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LEFT VENTRICULAR DIASTOLIC FUNCTION IN EARLY HYPERTENSION

Thesis presented by

Ibrahim Ibrahim Almuntaser

For the degree of Doctor of Medicine (MD)

Faculty of Health Sciences
University of Dublin
Trinity College
April 2008

Supervisor:

- **Prof. John Feely**

  Head and Professor, Department of Pharmacology and Therapeutics, Trinity College and Consultant Physician, St James's Hospital

Declaration:

This is to declare that this research thesis "Left Ventricular Diastolic Function in Early Hypertension" is entirely my own work and it has not been submitted as an exercise for a degree at any other University.

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IBRAHIN

Ibrahim Almuntaser

Dedicated to My Wife Huda,

Mother Fujra, Son Yaseen, and Daughters

Shahed and Saja

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I am indebted to my main supervisor **Prof. John Feely**, Head and Professor, Department of Pharmacology and Therapeutics, Trinity College and Consultant Physician, St James's Hospital, who gave me this opportunity, and allowed me to follow my own ideas and supported me throughout. Without him this project would not have been possible.

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ABSTRACT

LEFT VENTRICULAR FUNCTION IN EARLY HYPERTENSION

Ibrahim Ibrahim Almuntaser

This thesis presents the development of clinical applications of the relatively new ultrasound modality, TDI in conjunction with the earlier more established modalities of echocardiography. The contents of this thesis outline the investigations leading up to the recognition of the early diastolic dysfunction in hypertension. From there we examine the usefulness of new parameters of diastole, which allows us to measure the diastolic function in newly diagnosed untreated hypertensive patients.

Doppler echocardiography provides an important noninvasive method for the assessment and follow-up of patients with diastolic dysfunction (DD). However, no comprehensive consensus regarding diagnostic echocardiographic criteria for diastolic dysfunction has been reached, but guidelines have been proposed. We therefore assessed the prevalence of diastolic dysfunction using criteria provided by the Canadian consensus, American Medical Association, and European guidelines in patients with newly diagnosed hypertension. In addition, we assessed the same patients with a comprehensive series of Tissue Doppler parameters to define more accurately the prevalence of diastolic dysfunction in a population newly diagnosed hypertension.

In our study, the prevalence of LV diastolic dysfunction varied according to the criteria used. There was a high prevalence of LV diastolic dysfunction 59% using Canadian consensus guidelines of whom 27% had a pseudonormal pattern unmasked with Valsalva and 32% had impaired relaxation at rest. Significantly fewer 10%

patients were diagnosed using European guidelines or the American Medical Association guidelines 23%. Using TDI e'/a'<1, the prevalence of LV diastolic dysfunction was 59% identical to our findings using the Canadian consensus guidelines. In conclusion, current national consensus guidelines defining LV diastolic dysfunction vary widely and underdiagnose LV diastolic dysfunction in patients with newly diagnosed hypertension. TDI assessment is a rapidly and widely available tool that is as sensitive as the most stringent national guideline, and should be systematically incorporated into a more comprehensive assessment of LV diastolic dysfunction in this population. Physicians, in particular non-cardiac imaging specialists, should be cautious about echocardiographic reports describing diastolic dysfunction and ensure that the assessment of diastolic function is based on a comprehensive echocardiographic study integrating all available two dimensional, Doppler flow data and TDI.

Conversely, we assessed the prevalence of DD and its relationship with parallel arterial stiffening in newly diagnosed hypertension. Although this study does not answer the question whether arterial stiffness precedes LV diastolic dysfunction or these changes occur in parallel the coupling of LV diastolic dysfunction and arterial stiffness in early hypertension may put these patients at increased risk of cardiovascular events. Therefore routine screening for presymptomatic ventricular and vascular abnormalities as well as aggressive BP lowering strategies in newly diagnosed untreated hypertension may help to reduce the risk of early cardiovascular events in hypertension.

We used a novel index of myocardial stiffness to detect subtle changes of diastolic dysfunction, which was shown to be an important addition to the echocardiographic evaluation of hypertensive patients. This index may provide early detection of diminished myocardial function and may help identify patients requiring aggressive and targeted medical therapy.

Finally we evaluated whether anti-hypertensive treatment could influence left ventricular (LV) morphofunctional characteristics (induce LV hypertrophy regression and improvement of diastolic function) in newly diagnosed untreated hypertensive patients. Our finding showed that antihypertensive treatment may induce a significant improvement in LV diastolic function.

The general applicability of our findings will have to be confirmed and deepened in future studies, with larger number of subjects with different races. However this work has contributed to the strong potential of TDI and other echocardiographic techniques and indices that hopefully will contribute to the understanding and prevention of early complications related to hypertensive heart disease.

SUMMARY

Doppler echocardiography provides an important noninvasive method for assessment and follow-up of patients with diastolic dysfunction. However, no comprehensive consensus regarding diagnostic echocardiographic criteria for diastolic dysfunction has been reached, but guidelines have been proposed. We therefore assessed the prevalence of diastolic function using criteria provided by the Canadian consensus, American Medical Association, and European guidelines in patients with newly diagnosed hypertension. In addition, we assessed the same patients with a comprehensive series of Tissue Doppler parameters to define more accurately the prevalence of diastolic dysfunction in a newly diagnosed hypertensive population. Our findings demonstrate the wide variance in the diagnosis of diastolic dysfunction based on the current standard echocardiographic criteria. Thus current guidelines are of limited value and could be enhanced by the inclusion of TDI. Although this study does not answer the question whether arterial stiffness precedes LV diastolic dysfunction or these changes occur in parallel, the coupling of LV diastolic dysfunction and arterial stiffness in early hypertension may put these patients at increased risk of cardiovascular events. Therefore routine screening for presymptomatic ventricular and vascular abnormalities as well as aggressive BP lowering strategies in newly diagnosed untreated hypertension may help to reduce the risk of early cardiovascular events in hypertension. In our study, a novel index of myocardial stiffness based on the pressure volume relationship was shown to be a promising index in documentary early cardiac abnormalities in newly diagnosed untreated hypertensive patients and may be useful in deciding on aggressive BP lowering strategies. Our finding showed that antihypertensive treatment may induce a significant improvement in LV diastolic function.

This work has contributed to the strong potential of TDI and other echocardiographic techniques and indices that hopefully will contribute to the understanding and prevention of early complications related to hypertensive heart disease.

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CHAPTER 8

List of Abbreviations:

(Hz) Hertz

(TMD) Transmitral Doppler

(LV) Left ventricular

(TDI) Tissue Doppler imaging

(LVH) Left ventricular hypertrophy

(BP) Blood pressure

(CO) Cardiac output

(PR) Peripheral resistance

(RAS) Rennin-angiotensin system

(CR) Concentric remodelling

(CHR) Concentric hypertrophy

(ER) Eccentric remodelling

(IER) Inward eutrophic remodelling

(IHR) Inward hypertrophic remodelling

(LVDD) Left ventricular diastolic dysfunction

(CC) Canadian Consensus

(Eu) European

(AMA) American Medical Association

(EDPVR) End-diastolic pressure-volume relation

(IVRT) Isovolumic relaxation time

(NYHA) New York Heart Association

(CHF) Congestive heart failure

(PVF) Pulmonary vein flow

(DM) Diabetes mellitus

(DT) Deceleration time

(LA) Left atrial

(AR) Aortic root

(LVEDD) Left ventricular end-diastolic dimension

(LVESD) Left ventricular end-systolic dimension

(IVSD) Interventricular septal diameter

(PWD) Posterior wall diameter

(PWV) Pulse wave velocity

(AIx) Augmentation index

(CHD) Coronary heart disease

(VSM) Vascular smooth muscle

(LVMI) Left ventricular mass index

(BMI) Body mass index

(RWT) Relative wall thickness

(MPI) Myocardial performance Index

(ACE) Angiotensin converting enzyme

(BNP) B-type natriuretic peptide

(LVSI) Left ventricular stiffness index

(HCM) Hypertrophic cardiomyopathy

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- Almuntaser I, Brown A, Crean P, Murphy R, King G, Mahmud A, Feely J. Left ventricular function in early hypertension; are there reliable echocardiographic measures of diastolic function? **Dec 2006; EUROECHO10, Prague, Czech Republic.**

- Ibrahim Almuntaser, Usama Boles, Angie Brown, Ross Murphy, Peter Crean, Gerard King, Azra Mahmud, John Feely. Comparison of echo and

electrocardiogram characteristics in diagnosing early cardiac effects of hypertension. . **Oct.2007; ICS Scientific Meeting; Belfast, North of Ireland.**

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- Ibrahim Almuntaser, Angie Brown, Ross Murphy, Gerard King, Peter Crean, Azra Mahmud, John Feely. Comparison of the A-Ar interval with indices of LV diastolic function in patients with newly diagnosed hypertension. **Dec 2007; EUROECHO, Lisbon, Portugal.**

CHAPTER 1

CLINICAL APPLICATION OF ECHOCARDIOGRAM

CHAPTER 1

1.1 Basic physic of Doppler echocardiogram

Ultrasound is simply sound waves, like audible sound. Although some physical properties are dependent on the frequency, the basic principles are the same. Sound consists of waves of compression and decompression of the transmitting medium (e.g. air or water), travelling at a fixed velocity. Sound is an example of a longitudinal wave oscillating back and forth in the direction the sound wave travels, thus consisting of successive zones of compression and rarefaction. Transverse waves are oscillations in the transverse direction of the propagation (1) (Fig 1.1).

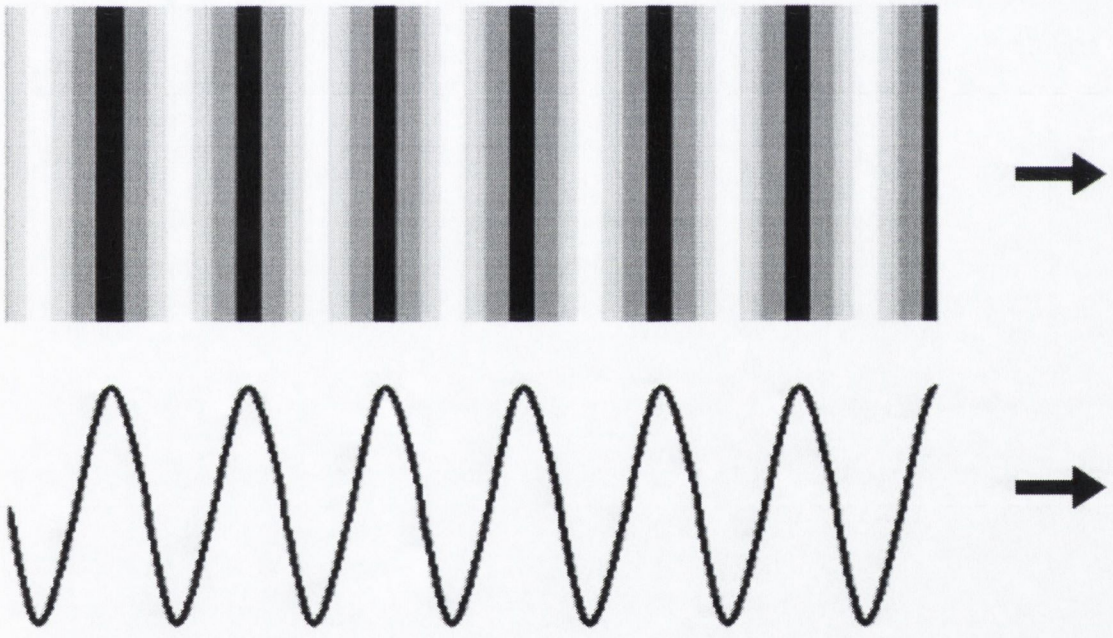


Fig. 1.1 Schematic illustration of a longitudinal compression wave (top) and transverse wave (bottom).

The audible sound frequencies are below 15 000 to 20 000 Hz, while diagnostic ultrasound is in the range of 1 - 12 MHz. Audible sound travels around corners, we can hear sounds around a corner (sound diffraction). With higher frequencies the sound tend to move more in straight lines like electromagnetic beams, and will be reflected like light beams. At higher frequencies the ultrasound behaves more like

electromagnetic radiation. Ultrasound is generated by piezoelectric crystals that vibrate when compressed and decompressed by an alternating current applied across the crystal, the same crystals can act as receivers of reflected ultrasound, the vibrations induced by the ultrasound pulse (1).

1.2 Doppler Echocardiography

The first description of the physical principles used in Doppler echocardiography is attributed to Johan Christian Doppler, an Austrian mathematician and scientist who lived in Salzburg the first half of the 19th century. Doppler's initial descriptions referred to changes in the wavelength of light as applied to astronomical events. In 1842, he presented a paper entitled "On the Coloured Light of Double Stars and Some Other Heavenly Bodies" where he postulated that certain properties of light emitted from stars depend upon the relative motion of the observer and the wave source. He suggested that the colored appearance of some stars was caused by their motion relative to the earth, the blue ones moving toward earth and the red ones moving away (2).

Doppler pulses can either be used as a pulsed Doppler, where a pulse is sent out, and the frequency shift in the reflected pulse is measured at a certain time. This will correspond to a certain depth, i.e. velocity is measured at a specific depth, which can be adjusted. The width is the same as the beam width, and the length of the sample volume is equal to the length of the pulse. The same transducer is used both for transmitting and receiving. One drawback with pulsed Doppler is that the Doppler shift is very small compared to the ultrasound frequency. This makes it difficult to estimate the Doppler shift from a single pulse, without increasing the pulse length too far. A velocity of 100 cm/s with an ultrasound frequency of 3.5 MHz results in a maximum Doppler shift of 2.3 KHz. The solution to this problem is shooting multiple

pulses in the same direction and produce a new signal with one sample from each pulse, the Doppler curve from this signal will be a new curve with the frequency equal to the Doppler shift. The pulsed mode results in a practical limit on the maximum velocity that can be measured. In order to measure velocity at a certain depth, the next pulse cannot be sent out before the signal is returned. The Doppler shift is thus sampled once for every pulse that is transmitted, and the sampling frequency is thus equal to the pulse repetition frequency (1).

As will be seen in this chapter, the technique may be used for detection of cardiac valvular insufficiency and stenosis as well as a large number of other abnormal flows. The current interest in Doppler echocardiography has reached a remarkable level in just the past few years. Doppler methods extend the use of cardiac ultrasound into the evaluation of normal and abnormal flow states and provide quantitative data that are essential in the clinical decision making process concerning patients with heart disease (3). It has achieved a prominent role in the clinical and research assessment of left ventricular diastolic function, providing beat by beat quantification of left ventricular inflow velocities with a technique that is non invasive, low cost, portable, and without hazard.

Diastolic filling can be quantified by measuring the peak velocity of early left ventricular filling (E wave cm/sec), the peak velocity of late left ventricular filling (A wave cm/sec), the E: A ratio, and deceleration time (ms) (fig 1.2). Consequently, the Doppler frequency shift associated with blood is greater than that of cardiac tissue, and the amplitude of the signals is lower. In conventional Doppler, the higher amplitude signals from moving tissue are purposely filtered out so that only blood signals are processed (2).

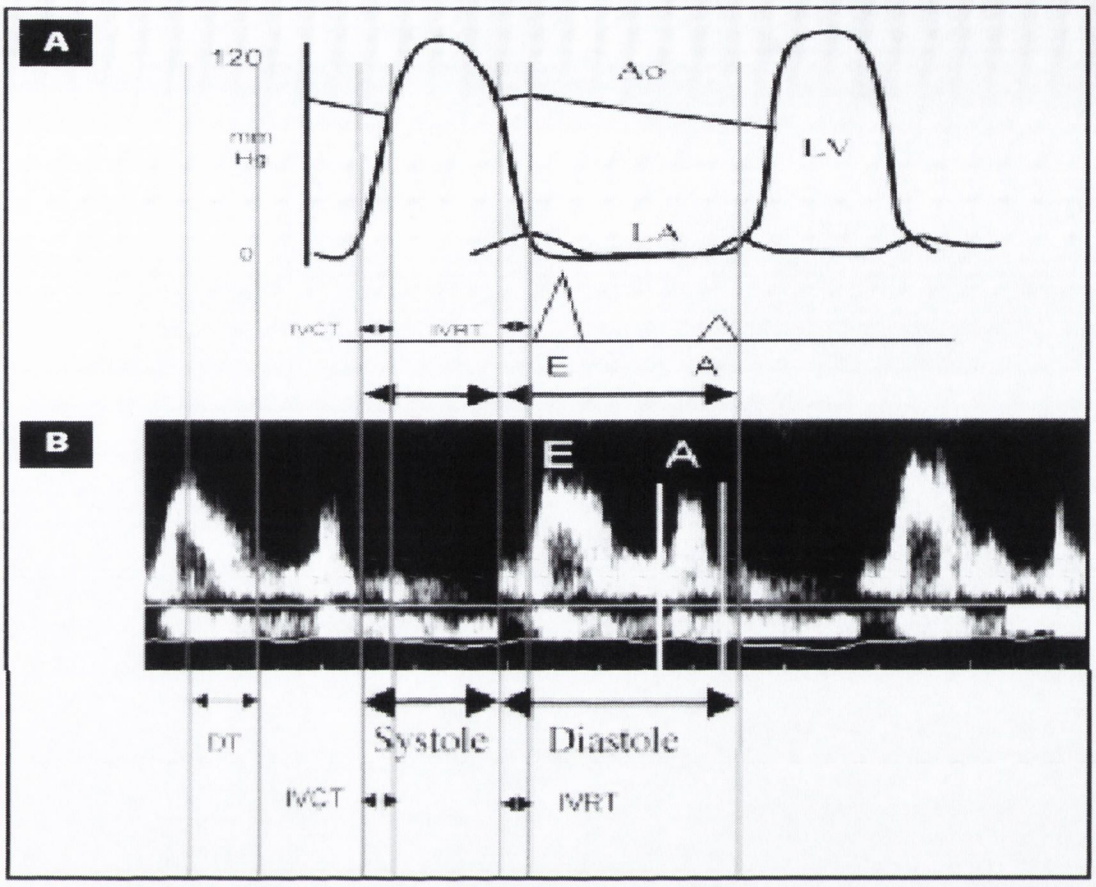


Figure 1.2. Schematic drawing showing (A) normal left atrial and ventricular pressures, (B) mitral inflow, resulting from atrioventricular gradients, in a healthy subject. Mitral inflow velocities were obtained by placing the PW Doppler sample volume between the tips of the mitral leaflets.

