revealed significant change in the E'/A' lateral (p=0.027) 95% CI (0.08; 0.47). No changes occurred in group 3.

Table 5.10 Diastolic variables for hypertension as risk factor

Not Hypertensive Hypertensive		**Group 1** (n=30) (n=2)	**Group 2** (n=28) (n=24)	**Group 3** (n=7) (n=21)
		mean (std)	mean (std)	mean (std)
RWT	Not hypertensive	0.38 (0.06)	0.44 (0.08)	0.50 (0.13)
	Hypertensive	0.53(0.18)	0.46 (0.15)	0.49 (0.12)
Mass (g)	Not hypertensive	202.9 (52.53)	230.18 (61)	272.29 (94.21)
	Hypertensive	258 (138)	251.54 (82.70)	246.86 (78.24)
Mass Index (cm/g)	Not hypertensive	101.93 (19.46)	114.25 (26.02)	134.71 (39.79)
	Hypertensive	120.5 (75.66)	122.38 (38.19)	131.67 (34.79)
E (cm/s)	Not hypertensive	82.43 (16.39)	69.71 (17.53)	72.71 (14.44)
	Hypertensive	87 (7.07)	70.91(15.94)	65.95 (14.72)
A (cm/s)	Not hypertensive	46.8 (11.18)	60.68 (10.08)	84.43 (13.06)
	Hypertensive	56.5(6.3)	68 (14.46)	79.09 (16.97)
E/A ratio	Not hypertensive	1.84 (0.53)	1.17 (0.31)	0.87 (0.14)
	Hypertensive	1.53(0.06)	1.08 (0.35)	0.84 (0.17)
E'/A' ratio sep	Not hypertensive	1,48 (0.42)	1.30 (2.30)	0.65 (0.18)
	Hypertensive	1.15 (0.32)	0.78 (0.30)	0.68 (0.17)
E'A' ratio lat	Not hypertensive	2.00 (0.76)	1.10 (0.36)	0.69 (0.10)
	Hypertensive	1.52 (0.32)	0.92 (0.27)	0.78 (0.26)
S' sep (cm/s)	Not hypertensive	9.53 (1.5)	8.46 (1.37)	7.71(0.75)
	Hypertensive	9 (9.24)	8.41(1.52)	7.90 (1.37)
S' lat (cm/s)	Not hypertensive	11.57 (2.16)	10.28 (2.17)	8.00 (1.30)
	Hypertensive	11 (1.41)	10.25 (2.00)	9.3 (2.12)
TEI	Not hypertensive	0.39 (0.12)	0.45 (0.11)	0.50 (0.10)
	Hypertensive	0.38 (0.20)	0.43 (0.14)	0.42 (0.15)

Diastolic variables related to the hypertension risk group revealed increase in group 1 in RWT (p=0.008) 95% CI (-1.12; 2.18), the E/A ratio (p=0.011) 95% CI (-0.47; 1.09) and the E'/A' ratio of the septum (p=0.004) 95% CI (-0.28; 0.94).
Group 2 demonstrated increase in the trans-mitral A peak (p= 0.044) 95%CI (-14.19; 0.45) and E'/A' lateral (p=0.032) 95%CI (-0.02; 0.37). No changes occurred in group 3.

Table 5.11 Diastolic variables for smoking risk factor

		Group 1	**Group 2**	**Group 3**
Non-smokers Smokers		(n=11) (n=21)	(n=37) (*n*=15)	(n=22) (n=6)
		mean (std)	mean (std)	mean (std)
RWT	Non-smokers	0.36 (0.05)	0.47 (0.12)	0.51 (0.12)
	Smokers	0.41 (0.09)	0.39 (0.06)	0.45 (0.11)
Mass (g)	Non-smokers	199 (32.77)	248.38 (71.33)	246.32 (74.60)
	Smokers	210.09 (68.29)	219.47 (71.49)	278.50 (107.07)
Mass index (g/cm^2)	Non-smokers	102.27 (13.43)	122 (32.38)	131.09 (34.08)
	Smokers	103.52(27.87)	108.13 (30.34)	137.33 (42.58)
E (cm/s)	Non-smokers	86.81(17.78)	71.67(13.67)	67.86 (15.76)
	Smokers	80.57 (14.89)	66.8(11.95)	66.83 (10.98)
A (cm/s)	Non-smokers	47.18 (10.04)	65.43 (10.23)	82.31(17.36)
	Smokers	47.52 (11.91)	60.66 (12.84)	73.50 (6.94)
E/A ratio	Non-smokers	1.92 (0.63)	1.12 (0.31)	0.83 (0.16)
	Smokers	1.76 (0.45)	1.13 (0.37)	0.91 (0.15)
E'/A' ratio sep	Non-smokers	1.45 (0.39)	1.10 (2.02)	0.69 (0.16)
	Smokers	1.46 (O.42)	0.92 (0.29)	0.60 (0.17)
E'A' ratio lat	Non-smokers	2.09 (0.90)	0.97 (0.34)	0.75 (0.25)
	Smokers	1.91 (0.65)	1.14 (0.31)	0.77 (0.16)
S' sep (cm/s)	Non-smokers	9.09 (1.57)	8.51 (1.32)	7.77 (1.30)
	Smokers	9.91 (1.67)	8.26 (1.70)	8.16 (0.98)
S' lat (cm/s)	Non-smokers	11.00 (2.09)	10.45 (2.29)	9.09 (2.06)
	Smokers	11.81 (2.11)	9.8 (1.37)	8.66(1.96)
TEI	Non-smokers	0.37 (0.14)	0.43 (0.12)	0.43 (0.12)
	Smokers	0.40(0.11)	0.46 (0.12)	0.48 (0.21)

The A peak velocities were significantly affected in group 2 with smoking as risk factor (p=0.004) 95 CI (-3.02; 12.55). No variables in any of the other groups revealed any significant abnormalities.

Table 5.12 Diastolic variables for cholesterol risk factor

		Group 1	**Group 2**	**Group 3**
No Cholesterol Hyperlipidemia		(n=30) (n=2) mean (std)	(n=25) (n=27) mean (std)	(n=21) (n=7) mean (std)
RWT	No Cholesterol	0.39(0.08)	0.44 (0.13)	0.48 (0.13)
	Hyperlipidemia	0.35 (0.07)	0.45 (0.09)	0.53 (0.09)
Mass (g)	No Cholesterol	205.30 (95.52)	257.40 (80.42)	249.00 (88.27)
	Hyperlipidemia	218.5 (43.13)	223.96 (60.10)	265.86(60.19)
Mass Index (g/cm^2)	No Cholesterol	103.03(24.32)	126.96 (38.10)	129.43 (37.56)
	Hyperlipidemia	104.00(14.14)	109.7 (23.19)	141.43 (27.86)
E (cm/s)	No Cholesterol	83.63(14.98)	71.68 (17.35)	68.09 (15.84)
	Hyperlipidemia	69.00(31.11)	68.96 (16.22)	66.28(11.45)
A (cm/s)	No Cholesterol	47.53 (11.5)	67.92 (11.46)	82.04 (17.57)
	Hyperlipidemia	45.5(2.12)	60.48 (12.98)	75.57 (9.50)
E/A ratio	No Cholesterol	1.83 (0.51)	1.08 (0.31)	0.83 (0.14)
	Hyperlipidemia	1.54 (0.76)	1.17 (0.34)	0.89 (0.20)
E'/A' ratio sep	No Cholesterol	1.48 (0.40)	0.78 (0.23)	0.65 (0.15)
	Hyperlipidemia	1.12 (0.53)	1.30 (2.35)	0.74 (0.19)
E'A' ratio lat	No Cholesterol	2.01 (0.74)	0.95 (0.23)	0.75 (0.24)
	Hyperlipidemia	1.45 (0.63)	1.08 (0.40)	0.76 (0.22)
S' sep (cm/s)	No Cholesterol	9.5 (1.69)	8.64 (1.22)	8.04 (1.16)
	Hyperlipidemia	9.5 (0.70)	8.25 (1.60)	7.28 (1.38)
S' lat (cm/s)	No Cholesterol	11.56 (2.16)	10.52 (1.93)	8.90 (2.18)
	Hyperlipidemia	11.00 (1.41)	10.03 (2.20)	9.28 (1.49)
TEI	No Cholesterol	0.38 (0.10)	0.42 (0.09)	0.46(0.14)
	Hyperlipidemia	0.54 (0.26)	0.45 (0.13)	0.39(0.12)

The A peak velocity of the trans-mitral flow showed significant decrease in group 2 that had high cholesterol (p=0.031) 95% CI (0.60; 14.28). No other variable in any other groups showed any abnormality (Table 5.12).

Table 5.13 Diastolic variables for ischemia as risk factor

		Group 1 (n=0) mean (std)	**Group 2** (n=31) mean (std)	**Group 3** (n=7) (n=21) mean (std)
Non-ischemic Ischemia				
RWT	Non-ischemic	#	0.46 (0.13)	0.44 (0.10)
	Ischemia	#	0.44 (0.09)	0.51 (0.12)
Mass (g)	Non-ischemic	#	229.77 (71.91)	253.71 (74.83)
	Ischemia	#	255.19 (70.86)	253.05 (85.29)
Mass Index (g/cm^2)	Non-ischemic	#	113.61 (32.87)	133.57 (76.93)
	Ischemia	#	124.48 (30.65)	132.05 (38.25)
E (cm/s)	Non-ischemic	#	71.35 (15.36)	67.28 (15.81)
	Ischemia	#	68.66 (18.69)	67.76 (14.70)
A (cm/s)	Non-ischemic	#	63.48 (12.27)	84.85 (19.16)
	Ischemia	#	64.90 (13.61)	78.95 (15.08)
E/A ratio	Non-ischemic	#	1.15 (0.30)	0.80 (0.17)
	Ischemia	#	1.09 (0.37)	0.86 (0.15)
E'/A' ratio sep	Non-ischemic	#	0.82 (0.27)	0.59 (0.17)
	Ischemia	#	1.40(2.66)	0.70 (0.16)
E'A' ratio lat	Non-ischemic	#	1.01 (0.26)	0.63 (0.23)
	Ischemia	#	1.02 (0.43)	0.80(0.22)
S' sep (cm/s)	Non-ischemic	#	8.74 (1.31)	8.14 (0.89)
	Ischemia	#	8.00 (1.51)	7.76 (1.33)
S' lat (cm/s)	Non-ischemic	#	10.54 (2.06)	8.71 (2.21)
	Ischemia	#	9.85 (2.08)	9.09(1.99)
TEI	Non-ischemic	#	0.45 (0.12)	0.35 (0.07)
	Ischemia	#	0.41 (0.11)	0.470.15)

No data available

Only the Tei index in group 3 increased in the ischemia group (p=0.012) 95% CI (-0.24; 0.01). No other variables demonstrated abnormalities.

Table 5.14 Diastolic variables for diabetes as risk factor

		Group 1	**Group 2**	**Group 3**
		n=32	n=48	n=25
Not diabetic		n=0	n=4	n=3
Diabetic		mean (std)	mean (std)	mean (std)
RWT	Not diabetic	#	0.45 (0.12)	0.49 (0.12)
	Diabetic	#	0.43 (0.02)	0.52 (0.12))
Mass (g)	Not diabetic	#	235.65 (64.45)	244.48 (77.89)
	Diabetic	#	292.75(137.08)	326 (88.47)
Mass Index (g/cm^2)	Not diabetic	#	116.02 (29.20)	128.52 (33.74)
	Diabetic	#	141.75 (58.23)	165 (37.04)
E (cm/s)	Not diabetic	#	70.81 (16.82)	68.08 (15.16)
	Diabetic	#	63.75 (15.04)	64.00 (11.53)
A	Not diabetic	#	63.89 (12.69)	80.92 (16.53)
	Diabetic	#	66.00 (14.9)	76.33(12.66)
E/A ratio	Not diabetic	#	1.14 (0.32)	0.85 (0.16)
	Diabetic	#	1.02 (0.39)	0.83 (0.09)
E'/A' ratio sep	Not diabetic	#	1.08 (1.77)	0.68(0.17)
	Diabetic	#	0.71 (0.29)	0.61(0.13)
E'A' ratio lat	Not diabetic	#	1.04 (0.33)	0.77 (0.24)
	Diabetic	#	0.78 (0.43)	0.65 (0.13)
S' sep	Not diabetic	#	8.41 (1.38)	7.84 (1.21)
	Diabetic	#	8.75 (2.21)	8.00(1.73)
S' lat	Not diabetic	#	10.25 (2.09)	8.97 (2.13)
	YES	#	10.50 (2.08)	9.33(0.57)
TEI	Not diabetic	#	0.44 (0.12)	0.43 (0.13)
	Diabetic	#	0.37 (0.05)	0.54 (0.23)

The diabetic risk factor group only revealed decreases in the Tei index of group 2 (p=0.040).