Previous study showed that, the analysis of transmitral Doppler (TMD) flow velocity (figure 1.2) has been used widely for the evaluation of left ventricular (LV) diastolic function. However, the great range of factors that may affect ventricular filling, especially those determining an increase in the diastolic pressure, may impose difficulties in the recognition of the abnormal filling pattern called pseudonormalization (moderate diastolic dysfunction). Progression of diastolic dysfunction with a successive increase in left-sided filling pressures makes Doppler echocardiography indexes of mitral flow return to "normal" (pseudonormalization). This advanced degree of diastolic impairment frequently requires special manoeuvres or other methods to unmask the underlying ventricular dysfunction (4).

1.3 TISSUE DOPPLER IMAGING

As well as blood flow, the Doppler principle can also be used to evaluate myocardial tissue velocities. The main principle is that blood has high velocity (Typically above 50 cm/s, although also all velocities down to zero), but low density, resulting in low intensity (amplitude) reflected signals. Tissue has high density, resulting in high intensity signals, but low velocity (typically below 20 cm/s). The difference in the applications used for the two sets of signals is mainly differences in filtering, applying a high pass filter in Doppler flow, and low pass filter in tissue Doppler (Although the latter is not absolutely necessary) (1).

Tissue Doppler imaging (TDI) (fig 1.3), was first described by **Isaaz et al. (1989), who** used the technique to measure the velocity of the posterior wall with an ordinary pulsed Doppler with low set of the frequency shift down to measure velocities below10 cm s (5). TDI thus enables the direct quantitative measurement of contraction and relaxation velocities of the cardiac muscle. Its usefulness has been demonstrated in the assessment of ventricular diastolic function, including the evaluation of cases that are difficult to interpret solely on the basis of the usual indexes obtained by TMD (6).

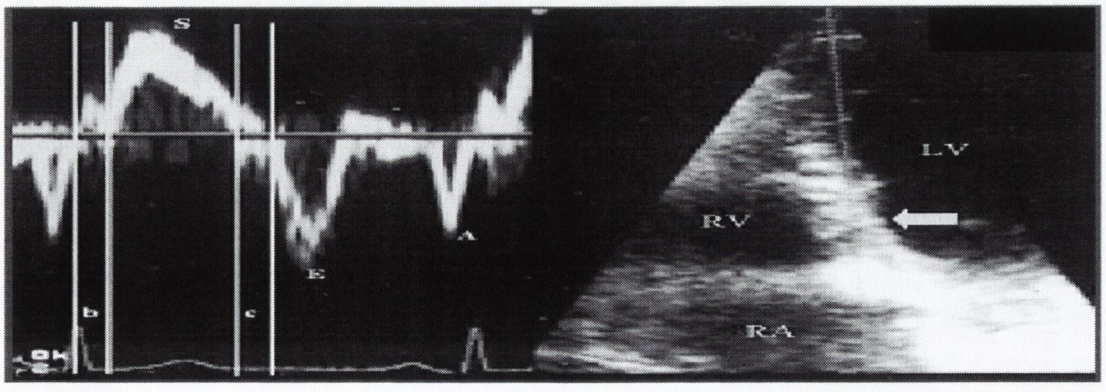


Figure 1.3. Longitudinal pulsed wave Doppler of the myocardium, 4 chamber view: the sample volume (arrow) is positioned at the basal level of the interventricular septum.("S"): Systolic phase; ("E"): Rapid filling_period; ("A"): Atrial contraction;("b"): Regional isovolumic contraction time (RIVCT); ("c"): Regional iso-volumic relaxation time (RIVRT); RV: right ventricle; LV: left ventricle;RA: right atrium.

The spectral TDI method provides higher temporal resolution and resolves all peak velocities. With this modality a sample volume is placed within the myocardium (either in the endocardium or the epicardium) and the low Doppler shift of frequencies recorded from the heart wall moving through the sample volume during the cardiac cycle is recorded. The pattern (Fig. 1.3) can be divided into two parts, systolic and diastolic, from which several measurements can be obtained: **1**. The systolic phase is characterized by a positive wave (S) preceded by the time taken for regional isovolumic contraction; **2.** The diastolic phase, which is more complex, is composed of 4 periods: **a**) regional isovolumic relaxation; **b**) the rapid filling period characterized by a negative wave (E); **c**) diastasis, and **d**) filling due to atrial contraction, represented by a second negative wave (A). The 2D-TDI method provides acceptable spatial resolution along the direction of the ultrasound beam but lower temporal resolution compared to pulsed TDI (pulsed measures peak velocities; color encodes mean velocities). The temporal resolution varies according to the system used and ranges from 100 msec in first generation to 10 msec in the new fully digital systems (7).

The possibility to perform such measurements was first described earlier by a Japanese group **(Yoshitoshi & Machii, 1966)**. The physical differences between the signal returning from moving blood and cardiac tissue motion is that the velocity in the hydraulic part (blood) is higher than in tissue (mechanical part) approximately a 10-fold (10 cm s) during normal circumstances. The result will be a lower Doppler shift in the myocardial wall than in blood. The tissue signal will have stronger amplitude because of more scatter returning from tissue than from blood. This will result in that the tissue Doppler signal could be recorded either by low pass filtering or gain damping, or with a combination of both (8).

1.3.1 Role of TDI in Clinical Diagnosis

A previous study by **(Garcia-Fernandez et al., 1999)** confirmed the utility of TDI in the detection of regional dysfunction associated with ischaemic heart disease. In that study, the myocardium was divided into sixteen segments according to the anatomy of the coronary circulation. TDI was then performed in each segment in both healthy controls and ischaemic heart disease patients. In diseased wall regions within the patient group, both the mean peak early diastolic velocity and the E/A diastolic velocity ratio were reduced, indicating abnormal myocardial relaxation in those areas. In addition, the regional isovolumetric time, defined as the time interval from the second heart sound to the onset of the E wave, was prolonged. No differences were observed in any of these parameters, between the normally perfused segments of ischaemic patients and the corresponding segments of the control group. These results suggest that by measuring myocardial velocities, TDI can be used to assess regional left ventricular function (9).

In 1994, Fleming et al presented the concept of transmyocardial gradients as indicators of myocardial viability. The advantage of using this parameter instead of general myocardial velocity is that it can be used to assess contractility at different levels in the heart wall, thereby evaluating the transmural extent of ischaemia (10). This study employed colour TDI, which has been described by **Mc Dicken et al, 1992 (**11**).** This mode of Doppler display superimposes a colour-coded representation of velocity onto an M-mode (time-motion) trace or two-dimensional image. The latter is a "slice" of the heart, similar to an anatomical section and produced by a fan of ultrasound beams, each beam conveying information concerning the depth of the interface from which it was reflected. This technique was used to detect the transmyocardial gradient, which was defined as "a gradual spatial change in the value

of velocity estimates", this arises from the contraction and relaxation of the muscle fibres while the epicardium remains relatively static. The greater endocardial than epicardial excursion also causes a change in wall thickness, which has been used previously as a reliable index of regional myocardial function. It was reported that, Doppler velocity gradients could be used to express left ventricular regional function (11).

1.3.2 Relationship between TMD and TDI

Figure 1.4 shows the correspondence between the normal pattern of TMD velocities obtained by mitral inflow and those obtained by mitral annular/myocardial TDI, in a healthy subject reflecting the major physiologic events that occur during the diastolic phase of the cardiac cycle (12).

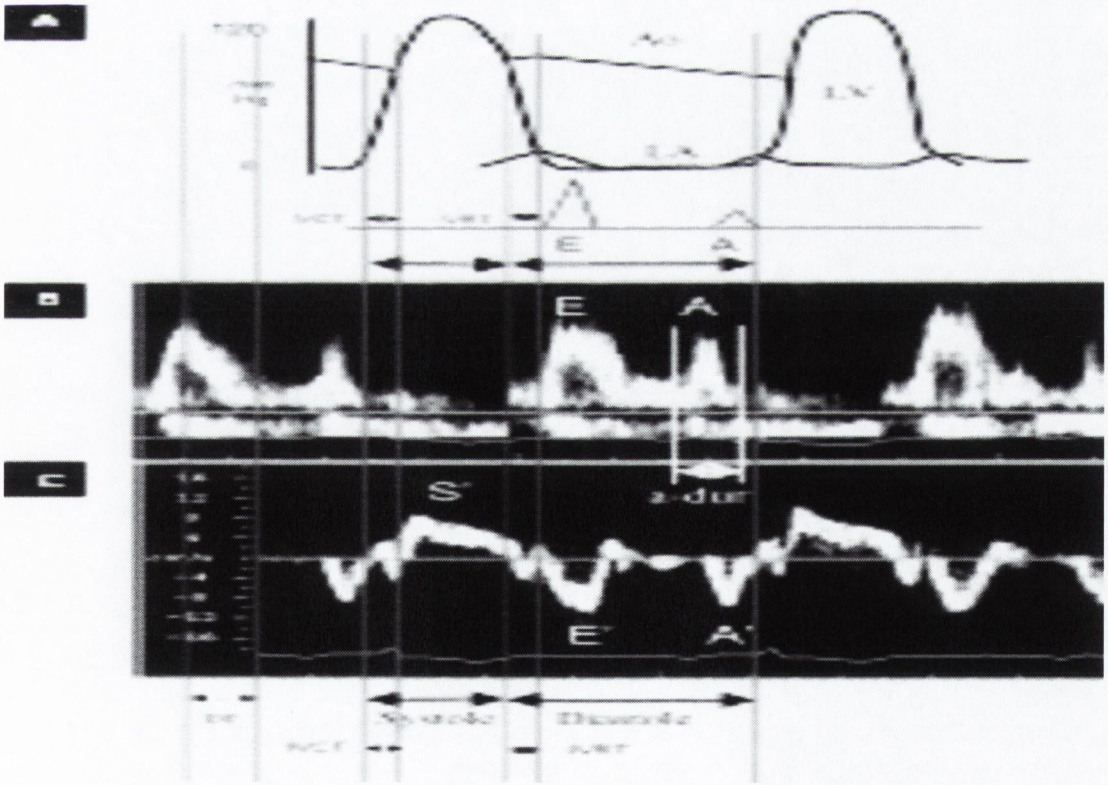


Figure 1.4. Schematic drawing showing (A) normal left atrial and ventricular pressures, (B) normal pattern of TMD and (C) TDI in a healthy subject.

Transmitral flow pulsed-wave Doppler echocardiography is the most conventional method to evaluate diastole. Although this method had initially determined what would become known as diastolic measurement pattern, It shows an important variation in E and A wave indices, and in the ratio between both waves (E/A) in view of changes induced by LV preload (13). Tissue Doppler is the method that assesses segmental myocardial velocity at both diastole and systole (14). In a study comparing the interventricular septum on TDI with that of transmitral flow in twenty patients with standard relaxation (E/A wave ratio <1), who received an infusion of 700 ml of physiological saline, a significant change was observed in the E/A velocity ratio measured by transmitral flow (E/A=0.7 ± 0.1 *vs.* 0.9 ± 0.1 P< 0.01), which was not observed in the TDI measurements (E'/A'=0.5 ± 0.1 vs. 0.5 ± 0.1. P=NS) (15). These results point to the fact that, peak early myocardial mitral annular diastolic velocity of TDI is relatively load independent and provides a more accurate assessment of LV filling pressure (16). Unlike biphasic mitral inflow E wave and E/A ratio, TDI E' wave and E'/A' ratio show progressive abnormality with increasing diastolic relaxation (17) (Figure 1.5) and, hence, can differentiate a pseudonormal from a normal Doppler mitral inflow pattern (17-19).

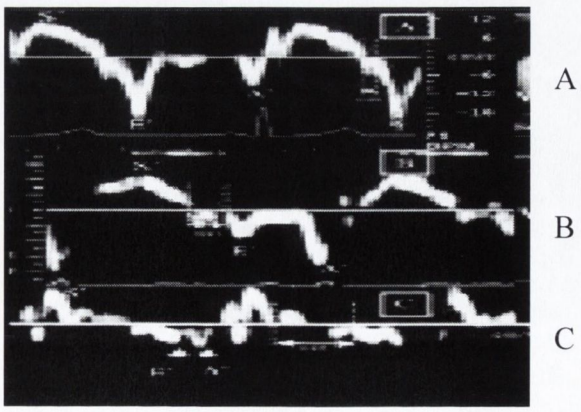


Figure 1.5. (A-C) Mitral annular pulsed-wave (PW) Doppler tissue imaging tracings in (A) a normal subject, (B) a patient with abnormal left ventricular (LV) relaxation, and (C) a patient with restrictive cardiomyopathy.

Myocardial TDI E'/A' wave ratio is helpful in the early assessment of diastolic dysfunction in patients with hypertension, (20) transplantation rejection, (21) or restrictive cardiomyopathy (22). Although recent observations suggest load dependency of the TDI E' wave, particularly in healthy human subjects with normal LV relaxation, (23) preload was found to have a minimal effect on TDI E' wave in the presence of abnormal LV relaxation in experimental animal models.

The advantage of TDI over the conventional ultrasound techniques is that TDI uses low-velocity and high amplitude Doppler signals, in contrast to mitral inflow, which uses high-velocity and low-amplitude signals. Doppler tissue velocities may be displayed either in spectral pulsed or in color-encoded M-mode or 2-dimentional mode. The color 2-dimentional method provides a high spatial but a low temporal and velocity range resolution (typically 16 velocity values). On the other hand, the spectral pulsed Doppler method provides the highest temporal and velocity range resolution. To interpret the velocities obtained by either spectral pulsed tissue Doppler, we must remember that they represent the component of motion of a given segment in a direction parallel to the imaging cursor. This motion is not only caused by myocardial contraction and relaxation but also by translation and rotation of the cardiac structures (6).

Previous studies have shown that the Doppler mitral flow velocity pattern may be falsely negative for diastolic dysfunction if the phenomenon of pseudonormalization is not taken into account. It has been implied that TDI may be relatively preload independent and could thus be superior to TMD recordings in identifying patients with diastolic dysfunction even in the presence of a normal Doppler mitral flow-filling pattern (24).

Peak early velocity of TDI (E) has been shown to correlate well with the time constant of isovolumic relaxation and appears to be relatively independent of preload. TDI have been found to be clinically useful in differentiating patients with restrictive cardiomyopathy from those with constrictive pericarditis whom LV relaxation is normal (6).

1.4 AIM OF THE STUDY

Doppler echocardiography provides an important noninvasive method for assessment and follow-up of patients with diastolic dysfunction (DD). However, no comprehensive consensus regarding diagnostic echocardiographic criteria for diastolic dysfunction has been reached, but guidelines have been proposed. We therefore assessed the prevalence of diastolic function using criteria provided by the Canadian consensus, American Medical Association, and European guidelines in patients with newly diagnosed hypertension. In addition, we assessed the same patients with a comprehensive series of Tissue Doppler parameters to define more accurately the prevalence of diastolic dysfunction in a newly diagnosed hypertensive population. Conversely, we assessed the prevalence of DD and its relationship with parallel arterial stiffening in newly diagnosed hypertension. We used a novel index of myocardial stiffness in detecting subtle changes of diastolic dysfunction in the same group. Finally we evaluated whether anti-hypertensive treatment could influence left ventricular (LV) morphofunctional characteristics (induce LV hypertrophy regression and improvement of diastolic function) in newly diagnosed untreated hypertensive patients.

CHAPTER 2

HYPERTENSION

CHAPTER 2

2.1 HYPERTENSION

2.1.1 INTRODUCTION

Hypertension is one of the most common diseases afflicting humans throughout the world. Because of the associated morbidity and mortality and the cost to society, hypertension is an important public health challenge. Over the past several decades, extensive research, widespread patient education, and a concerted effort on the part of health care professionals have led to decreased mortality and morbidity rates from the multiple organ damage arising from years of untreated hypertension. Hypertension is the most important modifiable risk factor for coronary heart disease (the leading cause of death in North America), stroke (the third leading cause), congestive heart failure, end-stage renal disease, and peripheral vascular disease (25). Therefore, health care professionals must not only identify and treat patients with hypertension but also promote a healthy lifestyle and preventive strategies to decrease the prevalence of hypertension in the general population.