Table 5.15 Diastolic variables for alcohol as risk factor

		Group 1	**Group 2**	**Group 3**
	No alcohol	(n=15)	(n=41)	(n=0)
	Alcohol user	(n=17)	(n=11)	(n=0)
		Mean (std)	Mean (std)	Mean (std)
RWT	No alcohol	0.39 (0.08)	0.45 (0.12)	#
	Alcohol user	0.39 (0.07)	0.43 (0.09)	#
Mass	No alcohol	203.33 (52.13)	244.66 (72.86)	#
	Alcohol user	209.00 (64.52)	222.82 (68.66)	#
Mass Index	No alcohol	103.47 (24.67)	120.44 (33.18)	#
	Alcohol user	102.76 (23.49)	108.91 (27.39)	#
E	No alcohol	80.06(16.84)	70.92 (17.51)	#
	Alcohol user	85.05(15.23)	67.81 (13.43)	#
A	No alcohol	44.4 (9.70)	66.12 (11.85)	#
	Alcohol user	50.05 (11.92)	56.36 (13.42)	#
E/A ratio	No alcohol	1.87 (0.58)	1.10 (0.35)	#
	Alcohol user	1.76(0.47)	1.21 (0.19)	#
E'/A' ratio sep	No alcohol	1.49 (0.48)	1.10 (1.92)	#
	Alcohol user	1.43 (0.35)	0.85 (0.19)	#
E'/A' ratio lat	No alcohol	1.97 (0.90)	0.98 (0.34)	#
	Alcohol user	1.97 (0.58)	1.16 (0.27)	#
S' sep	No alcohol	8.86 (1.64)	8.41 (1.44)	#
	Alcohol user	10.05 (1.47)	8.54 (1.43)	#
S' lat	No alcohol	10.53 (1.55)	10.09 (2.05)	#
	Alcohol user	12.41 (2.18)	10.90 (2.11)	#
TEI	No alcohol	0.42 (0.13)	0.44 (0.13)	#
	Alcohol user	0.36 (0.10)	0.43 (0.08)	#

No data available

Chapter 6
Discussion

Echocardiography and especially Doppler echocardiography are routinely used in cardiology practices. Clinically it is important to determine left ventricular diastolic function because of the role it plays in the evaluation of heart failure and the treatment of patients with isolated diastolic dysfunction. Trans- mitral flow velocity patterns obtained by pulsed Doppler echocardiography are widely used to evaluate global left ventricle diastolic function. These trans-mitral flow measurements are limited because patients with elevated global left ventricular end diastolic pressure may have a pseudo-normal flow pattern. This is why the newer method of tissue Doppler imaging was used in addition to trans-mitral flow to evaluate the diastolic properties of the study group. Left ventricular diastolic filling and systolic variables can be determined reliably by using these techniques. Diastolic filling abnormalities are broadly classified as either impaired relaxation or restrictive physiology (Yamada *et al*., 2002). Diastolic dysfunction is increasingly recognised as having an important influence on symptoms and hemodynamic status of the heart.

Diastole extends from aortic valve closure to mitral valve closure in four distinct phases.

- Isovolumetric relaxation represents the time from aorta closure till just before the mitral valve opens.
- Early filling accounting for up to 80% of the total ventricular filling.
- Diastasis represents the time when the left atrial and left ventricular pressures equalise and no flow occurs.
- Atrial systole accounting for the remainder of the ventricular filling.

Clinically it is important to evaluate the left ventricle diastolic function non-invasively and accurately. Left ventricle diastolic function and in particular left ventricular relaxation becomes impaired with age, even in the healthy population. This study's purpose was to measure the effect clinical variables have on these diastolic and systolic variables, as well as to evaluate the effects ageing has on diastolic variables.

The effects of ageing on the diastolic and systolic variables were evaluated with the use of pulse wave Doppler imaging. The major finding was that obesity poses a very big problem

and this risk factor had the most profound effect on the systolic and diastolic variables in this study. The results of this study suggest that it is important to include measurements of diastolic variables when using echocardiography during daily practice. Another observation of the study was that systolic variables did not change that much although diastolic variables did show abnormalities with age and with obesity. Sixty one percent of the study population was overweight with 19% being obese. Group 1 consisted of 41% overweight subjects, group 2 seventy percent and group 3 sixty eight percent (Fig 5.2). This study demonstrated that the measurement of systolic variables is not adequate to evaluate asymptomatic patients presenting at a general cardiology practice. Systolic variables showed little change but most of the diastolic variables changed. It also showed that changes occur with ageing, even in asymptomatic individuals.

6.1 Study population

The study population of 112 subjects was divided into three groups according to specific age ranges to try and get a more even distribution for the study population seen in this study. Group 2 and 3 consisted of patients seen in a general cardiology practice and group 1, recruited at the local university, as a control group. Less female patients were seen because less than a third of the general cardiology practice where the study was performed is female.

Clinical risk factors consisted of age, body composition, smoking, alcohol consumption, ischemia, hypertension and diabeties were included in the study. The most profound changes on diastolic variables occurred related age and body composition. Clinically significant cardiovascular disease was not present at the time the study but the ischemia group included patients who had previous ischemic incidents but were treated. Neither the amount of cigarettes nor the degree of alcohol consumption was considered in this study. All the hypertensive patients were on treatment.

Baseline characteristics of the 112 study subjects are summarised in table 5.1. The BMI increased with ageing, although the oldest group showed a decrease in BMI. It was clear that obesity played a significant role in all the groups and affected their diastolic variables.

6.2 Systolic variables

Commonly used parameters of left ventricular systolic function are left ventricle ejection fraction, fractional shortening as well as mean circumferential shortening. Based on histological studies the myocardium consists of circumferential fibres in the mid- wall and longitudinal fibers along the encocardial and epicardial layers (Grant, 1965; Greenbaum *et al*., 1981). Systolic function is determined by the sum of the contractions of these different fibres.

This study demonstrated that no significant differences occurred in the systolic variables with the ageing process (Fig 5.5). Previous studies done on left ventricle ejection fraction with radionuclide methods suggested a slight increase in ejection fraction with ageing (Pfisterer *et al*., 1985).

Age related changes in left ventricle systolic and diastolic function in clinically normal patients have also been described (Kitzman *et al*., 1991; Spirito *et al*., 1988). In these studies the isovolumetric relaxation time and the maximal late diastolic or A-wave flow velocity increased significantly with age. Changes specifically occurred in pulsed Doppler echocardiography (Kitzman *et al*., 1991 Spirito *et al*., 1988), in tissue Doppler imaging (Palka *et al.*, 1996) and with radio nuclide angiography (Bonow *et al*., 1988). In this study we had similar findings (See Table 5.6). Conversely the E-peak flow velocity and the deceleration time in early diastole and the E/A-ratio decreased significantly with age.

Another study (Gertenblith *et al.* 1977) reported that left ventricle pump function *in vivo* is minimally affected by ageing, based on studies performed using M-mode echocardiography. No obvious changes were observed in ejection fraction, shortening fraction or mean circumferential fibre shortening in the abovementioned study. When considering that the stroke volume, stroke volume index, cardiac output and cardiac output index did change significantly, one can speculate that the reason for these changes can be found in the filling of the left ventricle and therefore the diastolic variables.

The ejection time increased with age especially from group 1 to group 3. It can be speculated that the reason for this happening can be due to the larger stroke volume that was found with

ageing and therefore a longer time for ejection is necessary. These findings are in agreement with previous studies which demonstrated that with ageing the left ventricle ejection time increased (Gardin *et al*., 1987; Wanderman *et al*., 1981).

There was a notable increase in cardiac output with age (See Table 5.4). Since cardiac output is the product of stroke volume and heart rate, in our study results the cardiac output did not change therefore the only explanation could be found was that the atria contribution increased and therefore caused an increase in cardiac output. Stroke volume increased with ageing but the left ventricle contraction did not change thus, the explanation for the increased stroke volume could ascribed to the percentage atrial contribution or active filling that increased with ageing. Left-sided dimensions, left ventricle mass, and mass index, as well as the relative wall thickness of the study population increased with age (See Table 5.3). In previous studies an increase in myocardial fibrosis was found with age, together with increases in collagen tissue and myocardial mass (Gardin *et al*., 1979; Gertenblith *et al*., 1977; Yin *et al*., 1980). The older population also showed more hypertrophied left ventricles even when indexed to body size. The internal dimension in systole and diastole demonstrated no significant abnormalities, even when considering that the stroke volume increased (Table 5.4).

The results of this study suggests that, the left ventricle became more proficient in ejecting its content with age without increased systolic variables and with a decrease in the longitudinal function of the left ventricle muscle fibres. It can be speculated that the reason for this increase in cardiac output can be related to significant changes that occur in the diastolic variables, especially the atrial contribution: In this study there was a progressive decrease in the passive filling of the left ventricle with age. Increasingly more abnormalities of diastolic variables were found in the older population (Table 5.6).

The results of this study seems to indicate that the longitudinal fibers on the septal and the lateral walls became weaker with ageing (See table 5.5); while it seemed that the circumferential fibres stayed the same or even showed a slight increase in strength as demonstrated in this study. The tissue Doppler measurement of the muscle is independent of volume of the left ventricle and unaffected towards preload or afterload. It remains that, while cardiac output of the heart increases with age, the circumferential muscle stays the same and the longitudinal muscle becomes weaker with measureable diastolic adaptations especially a

larger atrial contribution. Thus the heart becomes more effective without much change in the systolic variables. This study illustrates the necessity to evaluate the diastolic variables as part of the routine follow-up of cardiology patients.

6.3 Diastolic variables

6.3.1 Trans mitral flow

Diastole can be divided into passive filling (E peak) and active filling (A peak). As the left ventricle ages or is affected by disease processes like hypertension and diabetes, the myocardial muscle becomes less effective and loses its ability to maintain stroke volume.

Common causes for diastolic dysfunction are ageing, ischemia, myocardial fibrosis, altered collagen composition, hypertension and left ventricular hypertrophy. The diastolic pressure-volume relationship during passive steady state of the left ventricle is governed by elastic myocardial properties (compliance) and reflects the interaction between the intrinsic forces, resisting this stretching from within the myocardium. Elasticity represents the individual properties of muscle, extracellular matrix and coronary blood vessels. Changes in these properties can occur when the relative quantity of collagen increases such as with hypertrophy, fibrosis or with scar formation due to myocardial infarction or infiltrative deceases such as amyloid (Stevenson *et al.*, 1989).

In this study E peak diminished in velocity with ageing. The deceleration time of the E peak also prolonged with ageing. The velocity of the passive filling of the left ventricle decreased as the study population aged (Table 5.6). It also took longer for the left ventricle to fill with blood during the passive filling phase. Keeping in mind that the left ventricle mass also increased with age, it means that the left ventricle takes longer to fill at a decreased velocity after the mitral valve opens. In the younger group passive filling was rapid with less time used to fill the left ventricle. In this group the E peak was almost always higher than the A peak. Deceleration time or filling time was also shorter in the younger group (Table 5.6). It was described earlier that the stroke volume increased with ageing although the left ventricle mass increased but the ejection fraction stayed the same. Results seem to indicate that passive filling or the first filling phase played a progressively smaller role in the filling of the left ventricle with ageing (Table 5.6).

Active filling or atrial contraction played an increasingly more important role in filling of the left ventricle in order to attain the stroke volume or even increase it. This correlated with previous studies where it was found that left ventricular function, particularly left ventricular relaxation, becomes impaired with age, even in healthy patients (Bonow *et al.*, 1988; Bryg *et al.*, 1987; Iskandrian *et al.*, 1986; Klein *et al.*, 1994; Miyatake *et al.*, 1984; Miller *et al.*, 1986; Spirito *et al.*, 1988). This impairment manifested as a decrease in the early diastolic flow (E wave) and a compensatory increase in the atrial systolic flow velocity (A wave) (Bonow *et al.*, 1988; Bryg *et al.*, 1987; Iskandrian *et al.*, 1986; Miyatake *et al.*, 1984; Miller *et al.*, 1986; Klein *et al.*, 1994; Spirito *et al.*, 1988).

This study showed that the A velocity increased significantly with ageing. The younger group had very low A-wave peak velocities. Most of the filling of the left ventricle occurs in the passive phase in the younger group but with age it changes so that active filling or atrial contraction becomes the dominant phase (Table 5.6). This occurs because the left ventricle stiffens with age and the atrium starts to play an increasingly more important role maintaining the normal stroke volume it order to uphold a constant cardiac output. To attain a better atrial contraction the left atrium needs to work harder and hold more blood. The left atrium enlarges due to increased work load and the larger effort needed to fill the left ventricle with blood. It was found in this study that left atrial size increased. In the younger group most of the filling occurred during passive filling so that less blood from the atrium was needed to fill the left ventricle. In the older group the left ventricle became stiffer with less passive filling of the left ventricle and more active filling.