2.2 HISTORICAL BACKGROUND

Stephen Hales measured blood pressure for the first time in 1773. Hales also described the importance of blood volume in blood pressure regulation. The contribution of peripheral arterioles in maintaining blood pressure, described as "tone," was first described by Lower in 1669 and subsequently by Sénac in 1783.The role of vasomotor nerves in the regulation of blood pressure was observed by such eminent investigators as Claude Bernard, Charles E. Edouard, Charles Brown-Séquard, and Augustus Waller. William Dayliss advanced this concept in a monograph published in 1923. Cannon and Rosenblueth developed the concept of

humoral control of blood pressure and investigated pharmacologic effects of epinephrine. Three contributors who advanced the knowledge of humoral mechanisms of blood pressure control are T.R. Elliott, Sir Henry Dale, and Otto Loew. Richard Bright, a physician who practiced in the first half of the 19th century, observed the changes of hypertension on the cardiovascular system in patients with chronic renal disease. George Johnson in 1868 postulated that the cause of left ventricular hypertrophy (LVH) in Bright disease was the presence of muscular hypertrophy in the smaller arteries throughout the body. Further clinical pathologic studies by Sir William Gull and H.G. Sutton (1872) led to further description of the cardiovascular changes of hypertension. Frederick Mahomed was one of the first physicians to systematically incorporate measurement of the arterial waveform as a part of a clinical evaluation. The recognition of primary, or essential, hypertension is credited to the work of Huchard, Vonbasch, and Albutt. Observations of Janeway and Walhard led to the recognition of target organ damage, which branded hypertension as the "silent killer." The concepts of renin, angiotensin, and aldosterone were advanced by several investigators in the late 19th and early 20th centuries. (25).

2.3 PATHOPHYSIOLOGY

Blood pressure (BP) is the product of cardiac output (CO) and peripheral resistance (PR), i.e., BP = CO X PR. CO is the volume of blood pumped by the left ventricle into the aorta per minute. PR relates to the viscosity of the blood and the width and elasticity of the peripheral arteries. For high blood pressure to develop there must be an increase in either CO or PR, or both. Initial rises in BP are usually due to increased CO, following increases in intravascular volume and venous return to the heart. The main hormone system involved in BP control is the rennin-angiotensin system (RAS) (26).

2.4 PATHOGENESIS OF HYPERTENSION

The pathogenesis of essential hypertension is multifactorial and highly complex. Multiple factors modulate the blood pressure for adequate tissue perfusion and include humoral mediators, vascular reactivity, circulating blood volume, vascular caliber, blood viscosity, cardiac output, blood vessel elasticity, and neural stimulation. A possible pathogenesis of essential hypertension has been proposed in which multiple factors, including genetic predisposition, excess dietary salt intake, and adrenergic tone, may interact to produce hypertension. Although genetics appears to contribute to essential hypertension, the exact mechanism has not been established (25).

The natural history of essential hypertension evolves from occasional to established hypertension. After a long invariable asymptomatic period, persistent hypertension develops into complicated hypertension, in which target organ damage to the aorta and small arteries, heart, kidneys, retina, and central nervous system may be evident. Commonly the progression begins with prehypertension in persons aged 10-30 years (by increased cardiac output) to early hypertension in persons aged 20-40 years (in which increased peripheral resistance is prominent) to established hypertension in persons aged 30-50 years, and, finally, to complicated hypertension in persons aged 40-60 years (25).

The early stage of hypertension has been described as high-output hypertension. High-output hypertension results from decreased peripheral vascular resistance and concomitant cardiac stimulation by adrenergic hyperactivity and altered calcium homeostasis. In contrast, the chronic phase of essential hypertension characteristically has normal or reduced cardiac output and elevated systemic vascular resistance. The

vasoreactivity of the vascular bed, an important phenomenon mediating changes of hypertension, is influenced by the activity of vasoactive factors, reactivity of the smooth muscle cells, and structural changes in the vessel wall and vessel caliber, expressed by a lumen-to-wall ratio. Patients who develop hypertension are known to develop a systemic hypertensive response secondary to vasoconstrictive stimuli. Alterations in structural and physical properties of resistance arteries, as well as changes in endothelial function, are probably responsible for this abnormal behaviour of vasculature. Furthermore, vascular remodeling occurs over the years as hypertension evolves, thereby maintaining increased vascular resistance irrespective of the initial hemodynamic pattern (25).

2.5 HYPERTENSION AND HEART

Hypertension is a major risk factor for cardiovascular morbidity and mortality. The presence of hypertension more than doubles the risk for coronary heart disease, including acute myocardial infarction and sudden death, and more than triples the risk of congestive heart failure as well as strokes (27).

Cardiovascular events in the hypertensive patients increase steadily with increases in arterial pressure. The individuals at greatest risk of suffering a cardiovascular event are those with the highest arterial pressures. However, mild to moderate hypertension is more common than severe hypertension, and much of the population burden of disease because of hypertension may be attributed to moderate rather than severe hypertension (28). Therefore, the level of the pressure and time of exposure appear to be key factors in determining the effect on the heart.

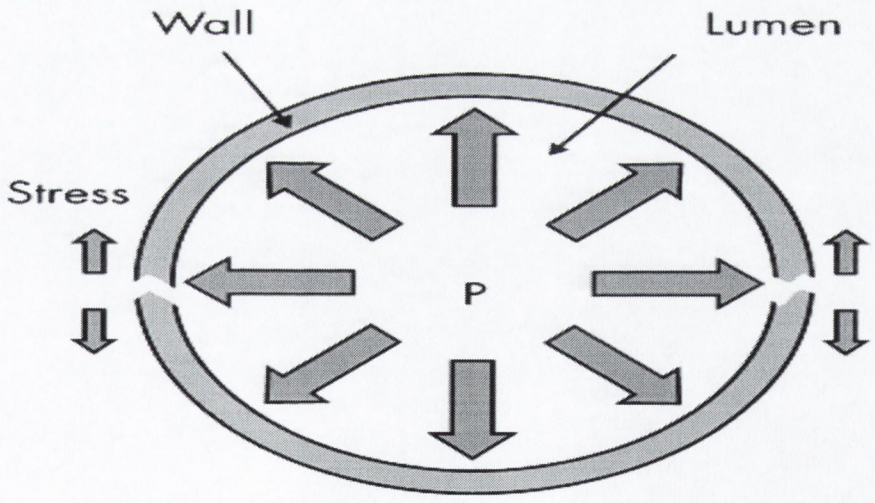
Several studies have shown that subjects with borderline to mild hypertension do not make up a uniform population because only some will develop hypertensive

complications. It is therefore difficult to identify those patients who will benefit most from antihypertensive therapy. In this respect, early cardiac abnormalities might represent an important clinical feature used for recognizing hypertensive patients who are at greater risk (29).

Patients with high blood pressure frequently have abnormalities of cardiac structure or function, including left ventricular hypertrophy, systolic and diastolic dysfunction and in extreme cases, overt heart failure. There may also be concomitant or related coronary heart disease and an increased risk of arrhythmias and sudden death (30).

2.6 STRUCTURAL CHANGES IN HYPERTENSION

Both the heart and arteries adapt their structure in response to altered load. This occurs physiologically (for example, during somatic growth) and pathologically in hypertension. Increased pressure exerts an increased load on a thin walled chamber or tube by increasing wall tension according to Laplace's law (fig 2.1) (31).



$$T = P \times R$$

(where T = tension, P = pressure, R = lumen radius)

$$\sigma = T/h$$

(where σ = stress, h = wall thickness)

Figure 2.1 Wall stress and tension in a thin walled tube or chamber (Laplace's law).

More complex expressions for wall tension in the heart or blood vessels exist, but this is a reasonable approximation. A rise in tension results in increased wall tensile stress. Normalisation of wall tensile stress can be achieved either by an increase in wall thickness or by a reduction in chamber/lumen diameter, or both.

2.6.1 Cardiac remodelling in hypertension and its functional consequences

Cardiac structure is influenced by pressure and volume loads (32). In hypertension changes in left ventricular structure occur in response to the increased pressure load and represent an attempt by the heart to normalise myocardial wall stress. The increased resistance primarily causes the increased pressure load in hypertension, although reduced compliance and possibly altered magnitude and timing of reflected pressure waves make a contribution (31).

2.6.2 Patterns of remodeling: relation to load

Hypertension is associated with a spectrum of structural change in the left ventricle (31). The pattern of change may reflect differences between individuals in terms of age, haemodynamics, 24-hour blood pressure profile, arterial stiffness, plasma volume, myocardial performance, neurohormonal status or genetic influences (33). Hypertensive changes can be classified as showing hypertrophy (an increase in left ventricular mass) or remodelling (normal left ventricular mass, abnormal relative wall thickness) (fig 2.2) (31).

Remodelling is seen in normal aging without hypertension and is probably an adaptation to preserve ejection fraction despite reduced midwall fibre function (34). It has become apparent that myocardial fibre shortening is reduced in human hypertension. Early clinical investigations assessed cardiac function using endocardial measurements. Recently, it has been appreciated that there is a discrepancy between shortening measured at the endocardium and at the midwall. Midwall shortening is

commonly reduced in left ventricular hypertrophy and the process of wall hypertrophy allows total wall shortening to remain normal in spite of a depression in fibre shortening—that is, the change in left ventricular geometry allows the chamber function to remain normal (35).

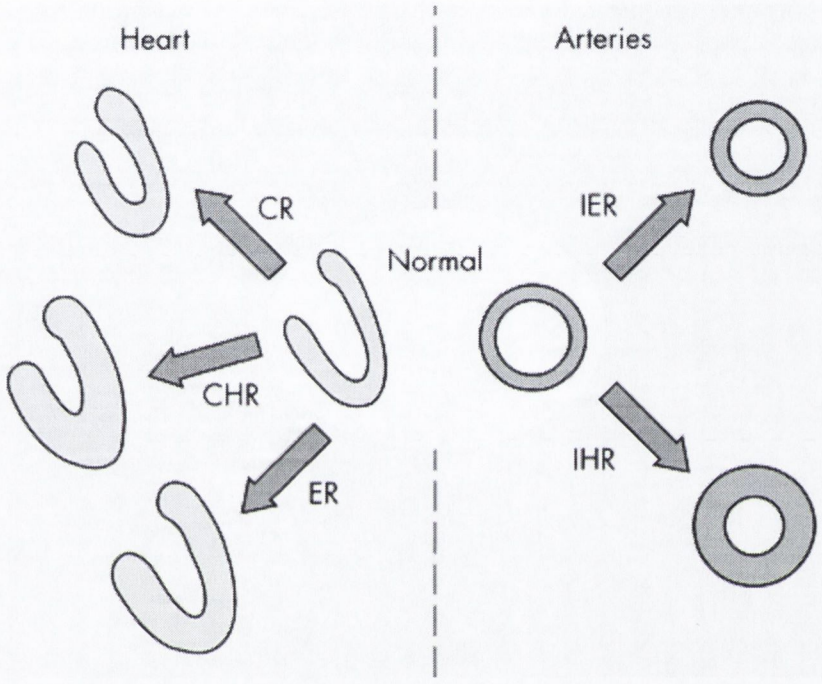


Figure 2.2.Major patterns of myocardial and vascular remodelling in hypertension. Concentric remodelling (CR); concentric hypertrophy (CHR); eccentric remodelling (ER); inward eutrophic remodelling (IER); inward hypertrophic remodelling (IHR).

Normal myocardium contains an interstitial fibrous network upon which the myocytes are arranged. Although hypertrophy primarily involves myocytes, the interstitial network also changes. This occurs initially in a perivascular distribution but progressively extends to cause a widespread interstitial fibrosis. In addition, replacement fibrosis may occur to replace necrotic or apoptotic myocytes. Increased interstitial fibrous tissue is probably important in cardiac dysfunction in hypertension, but the amount of fibrosis is not easy to measure clinically and so differential changes in myocyte hypertrophy and fibrosis cannot easily be assessed in patients (31).

Most hypertensives have normal left ventricular structure, but left ventricular hypertrophy predicts a poor prognosis, the almost threefold increased risk being independent of the blood pressure level (36). Whether individual remodelling patterns confer additional risk is disputed (Framingham study) and how left ventricular hypertrophy causes increased risk is uncertain. The increase in ventricular arrhythmias (37) and increased QT duration and QT dispersion seen in left ventricular hypertrophy (38) may account for the increased risk of sudden death, but other mechanisms such as impaired coronary perfusion could also be important. The electrical abnormalities are likely to be caused by heterogeneous conduction in the ventricle due to increased interstitial fibrosis. There is now increasing evidence that regression of left ventricular hypertrophy with antihypertensive treatment provides cardiovascular protection over and above the reduction in blood pressure levels (39), but again the mechanism of the risk reduction is uncertain.

2.6.3 Consequences of hypertrophy and remodelling

Active relaxation is impaired in hypertrophy and remodelling (40). The explanation for this is uncertain, although changes in intracellular calcium handling, ion exchangers, and ion channels are implicated (41). Cardiac hypertrophy is also associated with impaired coronary reserve. This may be caused by a number of mechanisms, including endothelial dysfunction, narrowing of small arteries, microvascular rarefaction, perivascular fibrosis, altered wall mechanics, and relative myocyte hypertrophy (42). A diminished coronary reserve will lead to myocardial ischaemia in the absence of epicardial coronary disease and may further impair relaxation. Left ventricular diastolic dysfunction may represent the first stage of cardiac involvement in hypertensive patients, reinforcing the importance of early examination of diastolic ventricular function in individuals with first referral

hypertension. Diastolic dysfunction in patients with hypertension may present as asymptomatic findings on noninvasive testing, or as fulminant pulmonary edema, despite normal left ventricular systolic function. Up to 40% of hypertensive patients presenting with clinical signs of congestive heart failure have normal systolic left ventricular function (43).

Structural changes of the coronary arteries and the increase in both interstitial myocardial fibrosis and in myocardial mass contribute to reduce the vascular coronary flow reserve (44). In addition, myocardial ischaemic episodes cause transient diastolic dysfunction (figure 2.3 & 2.4). LVH occurs not only as a result of pressure-related mechanical strain on the heart but also as a result of hormonally sensitive pathological cardiac overgrowth that results directly from stimulation of the renin-angiotensinaldosteronesystem (44).

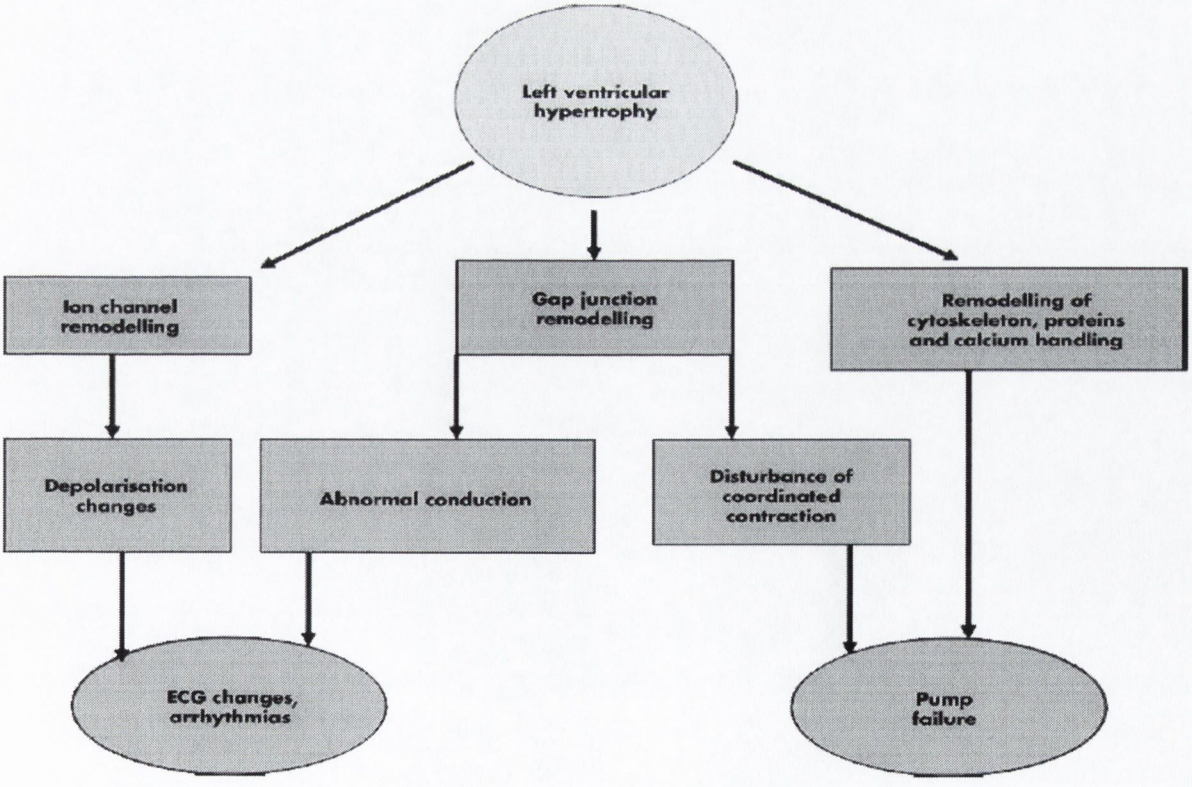


Figure 2.3. Left ventricular hypertrophy from an electromechanical perspective.

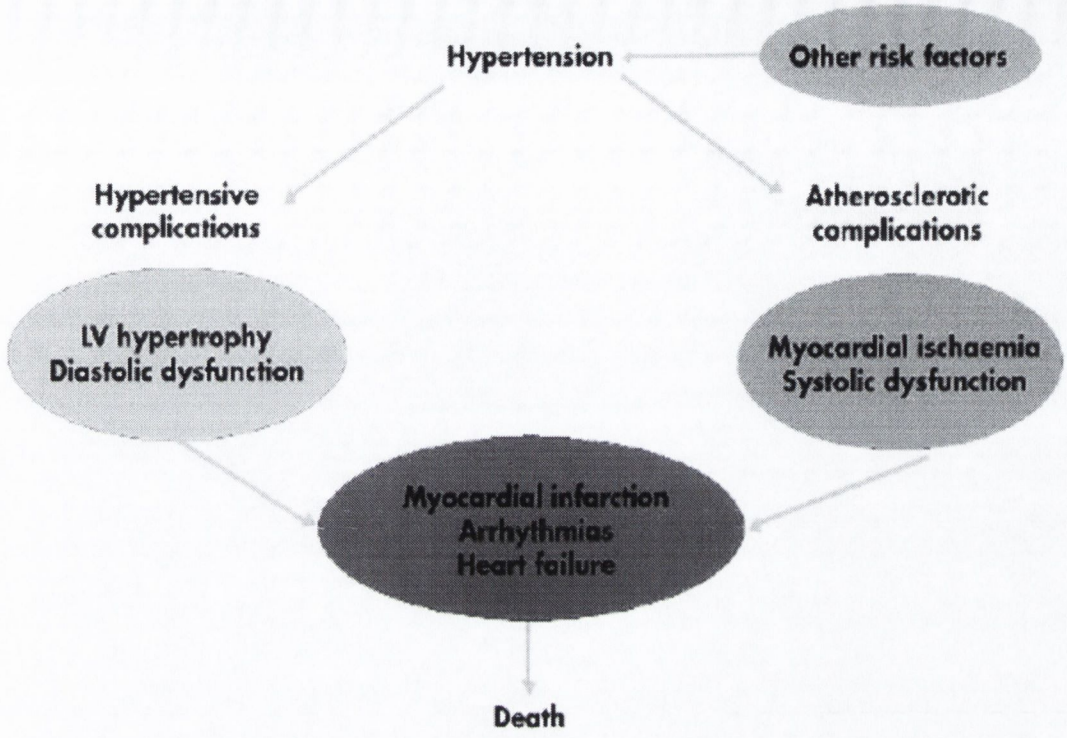


Figure 2.4.The risk for cardiac events in hypertension.

Hypertrophy of the left ventricle leads to heart failure through a variety of mechanisms (45). At first, mild hypertrophy allows the heart to overcome increases in vascular resistance. Over time, however, disruption of the normal myofibrillar architecture by cellular enlargement and increased matrix deposition causes a restrictive form of cardiomyopathy often called diastolic dysfunction. Diastolic dysfunction precedes the development of systolic dysfunction and overt failure in Hypertensive patients. Eventually, the hypertrophied ventricle can no longer maintain its output and the downward spiral of ventricular dilatation and symptomatic heart failure begins.

2.7 THE ARTERIAL SYSTEM IN HYPERTENSION

Hypertension has long been considered a hemodynamic disorder, the hallmark of which is an increased total peripheral resistance that is more or less uniformly distributed in the arterioles of the component organ circulations. In recent years, because of the introduction of new technologies and methods, it is now possible to obtain a meaningful assessment of the physiological role of the larger arteries, thereby providing an index of arterial distensibility and compliance and a new means to assess the role of pulsatile pressure and arterial stiffening in hypertension (46).

Stiffening of large arteries may be both a cause, particularly of systolic and a consequence of hypertension. There are several studies, including studies done by the University of Minnesota that confirm that as arterial pressure rises, acute and reversible stiffening of the large arteries occurs without a change in the structure of the artery. Arterial stiffness increases transiently as blood pressure rises. Arterial stiffening also increases because of the structure of the artery changes. Persistently elevated blood pressure accelerates atherosclerosis, arterial smooth muscle hyperplasia and hypertrophy, and collagen synthesis, thereby increasing arterial stiffness (47).

The aims of this study were to assess the prevalence of diastolic dysfunction and its relationship with arterial stiffness in newly diagnosed untreated hypertensive patients and also assess the response (after one and three months) to antihypertensive treatment.

CHAPTER 3

LEFT VENTRICULAR FUNCTION IN EARLY HYPERTENSION: ARE THERE RELIABLE ECHOCARDIOGRAPHIC MEASURES OF DIASTOLIC FUNCTION?

CAHPTER 3

3.1 LEFT VENTRICULAR PUMP FUNCTION

3.1.1 Introduction

The early detection of diastolic dysfunction is recognised as an important means of identifying patients at risk of developing heart failure with its associated increased mortality (48). Diastolic dysfunction may be commonly seen in hypertensive populations but its prevalence according to the literature varies from 18.6 to 51% (49,50). This disparity may in part be related to the different criteria used in the diagnosis of diastolic dysfunction. In one study the prevalence of diastolic dysfunction among 198 newly diagnosed hypertensives using Transmitral Doppler Echocardiography, with an E/A ratio of <1 as indicative of diastolic dysfunction, was 18.6% (49). On other hand, in a relatively large population of patients with treated systemic hypertension and normal left ventricular systolic function, the prevalence of diastolic dysfunction assessed by mitral and pulmonary vein flow Doppler was 51% (50).

Doppler Echocardiographic guidelines have been developed in an attempt to standardize the diagnosis and classification of diastolic dysfunction (51-53). The Canadian Consensus (CC) Group (51) classifies patients using transmitral Doppler with and without Valsalva (Table 1) with a similar grading system to the Mayo Clinic (54). The European Study Group on diastolic heart failure has also published criteria (52) (Table 2) using transmitral Doppler with cut off criteria, which relate strictly to the patients age group. Recently, the American College of Cardiology/American Medical Association (53) (AMA) has also published guidelines (Table 3) for the diagnosis of diastolic dysfunction which include E (TMD) /E' (TDI). Subjects with moderate or severe diastolic dysfunction need two Doppler criteria of American

guidelines to be so classified (53). Neither the Canadian consensus nor the European guidelines include tissue Doppler imaging (TDI) and though the American Medical Association guidelines include E/E', they do not include e' alone or the ratio E'/A'. We therefore compared the prevalence of diastolic function using criteria provided by the Canadian consensus, American Medical Association, and European guidelines in patients with hypertension and included the additional measurement of TDI E'/A'.

3.1.2 Description

The left heart can be analysed as a pump with an input (the pulmonary venous or mean left atrial pressure) and an output (which in simplest terms is the cardiac output = stroke volume × heart rate). The relationship between the input and output is the ventricular function curve or the Frank-Starling relationship (fig 3.1) (55).

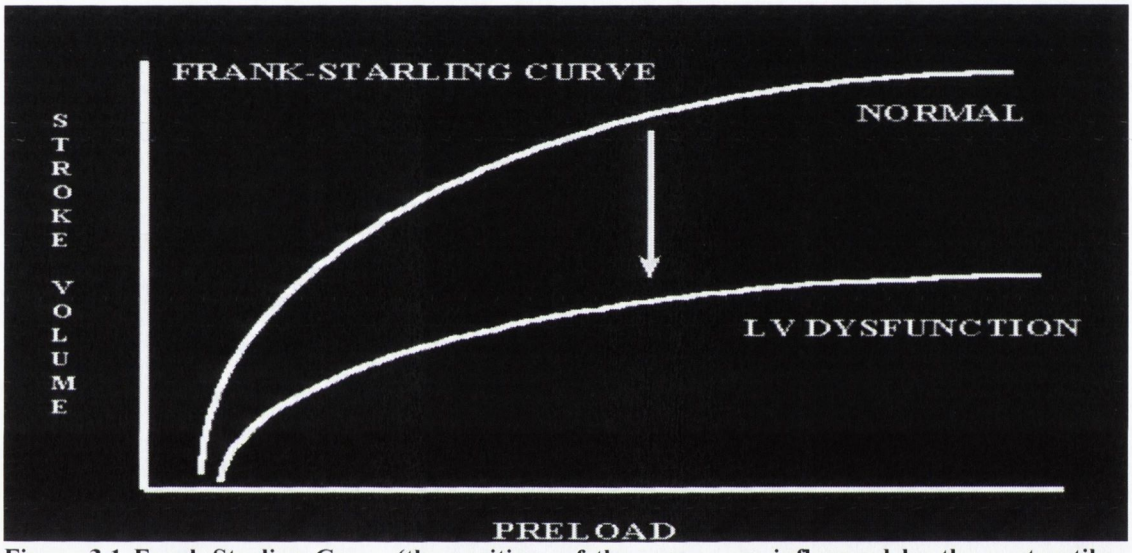


Figure 3.1 Frank-Starling Curve (the positions of the curves are influenced by the contractile state of the left ventricle)

It is important to recognise that this ventricular function curve represents a complex interaction of preload, afterload, and contractility (55).

The pump performance of the left ventricle depends on its ability to fill (diastolic performance) and to empty (systolic performance). The forward stroke volume is equal to the end-diastolic volume multiplied by the effective ejection fraction. Thus, the generation of stroke volume depends on the conversion of the filling pressure to end-diastolic volume (diastolic performance) and the generational stroke volume from the end-diastolic volume (systolic performance) (56).

3.1.2 Systolic performance

Left ventricular systolic performance is reflected in the ability of the left ventricle to empty. Because myocardial contractility is an important determinant of the left ventricle's systolic performance, systolic performance and contractility are frequently considered to be interchangeable. However, they are not the same because the systolic performance of the left ventricle is also importantly influenced by load and ventricular configuration. Thus, it is possible to have abnormal systolic performance despite normal contractility when left ventricular afterload is excessive. Alternatively, left ventricular systolic performance may be nearly normal despite decreased myocardial contractility if left ventricular afterload is low, as occurs in some patients with mitral regurgitation (55).

Left ventricular systolic performance can be quantified as the left ventricular emptying fraction or ejection fraction. In the presence of a left-sided valvular regurgitant lesion (mitral regurgitation or aortic regurgitation) or a shunt (ventricular septal defect or patent ductus arteriosus), the left ventricular stroke volume may be high, whereas the forward stroke volume (stroke volume minus regurgitant volume or shunt volume), which contributes to useful cardiac output, is lower. Accordingly, the effective ejection fraction is the forward stroke volume divided by end-diastolic volume (57,58).

The effective ejection fraction is a useful means to quantify systolic function because it represents the functional emptying of the left ventricle that contributes to cardiac output and is relatively independent of left ventricular end-diastolic volume over the clinically relevant range. An operational definition of systolic dysfunction is an effective ejection fraction of less than 50% (56-58).

When defined in this manner, systolic left ventricular dysfunction may result from impaired myocardial function, increased left ventricular afterload, and / or structural abnormalities of the left side of the heart (55).

If left ventricular contractile state and arterial properties remain constant as end-diastolic volume increases, the ejection fraction stays constant or increases slightly. Thus, an increase in the end-diastolic volume will allow for a normal forward stroke volume despite a reduced effective ejection fraction (55).

3.1.3 Diastolic Performance

For the left ventricle to function as a pump, it must not only empty but also fill. The left atrial (and pulmonary venous) pressure is the source pressure for left ventricular filling. Thus, normal left ventricular diastolic function can be defined as filling of left ventricle sufficient to produce a cardiac output commensurate with the body's needs with a normal pulmonary venous pressure (less than 12 mm Hg) (59).

In some instances this definition of normal integrated diastolic performance can be met despite clear abnormalities of left ventricular diastolic properties. For example, a compensated patient with a dilated cardiomyopathy may have an adequate cardiac output at rest without an elevated pulmonary venous pressure despite impaired relaxation and a very abnormal left ventricular diastolic pressure-volume curve (55).

A patient with systolic dysfunction (reduced effective ejection fraction) requires a lager end-diastolic volume to produce an adequate stroke volume and cardiac output. If the larger left ventricular end-diastolic volume can be achieved without an abnormally high pulmonary venous pressure, this can compensate for impaired systolic performance. However, if the larger end-diastolic volume requires an elevation of pulmonary venous pressure, the systolic dysfunction (i.e., reduced

effective ejection fraction) will result in diastolic dysfunction. Thus, when defined in this manner, systolic dysfunction in symptomatic patients is usually associated with diastolic dysfunction (55).

However, diastolic dysfunction frequently occurs in the absence of systolic dysfunction. As defined, diastolic dysfunction may be due to an obstruction to left ventricular filling or an external compression of the left ventricle, but it is usually considered to result from left ventricular abnormalities. Such left ventricular diastolic dysfunction may result from increased myocardial stiffness or impaired relaxation. Relaxation can be slow, decreased early diastolic filling, or incomplete, which impairs filling throughout diastole and decreased end-diastolic dispensability. In the pressure-volume plane, reduced dispensability is represented by a leftward and upward shift of the end-diastolic pressure-volume relation (EDPVR). When this occurs, significantly higher pressures are required to distend the left ventricle to achieve the same end-diastolic volume. If the shift in EDPVR is severe enough, filling of the left ventricle to the level sufficient to produce a normal stroke volume can only be achieved with an elevated pulmonary venous pressure that will be associated with pulmonary congestion. Thus, an alternation in diastolic dispensability may produce pulmonary congestion and congestive heart failure in absence of systolic dysfunction (60-62).

3.1.4 Physiology of Diastole

The cycle of myocardial contraction and relaxation is directly related to cytosolic calcium concentration. With electrical depolarisation, calcium enters the myocyte via slow calcium channels. This triggers the release of massive amounts of additional calcium stored in the sarcoplasmic reticulum. The calcium diffuses into the sarcomere, causing a conformational change in the troponin-tropomyosin complex

that permits myosin to interact with actin and the myocyte to contract. For the myocyte to relax, the process must be quickly reversed. Up to 90% of the calcium is actively removed by the calcium-ATPase pump in the sarcoplasmic reticulum and the rest by sodium-calcium exchange and other mechanisms (fig 3.2). Working against a 10,000-fold concentration gradient requires a high expenditure of energy one molecule of ATP is consumed for every two molecules of calcium removed by the calcium-ATPase pump (63).

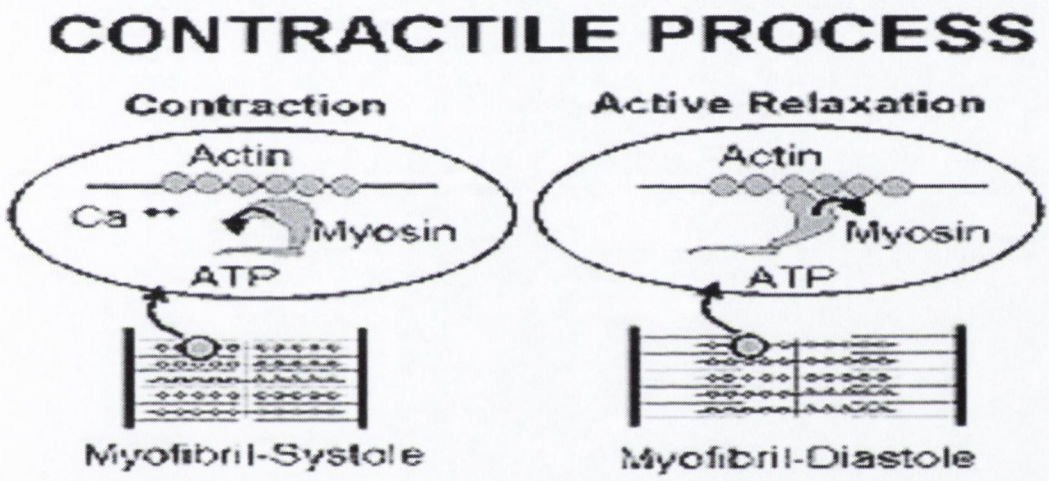


Figure 3.2 A schematic of the contractile process in the myocardium. (Gorcsan 2000).

The relaxation part of the cardiac cycle is subdivided into four phases: 1) isovolumic relaxation time (IVRT), 2) rapid filling, 3) slow filling (diastasis), and 4) atrial contraction (fig 3.3). In the first phase, between the time of aortic valve closing and mitral valve opening, calcium is rapidly removed from the cytoplasm and resequestered in the sarcoplasmic reticulum. The next phase begins when pressure in the left ventricle falls below that in the left atrium, causing the mitral valve to open and the left ventricle to begin filling; it ends when pressure in the two chambers is equalized. Although this rapid-filling phase comprises only about 30% of diastole, it accounts for up to 80% of left ventricular volume. The third phase is the slow-filling

phase. What little filling there is comes from pulmonary vein flow. With increased heart rate, this phase shortens more than the other three. The fourth phase, atrial contraction, contributes to 15% - 25% of the left ventricular volume under normal conditions, but can contribute to a maximum of 40% if left ventricular relaxation is diminished (63).