With ageing, there is a gradual decrease in the rate of myocardial relaxation as demonstrated by the increase in the deceleration time of the passive filling of the left ventricle (See Table 5.6). With normal left atrial pressure, the pressure crossover between the left ventricle and the left atrium occurs later and early transmitral pressure gradient is decreased. Hence the isovolumetric time becomes longer and the E velocity in normal subjects gradually declines. The reduced filling in early diastole delays the pressure equilibration between the left ventricle and the left atrium, resulting in a longer deceleration time. More blood is thus needed from the atrium to fill the left ventricle. The left atrium needs to adapt to this need and subsequently becomes enlarged. However due to this increased volume the pressure in the left atrium also rises. This results in effect that the ratio between the E peak and the A

peak decreases. The younger group demonstrated E/A ratios higher than 1 and the older groups E/A ratios were almost always below 1, confirming the effect of passive filling against the progressively higher A-peak velocities with age (Table 5.6).

It was demonstrated in previous studies that left ventricle function becomes impaired with ageing in healthy persons despite normal systolic function (Aronow *et al*., 1989; Gerstenblith *et al.*, 1977; Pearson *et al.*, 1991; Port *et al.*, 1980). It was also found that the peak E velocity of the transmitral flow decreases with age and the peak atrial systolic velocity increases with ageing, resulting in a decrease in their ratio (Bonow *et al*., 1988; Bryg *et al*., 1987; Iskandrian *et al*., 1986; Klein *et al.*, 1994; Miyatake *et al*., 1984; Miller *et al*., 1986; Spirito *et al*., 1988).

In experimental studies it was demonstrated that the myocardial fibre tension becomes greater with ageing, and the relaxation time is prolonged because of change in the active state properties (Lakatta *et al*., 1975; Schwartz *et al*., 1973; Weisfeldt *et al*., 1971). It is believed that the age-related decrease in diastolic function of healthy individuals is influenced not only by the impairment of the active myocardial relaxation, but also by increased left ventricle myocardial and chamber stiffness (Templeton *et al*., 1979). Furthermore, it was reported that nonuniformity of myocardial relaxation occurs in older patients (Bonow *et al.*, 1988). It is thus clear that diastolic function should properly assessed in all patients.

6.3.2 Myocardial velocities

Since Greenbaum *et al*. (1981) have reported the importance to evaluate the longitudinal function of the myocardial fibres, left ventricular systolic and diastolic function with the use of mitral annular motion (by M-mode echocardiography) and the tissue velocity (by tissue Doppler echocardiography) have been employed to evaluate these variables.

All moving objects intersected by ultra sound generate Doppler shift velocities. Tissue Doppler echocardiography analyses motion from relatively slow-moving reflectors such as left ventricular muscle. Traditional colour-flow Doppler evaluated relatively high velocity signals and “weak” ultrasound reflectors like red-blood cells (Kerut *et al.*, 2004).

This study evaluated the diastolic variables of the lateral aspects as well as the septal motion of the left ventricular mitral valve annulus. The variables that were measured were the early diastolic motion (E') and the late diastolic relaxation wave (A'). The measurement of these variables is not affected by the volume of the left ventricle and can be used to verify the presence of diastolic abnormalities. In this study significant decreases in the E' at the lateral as well as the septal annulus were detected with ageing (Table 5.6). The opposite happened with the A' where there was a significant increase in velocity at the lateral and septal annulus with ageing. This decreased the E'/A' ratio, especially of the lateral wall. In all the tissue Doppler variables measured, there were significant abnormalities illustrated with ageing (Table 5.7). It seems that the measurement of the TDI variables is important when analysing diastolic status of patients.

The E' at the lateral wall was greater than that of the septal wall, with the A' the same at the lateral and the septal wall in patients without diastolic abnormalities. The ratios of the lateral wall were greater than that of the septal wall ratios (Table 5.6). The same findings were present in a study done by Peverill *et al.* (2004), who also found that the E' were higher at the lateral than at the septal wall.
E' correlated with Torsion (Tau) suggesting that the E' is a marker of left ventricle relaxation. It was found with the trans-mitral flow that left ventricle relaxation decreased. Also, with tissue Doppler of the lateral and septal wall, it was evident that the relaxation took longer with ageing. The reason why the E' of the lateral wall is higher than that of the septal wall, may be found in a study done by Greenbaum *et al*. (1981) where they found that there are variations in the anatomy of the longitudinal myocardial fibres that run from the apex to the fibrous atrioventricular ring. He also found that these longitudinal fibres are mainly present in the subendocardial and sub epicardial layers of the left ventricular lateral wall and papillary muscles. Thus, there are fewer longitudinal fibres in the septal wall than in the lateral wall and the subepicardial longitudinal fibres also vary from the apical to the basal segments in the septum (Table 5.6).

When evaluating diastole in patients it is not adequate to only measure trans-mitral flow, as this is volume dependant, thus giving a false impression of the diastolic profile of the patient. In addition, it is important to measure tissue velocities of the lateral and septal walls of the left ventricle since these measurements are not influenced by volume loading of the left

ventricle. It was also observed in this study that tissue Doppler differentiates patients with normal profiles from those with pseudo-normal profiles (Table 5.6)

6.4 Risk factors

As a clinical tool, echocardiography has been important in defining the prevalence and magnitude of clinical risk factors on the cardiovascular system. It has established its value in determining the effects of these risk factors on the heart in order to help physicians to treat patients. Having defined the pathophysiologic relevance of specific echocardiographic variables in normal patients, it was also necessary to look at the effects clinical risk factors may have on these variables.

6.4.1 Group 1

In Table 5.8 it is apparent that the most common risk factor for group 1 was smoking and alcohol consumption. It should be pointed out that the amount the subjects smoked was not being quantified in this study. No diastolic or systolic variables changed in group 1 due to smoking or alcohol consumption. Smoking and alcohol consumption was evaluated in combination with other risk factors like obesity, which had considerable effects on the diastolic variables measured in group 1.

Significant increases were detected in the A velocity and the E/A ratio as well as the E'/A' ratio of the septum and the lateral wall. In a study done by Di Bello *et al* (2006) significant differences were found between obese and control groups with regard to the peak A-flow velocity, which was higher in the obese group compared to the control group. As a consequence, the E/A ratio was also significantly lower in obese patients similar to our results. They also found that the E'/A' ratios of the lateral and septal walls were negatively affected in the obese group. On tissue Doppler the only systolic variables in group 1 with obesity that increased were S'. This is probably due to the extra workload the left ventricle has in obese patients with increased muscle mass (see Table 5.3). Left ventricle mass increased considerably with obesity in group 1. It should be pointed out that all combination risk factors were related to lifestyle in group 1. They were all smokers, consumed alcohol,

were overweight and had high cholesterol. No changes in any measured variable were found in group 1 with cholesterol as an isolated risk factor.