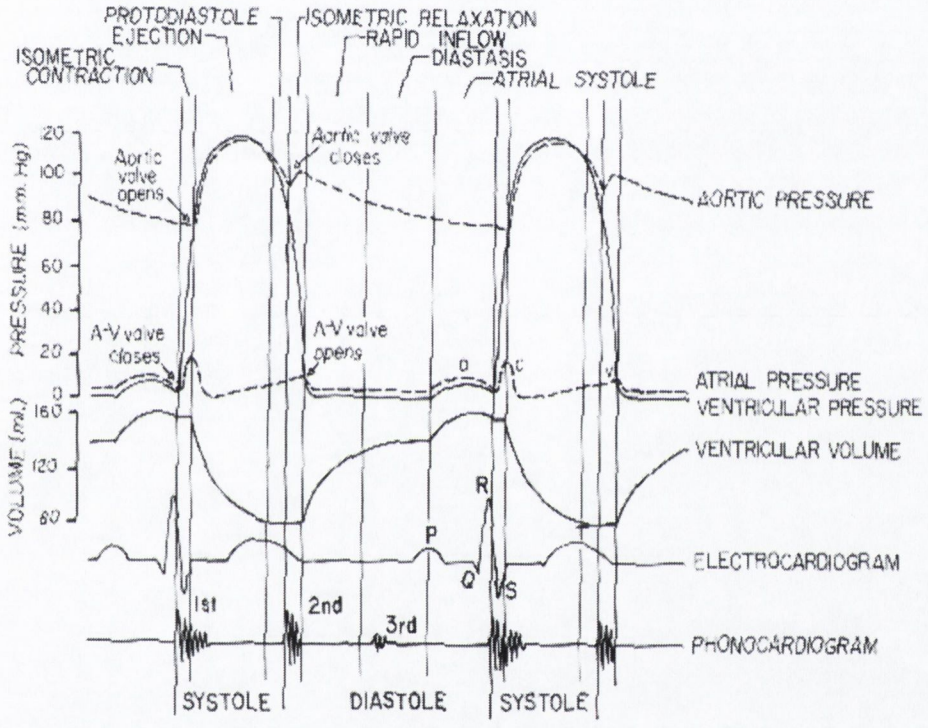


Figure 3.3 Left heart value for cardiac cycle events. The events of the cardiac cycle, showing changes in left atrial pressure, aortic pressure, ventricular volume, the electrocardiogram, and the phonogram.

Brutsaert and colleagues consider the first two phases to be the end of systole. By their definition, diastole would consist of phases 3 and 4. It would thus comprise about 50% of the cardiac cycle but at normal heart rates would contribute to the last 5% to 15% of the ventricular volume.

3.1.5 Assessment of Diastolic Function

Left ventricular diastolic dysfunction is increasingly recognized as an important cause of morbidity in patients with heart disease, particularly patients with hypertensive heart disease. Diastolic dysfunction refers to a condition in which abnormalities in mechanical function are present during diastole. Abnormalities in diastolic function can occur in the presence or absence of a clinical syndrome of heart failure and with normal or abnormal systolic function. Therefore, whereas diastolic dysfunction describes an abnormal mechanical property, diastolic heart failure describes a clinical syndrome (64).

Diastolic heart failure occurs when the ventricular chamber is unable to accept an adequate volume of blood during diastole, at normal diastolic pressures and at volumes sufficient to maintain an appropriate stroke volume. These abnormalities are caused by a decrease in ventricular relaxation and/or an increase in ventricular stiffness. Diastolic heart failure can produce symptoms that occur at rest (New York Heart Association [NYHA] class IV), symptoms that occur with less than ordinary physical activity (NYHA class III), or symptoms that occur with ordinary physical activity (NYHA class II) or only at levels of exertion that would limit normal individuals (class I) (65).

The Pattern of left ventricular filling can be analysed by radionuclide venriculography (gated blood-pool scanning) and cardiac catheterisation. However, they do not permit direct visualization of cardiac chambers, walls, valves, or pericardium. For these reasons, echocardiography is the best non-invasive means of evaluating left ventricular diastolic function. Tissue Doppler echocardiography (TDI) of the mitral annulus has been recently validated in clinical trials (63). The assessments obtained

by this technique were in excellent agreement with invasive measurements (63). Those obtained by TDI appeared to be relatively preload-independent, and thus particularly useful for evaluating isolated diastolic dysfunction (63).

3.1.6 Indices of Diastolic Function

Transmitral Doppler (TMD) flow velocity and TDI of the mitral annulus were obtained from the apical 4-chamber view. Sample volume was located between the tips of mitral leaflets and at the mitral annulus. TMD peak early diastolic E wave velocity (cm/s), peak late A wave diastolic velocity (cm/s), their ratio E/A, and deceleration time (ms) were recorded. The same measurements were repeated during phase II of the Valsalva maneuver. Tissue Doppler diastolic velocities were measured in the 2 and 4 chamber views. A 5mm sample volume was placed sequentially at the septal, lateral, inferior and anterior mitral annuli and averaged. The following measurements were recorded: early diastolic velocity (E') and late diastolic velocity (A') and their ratio. The ratio of early diastolic mitral inflow velocity (E) to TDI E' (E/E'), were calculated. Mitral inflow velocities (E wave, A wave, E/A ratio) and mitral annular velocities as measured by TDI: E' (early), A' (late), and E'/A' ratio are common indices of diastolic function (fig 3.4).

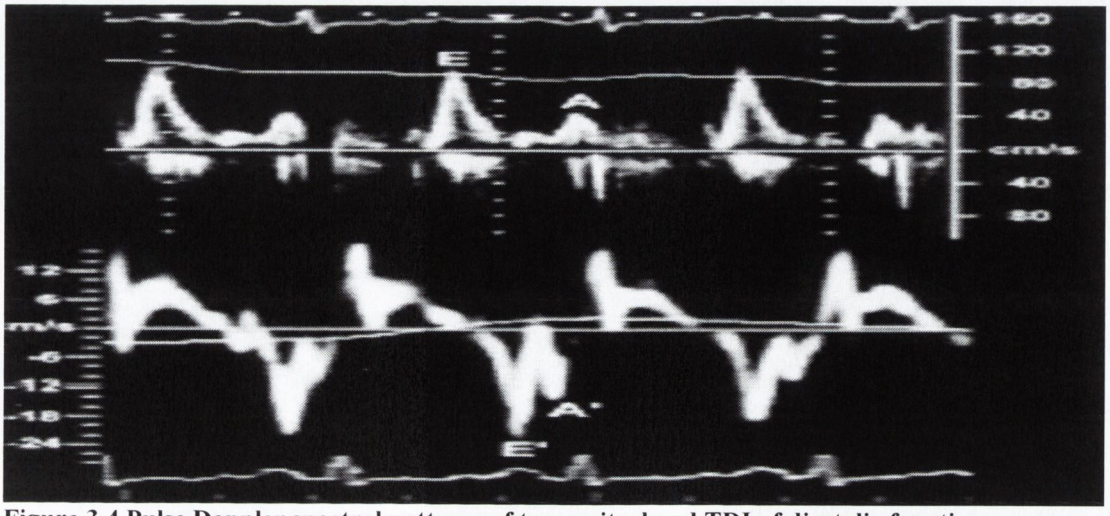


Figure 3.4 Pulse Doppler spectral patterns of transmitral and TDI of diastolic function

These indices may provide valuable information in individual subjects. As diastolic dysfunction progresses, there may be a period of pseudonormalization during which there is a combination of impaired relaxation and elevation of LV filling pressures. The use of TDI may provide additional information to enable the clinician to detect filling abnormalities when standard mitral flow velocities appear normal (66).

Echocardiographic phases of ventricular filling have been described as early (E) and late, or atrial (A). The latter is dependent upon atrial contraction and therefore is absent in atrial fibrillation. Characteristically, when diastolic dysfunction is present, a greater portion of end-diastolic volume is the result of late filling rather than early filling. Thus, the E/A ratios are reduced in diastolic dysfunction (66).

3.2 DIASTOLIC DYSFUNCTION

3.2.1 Description

Diastolic dysfunction can be defined as a condition in which myocardial relaxation and filling are impaired and incomplete; the ventricle is unable to accept an adequate volume of blood from the venous system, fill at low pressure, or maintain normal stroke volume. In most severe form, diastolic dysfunction results in overt symptoms of congestive heart failure (CHF). In modest diastolic CHF, symptoms of dyspnoea and fatigue occur only during stress or activity, such as exercise, when heart rate and / or end diastolic volume increase. In its mildest forms, diastolic dysfunction can be manifested as a slow or delay pattern of relaxation and filling with a little or no elevation in diastolic pressure and no cardiac symptoms. The myocardial relaxation impairment in diastolic dysfunction may also be accompanied by increased diastolic stiffness, or the diastolic stiffness may occur alone. When CHF is caused by an isolated abnormality in diastolic function, the ventricle chamber is not enlarged and the ejection fraction is normal (67).

Ventricular function is highly dependent upon preload as demonstrated by the Frank-Starling relationship (figure 1). Therefore, if ventricular filling (preload) is impaired, this will lead to a decrease in stroke volume. The term "diastolic dysfunction" refers to changes in ventricular diastolic properties that have an adverse effect on stroke volume (68).

3.2.2 Pathophysiology

Ventricular filling (i.e., end-diastolic volume and hence sarcomere length) depends upon the venous return and the compliance of the ventricle during diastole. A reduction in ventricular compliance, as occurs in ventricular hypertrophy, will

result in less ventricular filling (decreased end-diastolic volume) and a greater end-diastolic pressure (and pulmonary capillary wedge pressures) as shown to the right by changes in the ventricular pressure-volume loop. Stroke volume, therefore, will decrease. Depending upon the relative change in stroke volume and end-diastolic volume, there may or may not be a small decrease in ejection fraction. Because stroke volume is decreased, there will also be a decrease in ventricular stroke work (68).

A second mechanism can also contribute to diastolic dysfunction - impaired ventricular relaxation (reduced lusitropy). Near the end of the cycle of excitation-contraction coupling in the myocyte, the sarcoplasmic reticulum actively sequesters Ca^{++} so that the concentration of Ca^{++} in the vicinity of troponin-C is reduced allowing the Ca^{++} to leave its binding sites on the troponin-C and thereby permit disengagement of actin from myosin. This is a necessary step to achieve rapid and complete relaxation of the myocyte. If this mechanism is impaired (e.g., by reduced rate of Ca^{++} uptake by the sarcoplasmic reticulum), or by other mechanisms that contribute to myocyte relaxation, then the rate and perhaps the extent of relaxation are decreased. This will reduce the rate of ventricular filling, particularly during the phase of rapid filling (68).

An important and deleterious consequence of diastolic dysfunction is the rise in end-diastolic pressure. If the left ventricle is involved, then left atrial and pulmonary venous pressures will also rise. This can lead to pulmonary congestion and edema. If the right ventricle is in diastolic failure, the increase in end-diastolic pressure will be reflected back into the right atrium and systemic venous vasculature. This can lead to peripheral edema and ascites (68).

3.2.3 Aetiology of Diastolic Dysfunction

In 1991, Kitzman and colleagues demonstrated that pulmonary venous pressure, and hence left ventricular filling pressure, is elevated at rest in patients with isolated diastolic dysfunction. With exercise, the filling pressure further increases, but the left ventricular volume decreases. Even higher filling pressures would be required to fill the left ventricle and maintain normal cardiac output. Diastolic heart failure is an insidious disease. Insults to the myocardium are followed by a series of compensatory changes that are beneficial in the short run, but have long-term deleterious effects. Structural remodeling and other factors, including myocardial ischemia, left ventricular hypertrophy, increased heart rate, and abnormal calcium flux, can impair diastolic function and cause an increase in left ventricular filling pressures (69) (Table 3.4).

Both ischemia and hypertrophy impair relaxation in early diastole--ischemia by restricting the supply of high-energy phosphates required for rapid removal of calcium from the cytoplasm and hypertrophy by slowing the rate of myosin-actin dissociation. Hypertrophy also decreases left ventricular compliance in all phases of diastole (63).

The probability of ischemia or left ventricular hypertrophy increases with age. Additional correlates of aging, such as hypertension and increased interstitial collagen deposition, result in decreased left ventricular compliance. It is thus not surprising that old age is among the most frequently cited risk factors for isolated diastolic dysfunction (63).

Other leading causes of the condition are coronary artery disease, hypertension, diabetes, obesity, and aortic stenosis (Table 3.5). Up to 90% of patients with coronary

artery disease have abnormal diastolic function, and approximately 60% of patients with heart failure and normal systolic function have hypertension. Obese patients, with or without hypertension, also have an increased risk of heart failure due to diastolic dysfunction (63).

3.2.4 Diastolic Function in Systemic Hypertension

High blood pressure has a high prevalence in the general population and is one of the major risk factors for coronary heart disease. Early detection of changes in cardiac performance, before irreversible damage to the heart has occurred, can contribute substantially to a further decline in hypertension-related death (70).

Systemic hypertension places increased tension on the left ventricular myocardium that is manifested as stiffness and hypertrophy, which accelerates the development of atherosclerosis within the coronary vessels. The combination of increased demand and lessened supply increases the likelihood of myocardial ischemia and thereby leads to a higher incidence of myocardial infarction, sudden death, arrhythmias and congestive heart failure (71).

In patients with arterial hypertension and left ventricular hypertrophy an "impaired relaxation" pattern is often seen. This consists of reduced velocity) with consequent reduction in the E/A ratio. It is thought that these resting abnormalities are at least partly responsible for the dypsnea on exertion and diminished exercise capacity commonly found in hypertensive patients (72).

Several studies have shown that subjects with borderline to mild hypertension do not make up uniform population because only some of them have hypertensive complications. It is therefore difficult to identify those patients who really need antihypertensive therapy. In this respect, early cardiac abnormalities might represent

an important clinical feature used for recognizing hypertensive patients who are at greater risk (73).

Left ventricular diastolic dysfunction (LVDD) may represent the first stage of cardiac involvement in hypertensive patients, reinforcing the importance of early examination of diastolic ventricular function in individuals with first referral hypertension. Diastolic dysfunction in patients with hypertension may present as asymptomatic findings on non-invasive testing, or as fulminant pulmonary edema, despite normal left ventricular systolic function. Up to 40% of hypertensive patients presenting with clinical signs of congestive heart failure have normal systolic left ventricular function. (74).

Several reports have documented reduced LV filling rate as an early sign of cardiac involvement in hypertension occurring before LV hypertrophy becomes manifest or even before slight increases in LV mass develop (73).

Previous study demonstrated that, LVDD is much more common than previously reported in subjects with well-controlled type 2 diabetes who are free of clinically detectable heart disease (74). The high prevalence of this phenomenon in this high-risk population suggest that screening for LVDD in type 2 diabetes should include procedures such as the valsalva manoeuvre and pulmonary venous recordings to unmask a pseudonormal pattern of ventricular filling (74).

3.2.5 Pattern of Left ventricular Diastolic filling

Analysis of pattern of left ventricular filling can provide useful information about diastolic left ventricular performance. Patterns of left ventricular filling (normal, impaired relaxation, pseudonormal, and restrictive patterns) as recorded by diastolic Doppler mitral flow velocities are shown in figure 5. The **normal pattern** of left

ventricular filling is characterised by rapid filling early in diastole with some additional filling during atrial contraction. This normal filling pattern can be quantified by measuring the peak early diastolic filling rate or mitral flow velocity (E), the integral of early diastole filling or flow velocity, and the peak filling rate (A) or mitral flow velocity during atrial contraction. The relative attribution of early and late (atrial) filling is commonly expressed as the E/A ratio. In normal pattern there is a large E wave and a small A wave. There are three abnormal patterns of mitral filling representing progressively worsening LV diastolic performance. The normal pattern of left ventricular filling is altered in many patients with cardiac disease. With **impaired relaxation** the E wave is less than the A wave. The LV deceleration time is prolonged. In the **pseudonormalized pattern** the E wave is larger than A wave, however, deceleration time is shortened. In the **restrictive filling pattern**, E is much larger than A with a very short deceleration time (55).

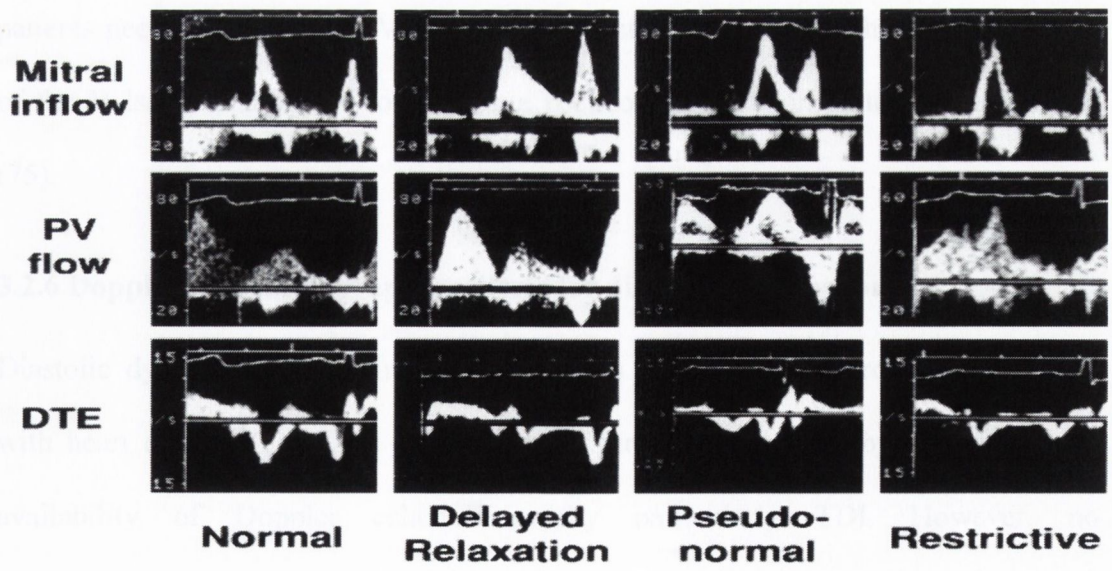


Figure 3.5. These are diagrams showing typical mitral inflow, pulmonary vein (PV) flow, and Doppler tissue echocardiographic (DTE) patterns of the various stages of diastolic dysfunction

The pseudonormal mitral inflow filling pattern is recognised as an important stage of diastolic dysfunction as it is considered an intermediary stage between impaired relaxation and restrictive filling and, thus, is a more advanced stage of LVDD (74). The pseudonormalization of the filling pattern is caused by higher filling pressures and is detected by the Valsalva manoeuvre, which acutely decreases filling pressures and unmasks the underlying impaired relaxation (74).

Previous study showed that prevalence of diastolic dysfunction in different condition such as diabetes mellitus (DM) type 2 was almost doubled when pseudonormalization was taken into account (74).

It has been observed clinically that many patients with the pseudonormalization pattern have signs and symptoms of heart failure, and have a poorer prognosis than patients with abnormal relaxation pattern. High-risk populations, such as hypertensive patients need screening for LV diastolic dysfunction by TDI, which included the use of the Valsalva manoeuvre to unmask a pseudonormalization pattern of LV filling (75).

3.2.6 Doppler echocardiographic criteria for diastolic dysfunction.

Diastolic dysfunction is frequently proposed as the underlying problem in patients with heart disease (76). This view has been further popularised by the widespread availability of Doppler echocardiography particularly TDI. However, no comprehensive consensus regarding diagnostic echocardiographic criteria for diastolic dysfunction has been reached, but guidelines have been proposed. The **Canadian Consensus Guidelines** (table 3.1) have published recommendations by American Society of Echocardiography for the measurement and reporting of diastolic

dysfunction using transmitral and pulmonary venous Doppler (51). The **European Study Group** (table 3.2) on diastolic heart failure has provided criteria, which relate to abnormal LV relaxation, abnormal LV filling, or reduced LV diastolic distensibility based on transmitral and pulmonary vein Doppler data (52). However, even these guidelines do not necessarily provide for echocardiographic identification of specific subgroups of patients with pseudonormal or restrictive filling patterns, potentially reducing their sensitivity for the diagnosis of diastolic dysfunction. Recently, the American College of Cardiology/American Medical Association guidelines (table 3.3) has also published echocardiographic Doppler criteria for classification of diastolic dysfunction in groups of patients with and without Congestive heart failure based on transmitral Doppler with and without valsalva, pulmonary vein Doppler and TDI E/E' ratio but not TDI E' alone or E'/A' ratio (53). Neither Canadian consensus nor European guidelines to include tissue Doppler imaging and American Medical Association guidelines include E/E' but not tissue Doppler imaging E' and E'/A'. In this chapter, we therefore, examined diastolic function using criteria provided by the Canadian consensus, American Medical Association, and European guidelines in patients with early hypertension and included the additional measurement of TDI E'/A'.

3.3 AIM

Diastolic dysfunction identifies patients at risk of developing heart failure. There remains no consensus as to the optimal measure(s) to define grades of Diastolic dysfunction. We therefore assessed the prevalence of diastolic function using criteria provided by the Canadian consensus, American Medical Association, and European guidelines in patients with newly diagnosed hypertension. In addition, we assessed the same patients with a comprehensive series of Tissue Doppler parameters to define

more accurately the prevalence of diastolic dysfunction in a newly diagnosed hypertensive population.

3.4 METHODS:

3.4.1 Study population:

One hundred and twenty consecutive untreated hypertensive patients (mean age 47±2.1 years, 62 men, 58 women) with a clinic blood pressure (BP)> 140/90 mmHg on three occasions and > 135/85 mmHg daytime ambulatory blood pressure were studied. Patients with secondary hypertension, ischemic heart disease, congestive heart failure, diabetes mellitus, atrial fibrillation, severe valvular heart disease or those on vasoactive drugs were excluded. The patients gave informed consent. Ethical approval was obtained from the local hospital ethics committee.

3.4.2 Echocardiographic measurements:

Assessment was done using a commercially available ultrasound system Phillips Sonos 5500 equipped with Doppler Tissue echocardiography capabilities. Baseline echocardiography examinations were done to rule out structural abnormality. We evaluated diastolic dysfunction using standard M-Mode and Doppler echocardiography. Diastolic dysfunction was defined using the criteria provided by the Canadian Consensus (Table 1), European (table 2), and American Medical Association Guidelines (Table 3) using transmitral Doppler (TMD) with and without Valsalva manoeuvre and tissue Doppler echocardiographic parameters. TMD of peak early E wave (peak early diastolic velocity) in cm/s, peak late A wave (peak late diastolic velocity) in cm/s, their ratio E/A, deceleration time (DT) and isovolumic relaxation time (IVRT) were recorded. The same measurements were repeated during phase II of Valsalva maneuver. In keeping with other studies Pulmonary vein flow (PVF) Doppler was difficult to obtain and not available in all patients so was not included in the analysis. The PVF may sometimes be within normal limits or difficult to obtain (51). It would therefore be useful to have a method of reducing left atrial

pressure such as Valsalva manoeuvre (51). Thus this technique may be useful in unmasking pseudonormalization of mitral inflow pattern, particularly when PVF is difficult to obtain (51). Tissue Doppler imaging (TDI) was measured and an average from four sites (lateral, septal, anterior, and inferior annulus) calculated. The following measurements were carried out: early diastolic velocity (E') and late diastolic velocity (A') and their ratio. M-mode measurements of left atrial (LA) size, aortic root (AR), left ventricular end-diastolic dimension (LVEDD), left ventricular end-systolic dimension (LVESD), interventricula septal diameter (IVSD) and posterior wall diameter (PWD) were recorded. Left ventricular ejection fraction was assessed qualitatively using the modified Simpson's rule.

3.4.3 Statistical Analysis:

Results were analysed with JMPIN version 5.0 (SAS for Windows). Results are expressed as mean±SEM and percentages and a $p<0.05$ considered significant. Relationships between inter & intraobserver variability was analysed using Spearman Rho correlations. Analysis of variance and Wilcoxon Rank Sum Test were used.

3.5 RESULTS:

The baseline characteristics of the study subjects are shown in Table 3.6. Depending on the criteria used there are significant differences in the prevalence of diastolic dysfunction, the diagnosis varying from 10 – 59% . Table 3.7 (a,b&c) shows a comparison of the prevalence of abnormalities in diastolic function based on the Canadian Consensus, European Study Group, and American Medical Association Guidelines There was a high prevalence of diastolic dysfunction at 59% (n=71) using Canadian consensus guidelines of which 27% (n=32) had a pseudonormal pattern unmasked with Valsalva manoeuvre and 32% (n=39) had impaired relaxation at rest (table 3.7a). Significantly fewer patients were diagnosed using European 10% (n=12) (table 3.7b), or American Medical Association guidelines 23% (n=27) of which 13% (n=15) had impaired relaxation and 10% (n=12) had a pseudonormal pattern (table 7c). TDI E'/A' (<1) (77) identified 59% (n=71) of patients with diastolic dysfunction, the same patients that were detected by the Canadian consensus guidelines which include the Valsalva manoeuvre. Mitral annular early diastolic filling E' wave velocity and the E'/A' ratio were significantly lower ($P<0.0001$) in all patients with diastolic dysfunction in all the three principles groups (table 3.7a,b&c). The estimated left ventricular filling pressure E/E' was significantly increased in patients with a pseudonormal pattern of diastolic dysfunction by Canadian and American guidelines ($P<0.0001$) (table 3.7a&c). In our study population, 59% of those who have diastolic dysfunction by Canadian guidelines or TDI E'/A' <1 have TDI E' of 7.6±0.09 (cm/sec). This is significantly lower than that seen in subjects with normal diastolic function (E'=17±0.4) ($P<0.0001$). Inclusion of the deceleration time or isovolumic relaxation time ($P<0.001$) had no effect on the classification of patients. . There was a significant difference in age ($P<0.001$) between patients with normal, pseudonormal

and impaired relaxation using the Canadian guidelines. Similarly, according to the American Medical Association guidelines, patients with impaired relaxation were significantly older ($P<0.01$) than the other two groups, however, there was no significant age difference between normal and pseudonormal groups. There was no significant difference in gender distribution when diastolic dysfunction was classified using the three different classifications.

There were no significant interobserver variations in LA size, IVSD, LVEDD, EF%, IVRT, and DT ($r=0.91$ to 0.97, $P<0.0001$). There were highly positive correlations of TMD and TDI parameters between the observers ($r = 0.99$, 0.98 & $P<0.0001$ respectively) (table 3.8). Intraobserver reliability was also excellent ($r=0.93$ - 0.99 & $P <0.0001$) (table 3.9).

3.6 DISCUSSION:

There is an increasing interest in the concept of diastolic dysfunction a sequela of chronic hypertension (78-80). This has been further popularised by the widespread availability of Doppler echocardiography and particularly TDI. An abnormality in left ventricular (LV) diastolic function with preserved systolic function is one of the earliest cardiac manifestations of systemic hypertension (81). These patients have increased endocardial and perivascular fibrosis and (82) the relationship of tissue velocities determined by TDI to regional interstitial fibrosis has been established (83,84) Preventing such consequences of hypertension through earlier and more aggressive BP control may be a means of reducing cardiovascular morbidity and mortality but despite the publication and widespread use of a series of national guidelines on the issue, there is widespread disparity in the methods and reported incidence of diastolic dysfunction.

These existing guidelines are regarded as useful in the diagnosis, and assessment of response to treatment of patients with diastolic dysfunction, but they do not incorporate comprehensive TDI measurements that are now widely available. Using TDI, diastolic dysfunction has been demonstrated in 26% of unselected patients with hypertension or diabetes (85). In another study of 520 patients using the Canadian guidelines the prevalence of diastolic dysfunction was 56% (68). Using the available guidelines alone we found a significantly higher prevalence of abnormalities with the Canadian, rather than with European or American criteria (59% vs. 10% vs 23% respectively). These same 59% were correctly identified by TDI parameters alone. Such a disparity in the reported incidence of diastolic dysfunction may extend beyond the hypertensive population. In a cross-sectional survey in Augsburg, Germany,

using the European Study Group echocardiographic criteria, only 11.1% were found to have diastolic abnormalities (86). Conversely, in a cross-sectional survey of 2042 randomly selected residents of Olmsted County, Minnesota, aged 45 years or older, using the American guidelines (table 3) (53), some 28% of people had diastolic dysfunction. Variance in these data may reflect a failure of consensus definitions rather than a genuine difference in population health.

One possible explanation for the different prevalence seen using the three classifications could be the lack of age standardization. The Canadian guidelines do not account for age; and our study does show a significant difference in age between patients with normal, pseudonormal and impaired relaxation. On the other hand, the European guidelines incorporate an age cut off of 50yrs and E/A <0.5 and the ages were similar in the two groups in our study when classified using the European guidelines. According to the American Medical Association guidelines, while patients with impaired relaxation were significantly older than the other two groups, there was no significant age difference between normal and pseudonormal groups in our study.
TDI has been shown to be correlated with age in healthy individuals, whose ages ranged from 21 to 69 years (87). Farias et al used a threshold value of mitral annular velocity (E') 12.5 cm/s for discriminating between normal and abnormal diastolic function (88). In contrast, Nagueh et al (89) and Sohn et al (87) reported lower values for E' and, in particular, their threshold value for discriminating between normal and abnormal was closer to 8.5 cm/s. However, the control groups in these studies were older and were identified only on the basis of having no symptoms or history of heart failure rather than on objective measurements of diastolic function. When control groups are so defined, it has clearly been shown that E' decreases with age (90,91). In

our study, it would appear more appropriate to use a value of E' close to 8.5 cm/s rather than 12.5 cm/s to distinguish between normal and abnormal diastolic function. In a previous study, TDI was used to unmask pseudonormalization of the mitral inflow pattern in patients (age 59 +/- 10 years) with coronary artery disease and heart failure. TDI E' < 7 cm/sec and E'/A' < 1 was used as a cut off point to diagnosis a pseudonormal pattern of diastolic dysfunction (92). In our patient population when TDI E' with a cut off of 8.5cm/s is used 48 % of patients were diagnosed as having diastolic dysfunction.

We also found that tissue Doppler imaging E'/A' correlated with transmitral flow velocity recordings incorporating the Valsalva manoeuvre, suggesting measurement of TDI E'/A' precludes the need to rigorously perform the Valsalva manoeuvre to unmask a pseudo normal pattern. This is particularly useful in elderly patients who may find it hard to perform the Valsalva manoeuvre.

3.7 STUDY LIMITATION:

In the current study, patients were classified on the basis of established echocardiographic grounds alone, without invasive confirmatory data. This group of patients had newly diagnosed hypertension; no subject had a restrictive pattern as is sometimes seen in chronic hypertension.

3.8 CONCLUSION:

Left ventricular diastolic dysfunction is prevalent in patients with newly diagnosed hypertension 59 % (n=71) based on Canadian guidelines and separately by measuring the TDI parameter E'/A' (<1) (77). Our findings demonstrate the wide variance in the diagnosis of diastolic dysfunction based on the current standard echocardiographic criteria. Thus current guidelines are of limited value and could be enhanced by the

inclusion of TDI. Physicians, in particular non-cardiac imaging specialists, should be cautious about echocardiographic reports describing diastolic dysfunction and ensure that the assessment of diastolic function is based on a comprehensive echocardiographic study integrating all available two dimensional, Doppler flow data and TDI. In the future newer techniques such as modified speckle tracking (93-95) may provide a useful adjuvant to TDI in the accurate delineation of diastolic dysfunction.

Table 3.1 Classification of diastolic function based on Canadian Consensus Guidelines.

	*TMD E/A Before Valsalva	TMD DT Before Valsalva	TMD E/A After Valsalva	TMD DT After Valsalva	**PVF S/D	PVF AR (m/s)	PVF AR-A (m/s)
Normal	1 – 2	150 - 200	1 – 2	>200	≥1	<0.35	<20
Impaired Pattern (Mild or mild to moderate)	<1	>200	<1	>200	≥1	<0.35	<20
Pseudonormal Pattern (Moderate)	1 – 2	150 - 200	<1	>200	0.5-<1	≥0.35	≥20
Restrictive Pattern (Severe)	>2	<150	Unchanged with Valsalva manoeuvre	Unchanged with Valsalva manoeuvre	<0.5	≥0.35	≥20

(* Transmitral Doppler) (** Pulmonary Venous Flow Doppler) (Valsalva Manoeuvre can be used instead of PVF particularly when PVF difficult to perform) (60)

Table 3.2 Classification of diastolic function based on European Study Group Guidelines.

	<50 years		>50 years		<50 years	>50 years	<30 Years	30-50 years	>50 years
	*TMD E/A	Deceleration time (m/sec)	TMD E/A	Deceleration time (m/sec)	**PVF S/D	PVF S/D	*** PER	PER	PER
Normal	>1	<220	>0.5	<280	<1.5	<2.5	>2.0 EDV	>1.8 EDV	>1.6 EDV
Diastolic Dysfunction	<1	>220	<0.5	>280	>1.5	>2.5	<2.0 EDV	<1.8 EDV	<1.6 EDV

(* Transmitral Doppler) (** Pulmonary Venous Flow Doppler) (***Early peak left ventricular filling rate (PFR) derived left ventricular contrast angiogram) (Based on European guidelines, diagnostic evidence of diastolic dysfunction consists of at least one of the above criteria) (61)

Table 3.3 Classification of diastolic function based on American Medical Association Guidelines.

	*TMD E/A Before Valsalva	TMD E/A After Valsalva	**PVF	***TDI E/E'
Normal	0.76 to 1.4	< 0.5	S≥D AR<A	<10
Impaired Pattern (mild)	≤ 0.75	< 0.5	S>D AR<A	<10
Pseudonormal Pattern (moderate)	0.76 to 1.4	≥0.5	S<D or AR >A+30 ms	≥ 10
Restrictive Pattern Reversible (severe)	>1.5	≥0.5	S<D or AR>A+30 ms	≥10
Restrictive Pattern Irreversible (severe)	>1.5	Unchanged with Valsalva manoeuvre	S<D or AR>A+30 ms	≥10

(* Transmitral Doppler) (** Pulmonary Venous Flow Doppler) (***Tissue Doppler Imaging) (Moderate or Severe diastolic dysfunction needs two Doppler criteria to be classified) (62)

Table 3.4 Factors increasing diastolic pressure

Impaired Ventricular Relaxation

- Hypertrophy
- Myocardial ischemia
- Hypertension
- Collagen deposition and fibrosis
- Regional asynchrony
- Increased preload, afterload
- Abnormal calcium flux
- Tachycardia

Decreased Ventricular Compliance

- Hypertrophy
- Hypertension
- Collagen deposition and fibrosis
- Cellular disarray
- Myocardial infiltration
- Pericardial constriction or restriction
- Right ventricle-left ventricle interactions

Table 3.5 Causes of abnormal diastolic function.