A recent study done by Di Bello *et al*. (2006) revealed all myocardial diastolic phases were altered in obese patients. Their study demonstrated the negative effects obesity has on the muscle and postulated that this be mediated by insulin resistance. They found that:

- Insulin may act as a growth hormone in the myocardium and hyperinsulinemia leads to increased left ventricle mass in rats (Holmang *et al.,* 1996).
- Hyperinsulinemia may lead to sodium retention that could cause a subclinical left ventricle myocardial dysfunction as a result of volume expansion (De Fronzo *et al.,* 1975).
- Hyperinsulinemia may lead to sympathetic nervous system activation (Anderson *et al.,* 1991).
- Insulin resistance is related to an increased pressor response to angiotensin II, which stimulates left ventricular hypertrophy and causes interstitial fibrosis (Gaboury *et al.,* 1994).

Forty-one percent of this group 1 was overweight and this should be regarded as significant when considering risk stratification for future cardiac events. When considering that even as the youngest group, obese indivuduals already showed diastolic changes, especially in the TDI variables where muscle is measured and not the volume differences (Table 5.8).

6.4.2 Group 2

The most common risk factor for group 2 was obesity. Seventy-one percent of this group were overweight (see Table 5.2). Smoking and alcohol consumption was not as important. Other risk factors included in this study started to play an increasingly important role in this group. Considering what Di Bello *et al*. (2006) found in their study, (as described in 6.5.1 about the effects of obesity on the heart muscle), it is apparent that similar abnormalities were present in this study.

Other risk factors that started to play an increasingly important role were hypertension (46%), cholesterol (52%), ischemia (40%), and diabetes (8%). The combination of risk factors also

increased in group 2 with more patients having more combinations of risk factors. Again, as in group 1, the lifestyle risk factors such as obesity, cholesterol and hypertension were prominent. Obesity became more relevant in this group with diastolic abnormalities as seen in Table 5.6.

Although the risk factors played an important role in group 2 with regard to risk stratification, only the E'/A' ratio of the lateral wall showed significant changes in the overweight group. In patients who had hypertension, A-peak velocity increased significantly, This could be due to increased left ventricle mass in hypertensive patients with associated increases in wall stiffness. In the smoking group A-peak velocity also increased significantly, as were the case with the cholesterol group (Table 5.8).

These changes may be due to the combination of ageing and certain risk factors. In previous studies it was observed that reservoir function of the LA were reduced with ageing (Barbier *et al*., 1999; Spencer *et al*., 1998; Spencer *et al*., 2001). Several studies have reported that the LA booster function is augmented with age and that the active emptying (A velocity) percentage of total emptying which is a marker of LA booster function, had a significant positive correlation with age (Anwar *et al.*, 2007; Spencer *et al.*, 1998; Spencer *et al.*, 2001; Triposkiadis *et al*., 1995).

The Tei index decreased in subjects who had diabetes in group 2. This can be due to diastolic changes that occur in diabetic patients as reported in a study performed by Annonu *et al*. (2001) where it was found that diabetic patients had lower mean E velocities and a lower deceleration slope than their control group. The same was found in this study with lower E velocities in the diabetic group although not significant lower (Table 5.14).

6.4.3 Group 3

The most common risk factor for group 3 was hypertension and ischemia with a prevalence of 75% (Fig 5.6). As in group 2, obesity also was a prevalent risk. Risk factors associated with life style were very prominent with both ageing and obesity playing an increasingly important role in this group. Diastolic abnormalities were present in this group. Hypertension and diabetes were more frequent in this group with more abnormal lifestyle risk factors. The

combination of risk factors that patients in this group displayed differed from group 1, with a higher incidence of ischemia and diabetes in patients with a combination of four or more risk factors (Fig 5.6).

No significant echocardiographic changes occurred in these risk groups and it followed a similar pattern as in the other groups where diastolic changes occur in specific risk groups due to the underlying pathophysiology. It seems that an equilibrium where no more changes occur is reached and the cardiac system equilibrates.

Only ischemia as risk factor prolonged the Tei index significantly in group 3. A velocities decreased with ischemia in group 3. Definite muscle changes occurred with both the lateral and septal walls E'/A' ratio increased in subjects with ischemia. This was due to a decreased E'.

In previous studies it was found that patients who had myocardial infarction, S' and the E' velocities were decreased even at rest (Duncan *et al*., 2001; Yu *et al*., 2007). The same were found in this study with the S' and E velocities decreased in patients who had ischemic events (Table 5.13).

6.5 Study limitations

Although thorough scientific rules and methods were employed in the execution of this study it is important to notice the limitations that might affect the results found in this study. The subjects of this study were not randomly selected because we wanted to look at the profile of patients presented at a general cardiology practice. The majority of the patients were male because dominantly male patients are seen at this specific cardiology practice. Most of the patients included in this study were Caucasian because few patients of other races were seen during the study period.

In this study the control group was younger. In reality, it is difficult to age-match normal control subjects to patients with impaired diastolic function because age itself is a cause of delayed left ventricular function. No attempt was made to assess the possible influence of medication on the diastolic and systolic variables measured in this study.

Myocardial ischemia because of coronary artery disease could not be ruled out as no coronary angiography was performed. However, all patients were free of angina. No effort was made to quantify alcohol consumption. This may cause discrepancies in the measurement with relation due to volume changes that may occur. Also, the degree of smoking was not determined.

Measurements of BMI were made on the basis of length and weight measurement and fat mass and percentage were not considered which may have an effect due to different body profiles in this study. It might be necessary in future studies of this kind to evaluate the somatotype of the study population in order to better determine the effect of obesity. It should also be pointed out that it was time-consuming doing all these systolic and diastolic variables and might play a role in a busy cardiology practice.

6.6 Conclusion

The study assessed left ventricular diastolic and systolic variables in 112 subjects divided in three age groups using echocardiography, Doppler echocardiography as well as tissue Doppler echocardiography. Two specific goals were specified in this study. The first goal was to determine what effect age has on these systolic and diastolic variables amongst the general South African population. In addition it was the author's intension to evaluate which effects certain clinical risk factors may have on these variables. It was clear in this study that the systolic component of the examination did not change much. Velocity of the longitudinal fibres decreased with advancing age but the circumferential fibres almost stayed the same. No abnormalities were detected in ejection fraction, shortening fraction and mean circumferential shortening except where ischemia was detected.