Common	Less Common
• Coronary artery disease • Hypertension • Aging • Diabetes mellitus • Obesity • Aortic stenosis	• Hypertrophic cardiomyopathy • Infiltrative cardiomyopathies • Endocardial fibroelastosis • Pericardial disease

Table 3.6 Baseline demographic and haemodynamic data in newly diagnosed hypertensive patients.

Variable	(N=120, mean±SEM)
Age (years)	47±2
Sex (m/f)	63/57
Height (cm)	170±2
Weight (kg)	84±2
Waist (cm)	95±3
Systolic blood pressure (SBP) mmHg	156±2
Diastolic blood pressure (DBP) mmHg	94±3
Mean arterial pressure (mmHg)	115±1.6
Heart rate (beats/min)	70±2

Table 3.7 (a). Left ventricular diastolic function based on Canadian Consensus Guidelines

	Normal	Impaired relaxation (Stage I)	Pseudonormal pattern (Stage II)	P value
No. Of Patients	49	39	32	NA
Age (years)	40±1	55±1	48±2	<0.001
Gender (M/F)	28/21	21/18	14/18	NA
LA (cm)	3.42±0.05	3.80±0.07	3.63±0.07	<0.01
IVSD (cm)	0.97±0.02	1.04±0.02	1.01±0.03	0.15
LVEDD (CM)	4.7±0.06	4.83±0.06	4.73±0.07	0.53
LV mass index (g/m^2)	94.65±3.18	106.69±4.79	91.93±4.80	0.04
TMD E (cm/sec)	78±2	56±2	75±2	<0.0001
TMD A (cm/sec)	57±2	75±2	66±2	<0.0001
TMD E/A ratio	1.4±0.04	0.7±0.01	1.1±0.01	<0.0001
DT ms	168±1	219±1	187±2	<0.0001
IVRT ms	83±1	110±1	84±4	<0.0001
TMD E cm/s Post Valsalva	69±2	54±1	51±2	<0.0001
TMD A cm/s Post Valsalva	56±2	75±2	69±2	<0.0001
TMD E/A Post Valsalva	1.2±0.04	0.7±0.01	0.7±0.01	<0.0001
DT ms Post Valsalva	220±2	254±3	239±2	<0.0001
TDI E' cm/s	17±0.4	7.8±0.1	7.7±0.2	<0.0001
TDI E'/A' ratio	1.5±0.05	0.6±0.01	0.7±0.01	<0.0001
TDI E/E' ratio	4.7±0.2	6.5±0.2	10±0.4	<0.0001

Table 3.7 (b) Left ventricular diastolic function based on European Guidelines

	Normal	Impaired relaxation (Stage I)	P value
No. Of Patients	108	12	NA
Age (years)	47±1	52±3	NA
Gender (M/F)	56/52	7/5	NA
LA (cm)	3.57±0.04	3.82±0.17	0.15
IVSD (cm)	0.99±0.01	1.06±0.05	0.15
LVEDD (CM)	4.76±0.04	4.87±0.10	0.41
LV mass index (g/m^2)	96.00±2.46	114.41±9.30	0.03
TMD E (cm/sec)	72±3	49±5	<0.0001
TMD A (cm/sec)	64±1	73±2	0.02
TMD E/A ratio	1.14±0.03	0.5±0.03	<0.0001
DT ms	186±2	218±2	<0.0001
IVRT ms	90±2	108±1	<0.001
TMD E cm/s Post Valsalva	60±1	48±2	<0.01
TMD A cm/s Post Valsalva	65±1	75±3	0.02
TMD E/A Post Valsalva	0.5±0.03	0.6±0.1	<0.001
DT ms Post Valsalva	234±2	250±18	<0.001
TDI E' cm/s	12±0.5	7.4±0.4	<0.01
TDI E'/A' ratio	1±0.5	0.6±0.03	<0.001
TDI E/E' ratio	6.75±0.3	6.3±0.4	0.85

Table 3.7 (c). Left ventricular diastolic function based on American Medical Association Guidelines

	Normal	Impaired relaxation (Stage I)	Pseudonormal pattern (Stage II)	P value
No. Of Patients	93	15	12	NA
Age (years)	46±1	56±2	48±3	<0.01
Gender (M/F)	45/48	10/5	8/4	NA
LA (cm)	3.53±0.04	3.94±0.14	3.71±0.10	<0.01
IVSD (cm)	0.98±0.01	1.09±0.04	1.04±0.04	0.01
LVEDD (CM)	4.74±0.04	4.91±0.09	4.82±0.11	0.36
LV mass index (g/m^2)	94.87±2.49	115.06±9.67	99.33±7.38	0.13
TMD E (cm/sec)	71±2	51±3	82±3	<0.0001
TMD A (cm/sec)	62±1	76±3	74±3	<0.0001
TMD E/A ratio	1.2±0.03	0.6±0.02	1.1±0.02	<0.0001
DT ms	185±2	222±3	184±4	<0.0001
IVRT ms	89±2	107±1	94±8	<0.001
TMD E cm/s Post Valsalva	62±2	49±2	52±3	<0.001
TMD A cm/s Post Valsalva	63±1	78±3	73±3	<0.001
TMD E/A Post Valsalva	1±0.03	0.6±0.02	0.7±0.1	<0.0001
DT ms Post Valsalva	231±2	263±3	243±4	<0.0001
TDI E' cm/s	13±0.5	7.5±0.3	6.8±0.8	<0.0001
TDI E'/A' ratio	1.1±0.05	0.6±0.02	0.65±0.02	<0.0001
TDI E/E' ratio	5.7±0.4	6.7±1.2	12±2	<0.0001

Table 3.8 Correlation coefficients of interobserver variability in echocardiographic parameters

	Interobserver	P value
LA (cm)	R=0.97	<0.0001
IVSD (cm)	R=0.91	<0.0001
LVEDD (cm)	R=0.92	<0.0001
EF%	R=0.91	<0.0001
IVRT ms	R=0.94	<0.0001
TMD E (cm)	R=0.99	<0.0001
TMD A (cm)	R=0.98	<0.0001
TMD E/A ratio	R=0.99	<0.0001
DT ms	R=0.95	<0.0001
Post Valsalva E (cm)	R=0.98	<0.0001
Post Valsalva A (cm)	R=0.98	<0.0001
Post Valsalva E/A ratio	R=0.98	<0.0001
TDI E'	R=0.97	<0.0001
TDI E'/A' ratio	R=0.98	<0.0001
E/E'	R=0.95	<0.0001

Table 3.9 Correlation coefficients of intraobserver variability in echocardiographic parameters.

	Intraobserver	P value
LA (cm)	R=0.99	<0.0001
IVSD (cm)	R=0.97	<0.0001
LVEDD (cm)	R=0.98	<0.0001
EF%	R=0.99	<0.0001
IVRT ms	R=0.93	<0.0001
TMD E (cm)	R=0.99	<0.0001
TMD A (cm)	R=0.99	<0.0001
TMD E/A ratio	R=0.99	<0.0001
DT ms	R=0.95	<0.0001
Post Valsalva E (cm)	R=0.99	<0.0001
Post Valsalva A (cm)	R=0.99	<0.0001
Post Valsalva E/A ratio	R=0.99	<0.0001
TDI E'	R=0.98	<0.0001
TDI E'/A' ratio	R=0.99	<0.0001
E/E'	R=0.97	<0.0001

CHAPTER 4

DIASTOLIC DYSFUNCTION AND ARTERIAL STIFFNESS IN EARLY HYPERTENSION

CHAPTER 4

4.1 ARTERIAL STIFFNESS

4.1.1 Introduction

Arterial stiffness has proved to be an independent marker of cardiovascular risk in a hypertensive population and of greater importance than any single measurement of blood pressure (96-98). One of the most prominent features in the aortic pressure waveform of an older individual is the presence of a late systolic peak (99,100), which can be explained by the phenomenon of arterial wave reflection. The left ventricular ejection generates a pressure wave that travels faster than blood itself and when it encounters high resistance arterioles in the periphery it is reflected back towards the heart. In healthy elastic arteries, the pulse wave velocity (PWV) is optimal such that the reflected wave arrives at the aorta during diastole and will increase coronary perfusion. As arteries stiffen the PWV increases consequently the reflected wave arrives too early at the heart before the aortic valve is closed, i.e., during systole. This increases left ventricular after-load and minimise coronary perfusion pressure resulting in left ventricular hypertrophy, left ventricular failure on the one hand and subendocadial ischaemia and coronary heart disease on the other (101). The early and accentuated reflections in the aorta also augment the late systolic pressure. The extent of this wave reflection is expressed as augmentation index (AIx) and is a significant predictor of coronary heart disease (CHD) (102) and an independent prognosticator of cardiovascular morbidity and mortality in patients with end stage renal disease (103). PWV is a measure of aortic stiffness and firmly established as an independent predictor of cardiovascular events in a hypertensive population (104,105).

Left ventricular dysfunction occurring in diastole has been relatively neglected in comparison with systolic function. A recent cross-sectional community survey in

Minnesota showed some 27% of the population over 45 years to have diastolic dysfunction, which was predictive of all cause mortality (106). It is recognised that some 50% of patients presenting with the signs and symptoms of heart failure have a normal left ventricular ejection fraction but abnormality in the diastolic properties of the left ventricle (107-109) and a history of hypertension is common. It is now recognised that abnormalities of left ventricular function, commonly seen in hypertension may occur also in the absence of hypertensive left ventricular hypertrophy. In a recent study of 105 hypertensive patients, mean age 51, on no treatment; diastolic dysfunction was present in up to 60% of newly diagnosed patients. Of these only 16% had left ventricular hypertrophy (110). In older hypertensive patients without left ventricular hypertrophy increased pulse pressure at night is an independent predictor of abnormal left ventricular diastolic filling (111). It is known that offspring of hypertensive parents have an increased risk of developing essential hypertension. In a comparison of offspring of essential hypertensive parents before any increase in blood pressure or cardiac morphological changes appeared (112). A high augmentation index may also be an early marker for vascular changes associated with hypertension. Normotensive offspring of families with essential hypertension had a greater degree of arterial stiffness measured by augmentation index than control subjects (112).

We hypothesised that such arterial stiffness may not be just confined to the vasculature but may extend into the heart in early hypertension. We therefore compared left ventricular diastolic function as a marker of ventricular stiffness, to late systolic pressure augmentation in the aorta, representative of stiffness, in more muscular arteries and PWV, as a surrogate for aortic stiffness, in newly diagnosed untreated hypertensive patients.

4.1.2 Structural Features of the Arterial Tree

The basic architecture of arteries (fig 4.1) is usually described in terms of cross-sectional arrangement of cells and extracellular matrix.

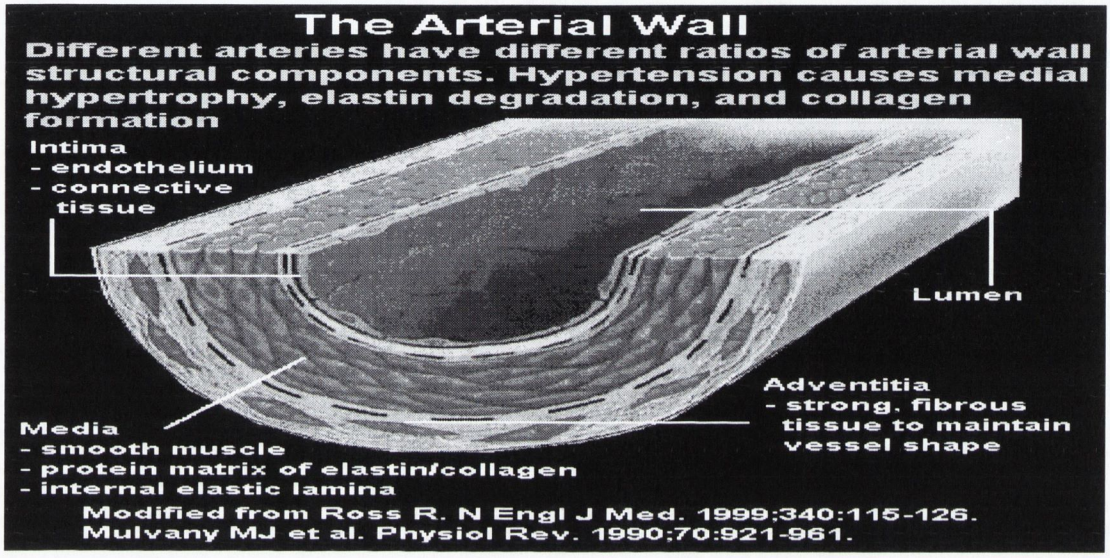


Figure 4.1 Arterial wall structures

The latter consists, within the media, of lamellae of elastic material with intervening layers of vascular smooth muscle (VSM) cells, collagen fibers, and ground substance (113,114). However, the distribution of elastin and collagen varies markedly along the longitudinal aortic axis (115). In the proximal aorta, elastin is the dominant component, whereas in the distal aorta, the collagen-to-elastin ratio is reversed, and in peripheral arteries, collagen predominates. The transition occurs rapidly over the distal 5 cm of the thoracic aorta above the diaphragm and over a similar distance in the branches leaving the arch of the aorta. Thereafter, VSM cells largely predominate. Thus, it is anatomically justified to divide the arterial tree into 2 compartments, proximal and distal. During development, VSM cells of different embryonic origin clearly reflect the differences in anatomic locations (116). In the abdominal aorta and small muscular arteries, the smooth muscle cells are of mesodermal origin, whereas

those of the aortic arch and thoracic aorta are mainly derived from the ectodermal cardiac neural crest (117). The participation of VSM cells of ectodermal origin is essential in the formation and organization of elastic laminae and tenso-receptors in the great vessels (113). These changes of VSM cells as a function of distance from the heart have been further confirmed by studies of the chemical properties and of gene expression of elastin and collagen along the aorta (113,114).

Theoretically, the characteristics and amounts of collagen are determined at a very young developmental stage and thereafter remain quite stable because of very low turnover. Nevertheless, the proportion of collagen type I and III differs markedly between the different species and has a substantially differential mechanical effect on stiffness and distensibility of the vessel wall (118). In addition, several neurohumoral factors, particularly those related to the angiotensin II and aldosterone systems, may modulate collagen accumulation (119). Collagen may also be subjected to important chemical modifications, such as breakdown, cross-linking, or glycation, resulting in marked changes in stiffness (120). Finally, in central conduit arteries, large amounts of collagen are observed in the adventitia, thus contributing to alter arterial mechanical properties (117). Collagen is principally responsible for the discontinuities of the vessel wall, mainly at the vessel bifurcations. It greatly modifies arterial rigidity and the transit of wave reflections, thereby increasing thoracic aorta PP. In turn, the increased cyclic stress causes fragmentation and fracture of elastin and calcifications, particularly in the elderly (120).

4.2 BASIC PRINCIPLES OF ARTERIAL FUNCTION

Understanding arterial physiology provides a background for evaluation of new techniques and interpretation of the results of clinical studies.

4.2.1 Pressure-volume relationships, compliance, and elastic properties.

Arteries act to convert cardiac pulsations into a more constant flow pattern in the distal circulation to meet the continuous needs of peripheral tissues for oxygen and substrate delivery. This conversion is performed in the proximal vessels by the retention, during systole, of a portion of each cardiac stroke volume for release during diastole (fig 4.2) (121).

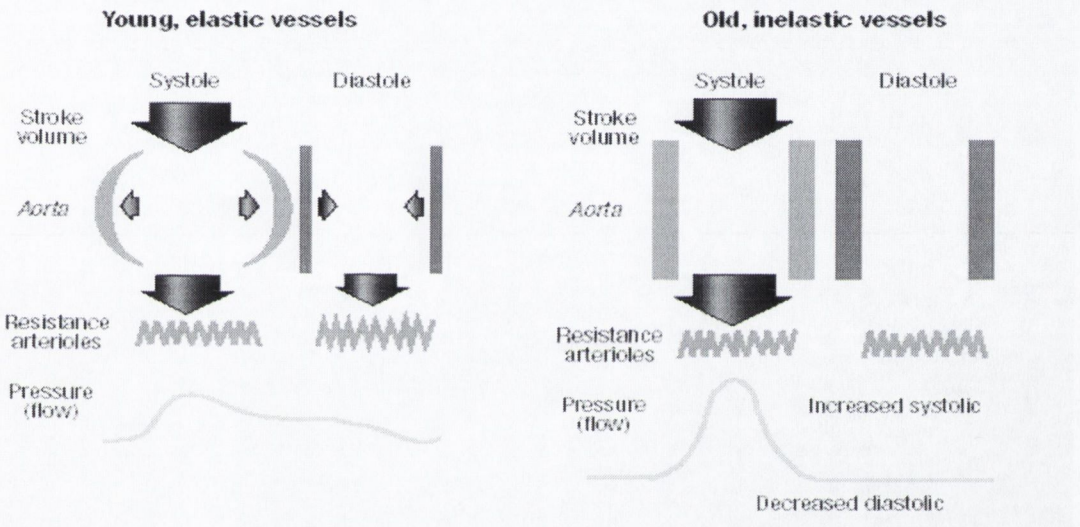


Figure 4.2 Aging and arterial stiffness.