Increases were detected in the stroke volume of the subjects as well as the cardiac output. It was speculated that this might be due to changes in diastole. This was confirmed with almost all the diastolic variables changing with age. The transmitral E peak decreased in velocity with age and the deceleration time increased, indicating that the left ventricle becomes less compliant with age. However, the A velocity increased with advancing age. It was apparent that with advancing age the atrium starts to play a more active role in the filling of the left ventricle in order to maintain a normal or even increased stroke volume and cardiac output.

These age-related transitional changes in diastolic function were similar in the whole study population surveyed, and confirmed the necessity of evaluating patients in a general cardiology practice for abnormalities in diastole. It was found that the E peak decreased with advancing age, with a subsequent increase in the atrial velocity. It is important to measure the ratios of the trans-mitral flow as well as the tissue Doppler velocities as a minimum examination.

Obesity was the most important clinical risk factor and had the most profound effect on all the subjects. Obesity played an important role in abnormalities found in the study population, especially the diastolic variables. It was observed that in the obese group abnormalities in diastole were more profound compared to the normal weight group (See Table 5.6). The second major finding of this study was that obesity is an important problem amongst affluent South African population with profound effects on the patient's heart health. Life style changes should be considered for better health status of patients seen in a general cardiology practice.

However, if abnormalities are detected in these ratios a thorough examination should be done. Abnormalities in diastolic variables in this study were detected looking at the ratios of the trans-mitral flow as well as Doppler echocardiography. Another important variable that should be included in an echocardiographic evaluation should be the IVRT because it also showed significant increase with age and especially in obesity. Special attention should be paid to the measurement of the A peak as it related to various abnormalities in the ischemic group as well as with ageing. The A peak showed an important increase in the ageing subjects.

In conclusion, this study emphasized the profound effect ageing and obesity have on the systolic and diastolic variables of patients and the importance of measuring these abnormalities as part of the general echocardiographic examination, especially since this is not routinely done in most practices in South Africa.

6.7 Recommendations

Future aims should focus on constructing a practical time-friendly algorithm for evaluating left ventricular diastolic function, utilising the combination of age-adjusted values for trans mitral flow velocities as well as tissue Doppler velocities to be done on all patients seen in a general cardiology practice. In addition, further studies could be aimed at the obesity problem and the negative effects it has on cardiology patients and what effect lifestyle changes may have on these patients' diastolic and systolic profiles.

Chapter 7

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Appendices

Appendix	A	Patient Information Form
Appendix	B	Patient Consent form
Appendix	C	Echocardiography Data Sheet

Appendix A

Patient Information Form

INFORMATION DOCUMENT ***Datum:_____***

Title of study: **A comparative study of the systolic and diastolic components of the cardiac cycle of Caucasian patients with abnormal muscle performance index against patients with normal muscle performance index.**

Welcome ladies and gentlemen and thank you for having me to tell to about our research study.

We, Prof. E van den Heever-Kriek and Mnr. JJ Steyn are doing research on muscle performance index of the heart muscle. In this study we want to learn about "the muscle performance index of the heart". The study involves measurement of the time intervals of the heart with echocardiography to determine if the functionality of the heart's performance is influenced. This means that we are going to measure systole (contraction) and diastole (relaxation) of the heart with Doppler (sound waves) and use this information in a formula to determine if the heart is working properly. By knowing this we can also determine which part of the heart's systole (contraction) or diastole(relaxation) is causing problems for the normal functioning of the heart. The study is aimed at 120 male or female South African patients that must undergo routine cardiological examination.

I should like to point out to you that this is a study involving research and not routine care. Your participation in the study will not affect your routine medical care in anyway. We are therefore asking you to participate in this research study. For this study to take place, we will need you to consent to the following:

- That your routine echocardiography information would be made available to Prof. E van den Heever and Mr. JJ Steyn for the sole purpose of the research study.
- That muscle performance index may be done as part of the echocardiography examination.

The research project is very safe. There should be no safety concerns regarding the echocardiogram because it is part of your normal consultation. Also note that, you will not be paid for your participation in this study.

Your participation in the study is voluntary, and your refusal to participate will involve no penalty or loss of medical benefits to which you are otherwise entitled. You are at liberty to withdraw from this project at any stage without giving reasons. Your withdrawal will not be held against you, and your consultations and treatment with your physician will continue as if you were never enrolled in the project.

The confidentiality of this study is of utmost importance. Efforts will be made to treat your medical records confidentially, but absolute confidentiality cannot be guaranteed. Personal information may be disclosed if required by law. The Ethics Committee for Medical research may also inspect and/or copy your research records for quality assurance and data analysis. Publication of the results of this study will in no way lead to individual or cohort identification.

You may contact us any time if you have questions about the research or if you are injured as a result of the research.

Contact Details of the Researchers:

Prof. E van Heever-Kriek: (0827705356)
Mr. JJ. Steyn: (0823712887)

You may also contact the **Secretariat of the Ethics Committee** of the Faculty of Health Sciences, UFS at telephone number
(051) 405 2812 if you have questions about your rights as a research subject.
We thank you very much for your cooperation

INLIGTINGDOKUMENT ***Datum:***

Titel van die studie: **'n Vergelykende studie tussen die sistoliese en diastoliese komponente van die kardiale siklus van blanke pasiente met abnormale spier funksionaliteit indeks teenoor pasiente met normale spier funksionaliteit indeks.**

Welkom by hierdie studie dames en here en dankie vir die geleentheid om julle in te lig aangaande hierdie studie.

Ons , Prof E van den Heever –Kriek en Mnr J.J. Steyn is besig met navorsing oor die spierfunksionaliteit indeks van die hart. In hierdie studie wil ons meer leer aangaande die hartspier funksionaliteits indeks.

Die studie behels die meting van tyds-intervalle van die hartsiklus met eggodardiograpfie (hart sonar) om te bepaal wat die funksionaliteits indeks van die hart beinvloed. Dit beteken dat ons sistool (sametrekking) en diastool (ontspanning) van die hart deur middel van Doppler (klankgolwe) gaan meet en die informasie wat ons kry sal gebruik om te bepaal of die hart normaal funksioneer.

Deur hierdie kennis te vergader sal ons kan bepaal watter deel van die hart se sistool of diastool verantwoordelik is vir probleme aangaande die normale funksionering van die hart. Die studie beplanning sluit in 120 manlike en vroulike Suid Afrikaanse patiënte wat roetine kardiologie ondersoeke moet ondergaan.

Ek wil dit onder U aandag bring dat hierdie 'n navorsingstudie is en nie roetine evaluasie nie. U deelname aan die studies al nie u roetine mediese sorg op enige manier beinvloed nie. Dis waarom ons u vra om deel te neem aan hierdie studie. Om aan die studie deel te neem moet u toestemming tot die volgende verleen.

- Dat u roetine eggokardiografiese data aan die navorsers Prof E van den Heever asook Mnr JJ Steyn vir die uitsluitlike doel van hierdie navorsing bekend gemaak mag word.
- Dat die spier funksionaliteits indeks gedoen mag word as deel van die eggokardiografiese ondersoek.

Die navorsings projek is baie veilig vir U as pasiënt. Die doen van die eggokardiogram is veilig vir u aangesien dit deel uitmaak van die normale konsultasie hartsonar. Neem ook kennis dat U nie vergoed sal word om deel te neem aan hierdie studie nie.

U deelname aan hierdie studie is dus vrywillig en indien u sou verkies om nie deel te neem aan die studie nie sal u geen van die normale mediese voordele verbeur nie. U mag enige tyd van die studie onttrek sonder om enige rede te verskaf. U ontrekking van die studie sal nie teen u gehou word nie en U konsultasie en behandeling by die kardioloog sal voortduur asof u nooit aan die studie deelgeneem het nie.

Die konfidensialiteit aangaande hierdie studie is van uitstaande belang. Daar sal stappe geneem word om u mediese rekords konfidensioneel te hanteer maar absolute konfidensialiteit kan nie gewaarborg word nie. Persoonlike inligting moet verskaf word indien 'n hof so beslis. Die Etiese komitee vir mediese navorsing mag ook die navorsings data inspekteer en/of die navorsings data dupliseer vir gehalte versekering asook om die data te analiseer.

Indien die navorsing gepubliseer word sal U naam beslis nie bekend gemaak word nie.

Ons bedank u hartlik vir u samewerking. Ons beantwoord graag enige van u vrae.

Kontakbesonderhede van die Navorsers**: –**

Prof E van den Heever-Kriek (Projekleier/Studieleier) Cell nr: 082 770 5356

Mnr. JJ. Steyn (Navorser) Cell nr: 082 3712887

Kontakbesonderhede van NEK Sekretariaat en Voorsitter **–** vir rapportering van klagtes/probleme

Telefoonnommer: 051-405 2812

Appendix B

Patient Consent Form

CONSENT TO PARTICIPATE IN RESEARCH

You have been asked to participate in a research study; “

You have been informed about the study by Mr. JJ. Steyn.
You may contact any of the following people any time if you have questions about the research or if you are injured as a result of the research.

Prof. WMJ van den Heever-Kriek at 082 7705356 (Project leader/Study leader)
Mr JJ Steyn at 0823712887 (Researcher)

You may also contact the **Secretariat of the Ethics Committee** of the Faculty of Health Sciences, University of the Free State at telephone number **(051) 4052812** if you have questions about your rights as a research subject.

Your participation in this research is voluntary, and you will not be penalized or lose benefits if you refuse to participate or decide to terminate participation.

If you agree to participate, you will be asked to fill a questionnaire and you will also be given a copy of this document as well as the participant information sheet, which is a written summary of the research.

“The research study, including the above information has been verbally described to me. I understand what my involvement in the study means and I voluntarily agree to participate”.

_____ _____
Signature of Participant Date

_____ _____
Signature of Witness Date

Toestemming tot deelname aan navorsing

U is gevra om deel te neem aan die navorsingstudie “n Vergelykende studie tussen die sistoliese en diastoliese komponente van die kardiale siklus van blanke pasiente met abnormale spier funksionaliteit indeks teenoor pasiente met normale spier funksionaliteit indeks”.
U is ingelig aangaande die studie deur Mr JJ Steyn.
U mag enige van die volgende mense skakel indien U enige vrae aangaande die navorsing studie het of as U ‘n besering opdoen as gevolg van die navorsing.
Prof WMJ van den Heever-Kriek at 082 7705356 (Studie leier)
Mr JJ Steyn at 0823712887 (Navorser)
U kan die Sekretariaat van die Etiekkomitee van die Fakulteit Gesondheidsweteskappe, UV by telefoonnommer (051) 4052812 kontak indien u enige vrae het oor u regte as ‘n proefpersoon.

U deelname aan die studie is vrywillig en U sal nie gepenaliseer word of enige voordele verloor indien U sou besluit om nie verder aan die studied eel te neem nie.

Indien U sou besluit om deel te neem sal U gevra word om die vorm te onderteken en ‘n kopie van die inligtings vorm sal aan U oorhandig word. Hierdie is ‘n opsomming van die navorsings projek.

Die navorsings studie asook die bogenoemde informasie is verbaal aan my verduidelik. Ek verstaan wat my doel in die studie is en gee toestemming om deel te neem aan die studie.

_____ _____
Handtekening van pasient Datum

_____ _____
Handtekening van navorser Datum

Appendix C

Echocardiography Data Sheet

DATA SHEET

SUBJECT'S RESEARCH NUMBER	
AGE	
WEIGHT	
LENGHT	
B.S.A.	
B.M.I.	
HEART RATE	
MALE OR FEMALE	

EJECTION FRACTION	
SHORTENING FRACTION	
MEAN SIRCUMFERENTIAL SHORTENING	
EJECTION TIME	
SEPTUM DIMENSION SYSTOLE	
SEPTUM DIMENSION DIASTOLE	
POSTERIOR WALL THICKNESS SYSTOLE	
POSTERIOR WALL THICKNESS DIASTOLE	
LEFT VENTRICLE INTERNAL DIMENSION SYSTOLE	
LEFT VENTRICLE INTERNAL DIMENSION DIASTOLE	
LEFT ATRIAL DIMENSION	
RELATIVE WALL THICKNESS	
LEFT VENTRICLE MASS	
LEFT VENTRICLE MASS INDEX	
STROKE VOLUME	
STROKE VOLUME INDEX	
CARDIAC OUTPUT	
CARDIAC INDEX	

TRANS MITRAL E VELOCITY	
TRANS MITRAL A VELOCITY	
DECELERATION TIME	
E/A RATIO	
ISOVOLUMETRIC RELAXATION TIME	
ANNULAR E TDI SEPTUM	
ANNULAR A TDI SEPTUM	
EM/AM RATIO SEPTUM	
ANNULAR SM SEPTUM	
ANNULAR E TDI POSTERIOR	
ANNULAR A TDI POSTERIOR	
EM/AM RATIO POSTERIOR	
ANNULUR SM POSTERIOR	

M TO M DISTANCE	

Notes