Systolic hypertension and wide pulse pressure are markers of diffuse arteriosclerosis, which is also characterized by decreased vascular compliance or increased vascular stiffness. Increased large-arterial stiffness contributes directly to the observed age-related increase in systolic pressure and to the corresponding age related decrease in diastolic pressure. As a result of these changes, pulse pressure (systolic minus diastolic) also increases with age. If there is a concomitant increase in cardiac output or in systemic vascular resistance, there is systolic hypertension. The hemodynamic explanation of how stiff vessels lead to wide pulse pressure relates directly to the loss of elastic recoil function of the aorta and its first branches. In a normally elastic,

young aorta, a fraction of each cardiac stroke volume is retained in the proximal arteries during systole. Subsequent elastic recoil delivers that stroke volume "remnant" to the periphery during diastole, resulting in a relatively smooth flow profile and a narrow pulse pressure (fig 4.2, left panel). In a rigid aorta (fig 4.2, right panel), the absence of elastic recoil causes the full stroke volume to be delivered through the resistance arterioles during systole. There is minimal or no diastolic flow, resulting in increased systolic pressure, decreased diastolic pressure, and increased pulse pressure, all of which characterize the hypertension of old age (122).

Blood vessels with high compliance (i.e., low stiffness) experience only a small systolic pressure increase with a relatively large increase in volume. Individuals with compliant central arteries, therefore, exhibit relatively narrow pulse pressure (systolic minus diastolic pressure), which reflects low aortic wall tension and, usually, low left ventricular workload. Conversely, stiff central vessels (with a reduced capacity to be distended) cannot absorb more than a small fraction of each cardiac stroke volume without a substantial increase in pressure. As a result, individuals with stiff central arteries exhibit relatively high systolic and pulse pressures and a low diastolic pressure. Each component is stretched or loaded differently at different initial pressure levels. From a combined structure-function perspective, stiffness, compliance, and distensibility depend on the behavior of specific structural elements within the arterial wall, especially muscle, elastin, and collagen, which bear the pressure on the wall at different levels of distention (122).

4.2.2 Pressure-flow relationships, pulse wave, and wave reflection.

Impedance is the relationship between time varying pressure and the flow it generates. It includes the resistance to flow, the energy used to accelerate the blood column, and

the energy stored during elastic distention. Throughout the cardiovascular system, there are many sites at which changes in impedance occur, including arterial branch points, areas of turbulence or stagnation of flow, and areas where the lumen diameter changes abruptly. Changes in impedance are important by virtue of their effects on the transmission of pressure and velocity waves within the peripheral circulation (122).

Arterial pulse waves are compression waves generated by the force of each cardiac contraction. These compression waves both the pressure (or pulse) wave and the associated velocity wave that can be detected by Doppler analysis travel at a rate somewhat greater than the velocity of the column of blood. Pressure and velocity waves fluctuate between a minimum and a maximum, each with distinct waveforms. When a pressure wave traveling downstream reaches a zone of increased impedance, a fraction of that wave is reflected backward toward the heart, with the magnitude of the reflection proportional to the magnitude of the local impedance (fig 4.3). In younger subjects (fig 4.3, right panel), the reflected wave (arrow) returns to the aortic root during diastole. As vessels get stiffer during the aging process (figure 3, left panel), pulse wave velocity (PWV) increases and the reflected wave returns during late systole (arrow), where it summates with the forward systolic wave to augment central systolic pressure and increase ventricular afterload (122).

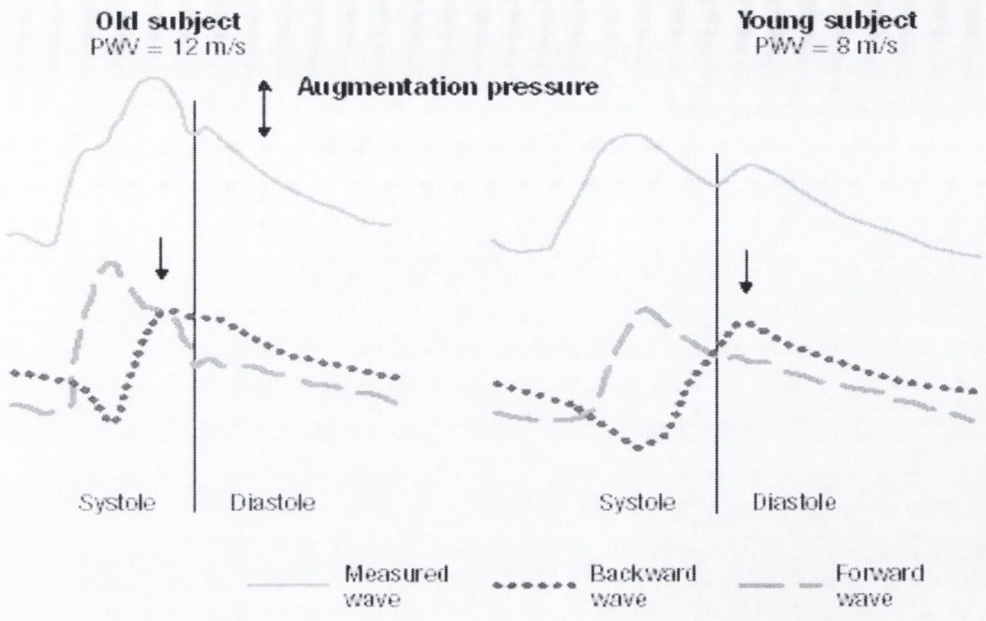


Figure 4.3. Pulse wave velocity and aging.

4.3 CONTRIBUTION OF ARTERIAL STIFFNESS AND LEFT VENTRICULAR DIASTOLIC FUNCTION.

Diastolic function is traditionally determined echocardiographically from the peak early (E) and late (A) diastolic mitral annular velocities, but tissue Doppler studies, are not routinely sought in clinical practice and may greatly expand our understanding. Diastolic dysfunction is particularly common and found in 50% of patients with type II diabetes (123). Arterial stiffness is of particular relevance in hypertension as it may consider as a significant haemodynamic parameter to predict morbidity and mortality outcomes (124).

4.4 Aim

To examine the relationship between LV diastolic function and arterial stiffness by comparing both large elastic and smaller muscular arterial stiffness, measured respectively aortic pulse wave velocity (PWV, Complior) and wave reflection by applanation tonometry (Sphygmocor) as augmentation index (Alx, height of late

systolic peak divided by pulse pressure), with (E) peak early diastolic and (A) late diastolic velocities and their ratio using TDI and transmitral inflow Doppler echocardiography.

4.5 METHODS

4.5.1 Study population:

We studied 104 consecutive (mean age 47±1, mean±SEM) newly diagnosed untreated hypertensive patients (BP > 140/90 mmHg and ambulatory BP > 135/80 mmHg). Patients with secondary hypertension, peripheral vascular disease, ischemic heart disease, congestive heart failure, severe valvular heart disease, diabetes mellitus, cerebrovascular disease, endocrine pathologies, and atrial fibrillation were excluded. The patients were not receiving any vasoactive drugs, oral contraceptives or hormone replacement therapy and abstained from smoking, caffeinated drinks or alcoholic beverages in the previous 12 hours. The patients gave informed consent, the study had institutional ethics committee permission.

4.5.2 Pulse Wave Analysis

Applanation tonometry was used to record radial artery pressure waveform continuously and mean values of at least two screens of pulse waves of good quality were used for analysis. On the basis of the collected data, an averaged radial pressure waveform was generated and a corresponding aortic pressure waveform and BP calculated by the validated transfer function (SphygmoCor, Version 8.0, AtCor Medical, Australia). The aortic pressure waveform was used to calculate the AIx (difference in height between the first and second systolic peaks expressed as a percentage of PP). The subendocardial viability ratio (Buckberg ratio), an indirect measure of subendocardial perfusion, was also generated (125,126). Buckberg et al. have demonstrated that the ratio of the area of the diastolic phase (diastolic pressure time index: DPTI) to that of the systolic phase (time tension index: TTI) in the central aortic profile has a close correlation with the blood supply to the subendocardium. This ratio was designated as the subendocardial viability ratio (SEVR) (127). Aortic PWV was measured using the foot-to-foot method with the automated system

(Complior, Artech Medical, France). The carotid and femoral arterial pressure waveforms were recorded simultaneously with two pressure-sensitive transducers placed over the two arterial points and the transit time of the pressure pulse calculated by the computer software. The distance between the two arterial sites was measured on the body surface with a tape measure and the PWV is calculated as distance divided by the transit time in meters per second. A minimum of 12 successive readings are used for analysis to cover a complete respiratory cycle (fig 4.3).

4.5.3 Echocardiography

Echocardiograms were obtained with Phillips Sonos 5500 cardiac ultrasound system with color flow and TDI abilities. The system was equipped with 2.5 and 3.5 MHz transducers. Two-dimensional (2-D) echocardiography was performed followed by a Pulsed Wave Doppler study. The images obtained included the apical four chamber and two chamber views so that blood flow measurements could be made across the mitral valve. Pulsed wave TDI was performed by activating this function on the Agilent 5500 system. TDI was measured and an average from four sites (lateral, septal, anterior, and inferior annulus) calculated. The characteristic velocity profile of diastole was obtained in all patients. Peak early (E') and late (A') diastolic mitral annular velocities were recorded as well as the E'/A' ratio; IVRT was measured as the time between the closing artifact of the aortic valve and the earliest detection of transmitral blood flow and the deceleration time (DT) of the E wave (time elapsed between peak E velocity and the point where the extrapolated deceleration slope of the E velocity crosses the zero baseline). The wall motion velocity pattern was recorded by TDI, and the peak early diastolic (E`) and the peak atrial systolic velocity (A`) recorded and their ratio calculated. The estimation of left ventricular filling by Tissue Doppler Imaging has been shown to be superior to the transmitral flow

velocities (128). M-mode measurements of diastolic left ventricular wall thickness and cavity diameter were used for calculation of left ventricular mass and indexed to height $^{2.7}$ (LVMI). Relative wall thickness was defined as the sum of septal and posterior wall thickness divided by end-diastolic dimension. Ejection fraction was calculated by the method of disc summation based on Simpson's rule. Left ventricular systolic function was assessed as mid-wall shortening based on mathematical models (129). Left atrial area was traced in an apical four-chamber view.

4.5.4 Statistical Analysis

The statistical analysis was performed with JMP version 5.0 (SAS for Windows). Significant differences between the groups were determined using Wilcoxon Rank Sums test for continuous variables and the chi-square test for categorical data. Relationships between continuous variables were analysed using non-parametric tests (Spearman Rho). To analyse if there was an independent relationship between PWV and AIx and the measures of diastolic dysfunction, stepwise regression analysis was used. In the first model, we took TDI derived E`/A` as the dependent variable because of E'/A' both are tissue indices, in contrast to standard transmitral Doppler filling indices, TDI early diastolic velocities are not significantly affected by physiological manoeuvres that alter preload. Thus TDI velocities during early left ventricular diastole may provide a better index of diastolic function in cardiac patients by providing a preload independent assessment of left ventricular filling (130), and in recent study TDI E'/A' <1 was correlated with transmitral flow velocity recordings incorporating the Valsalva manoeuvre, suggesting measurement of TDI E'/A' precludes the need to perform the Valsalva manoeuvre to unmask a pseudonormal pattern (131)" and AIx, age, mean arterial pressure, gender, heart rate, BMI, waist-hip ratio, smoking status, relative wall thickness, midwall fractional shortening, total

cholesterol and glucose as independent variables. In the second model, AIx was substituted with PWV. Results are expressed as mean±SEM, $P<0.05$ considered significant.

4.6 RESULTS

The clinical characteristics of the patient population are summarised in Table 4.1.

Table 4.2 & 4.3 compare clinical characteristics of the hypertensive patients based on TDI E`/A` as it has been reported by Sohn et al. There was no significant different in age ($P<0.01$) as well as body size, gender balance and waist-hip ratio between TDI E`/A`<1 and TDI E'/A' >1 groups.

Hypertensive patients with TDI E'/A'<1 have higher values for systolic and diastolic BP ($P<0.05$), heart rate ($P<0.05$), and relative wall thickness ($P<0.01$) compared to subjects with TDI E'/A'>1.

The PWV (10.4±0.2) ($P<0.001$) and AIx (33±1) ($P<0.0001$) were significantly higher in hypertensive with TDI E'/A<1 than those with TDI E'/A'>1 (9.4±0.02 & 24±2) respectively. However, Buckberg ratio was lower ($P<0.05$) in patients with TDI E'/A'<1 than those with TDI E'/A'>1.

Table 4.4 shows the correlation coefficients of TDI E`/A`, AIx, and PWV with other clinical parameters. TDI E`/A` showed a significant relationship with left ventricular relative wall thickness ($R=-0.36$, $P<0.0001$), and left atrial size ($R=-0.25$, $P<0.01$) but not with aortic root diameter, LVMI or midwall fractional shortening. Table 4 also shows that there was no significant association between AIx and RWT, LVMI, left atrial dimension or midwall fractional shortening. However, there was a significant relationship between PWV and RWT($R=0.20$,$p<0.05$) but not with LVMI, left atrial dimensions or mid-wall fractional shortening.

TDI E' and E`/A` were significantly correlated with Alx (R=-0.46, P<0.0001) & (R=-0.49, P<0.0001) respectively (fig 4.4). There was no significant relationship between IVRT and Alx. TDI E' and TDI E`/A` were inversely correlated with PWV (R=-0.45,P<0.0001)&(R=- 0.50,P<0.0001, fig 4.4) respectively.

Figure 4.5 showed that in newly diagnosed hypertensive patients, TDI E`/A` was significantly correlated with Buckberg ratio (adjusted for age and BP).

Table 4.5 (a & b) shows a multiple regression analysis with TDI E'/A' as a dependent variable with Alx and PWV. Alx was an independent determinant of TDI E`/A` in addition to age, RWT and heart rate (Table 4.5a). However when AIx was replaced by PWV in the stepwise regression model, only age, RWT and heart rate entered the model (Table 4.5b) with no independent contribution from PWV.

4.7 DISCUSSION

The heart is one of the target organs affected by high blood pressure, but the most common cause of death in hypertension is disease of the large artery walls (132). Stiffness of the arterial wall is a risk factor for atherosclerotic and diastolic heart failure (133) and appears to be increased in arterial hypertension (134). Asymptomatic organ damage may precede cardiovascular events in hypertension (135). Our study shows that LV diastolic dysfunction in newly diagnosed untreated hypertensive patients may be closely linked to arterial stiffness.

Pulse wave velocity (PWV) and the augmentation index (AIx) are widely used as arterial stiffness indices (136). The prognostic significance of Alx (102,103) and PWV (102-105) is well established. Reduced arterial compliance based on pulse pressure method was associated with progressively abnormal diastolic function in treated hypertensive patients with exertional dyspnoea, independent of LV mass, although they did not adjust for anti-hypertensive treatment in the multivariate analysis (137). Our findings consistent with previous studies, which have shown a relationship between other indirect measures of arterial stiffness and impaired left ventricular relaxation in different populations although this is the first study to show such a relationship in early untreated hypertension (137-139). Arterial stiffness which measured by stiffness index (138) (ß = ln (Ps/Pd)/(Ds-Dd/Dd) (Ps and Pd are systolic and diastolic blood pressure in the brachial artery measured by an automated sphygmomanometer (Omron 705CP, Tokyo, Japan), and Ds and Dd are the maximal and minimal diameters of the right common carotid artery measured by ultrasonic high resolution wall tracking) in healthy subjects and patients with left ventricular dysfunction was inversely related to LV subendocardial function assessed by TDI,

which was independent of age, BP and LV mass. However, they did not adjust these relationships for antihypertensive therapy in the multivariate analysis.

Using more sensitive measures of ventricular and arterial function (140), we have assessed a newly diagnosed untreated hypertensive population to identify subtle cardiac abnormalities for early intervention. We observed that LV diastolic dysfunction had a relationship with AIx independent of either LV mass or relative wall thickness.

A previous study, which assessed LV diastolic function, and it's relation with LV geometric pattern showed that blood pressure and LV wall thickness both have independent influence on LV diastolic function. A multivariate analysis showed that age was the strongest determinant for conventional E/A, followed by systolic BP, heart rate and RWT (141). LV diastolic dysfunction has been found to be common in patients with hypertension, even before LVH develops (142). Approximately half of the patients with overt congestive heart failure (CHF) have diastolic dysfunction without reduced ejection fraction (143). With the development of ventricular hypertrophy, a normal LV filling pattern is uncommon with the development of ventricular hypertrophy (144). Furthermore, it has been made clear recently that myocardial ischemia and fibrosis are two important factors associated with diastolic dysfunction in hypertension (142).

It has been reported that AIx has a complementary value to aortic distensibility in the assessment of left ventricular diastolic dysfunction in Behcet's disease (145). As suggested in our study, AIx predicted TDI E`/A` independently of mid-wall fractional

shortening in newly diagnosed untreated hypertension. LV diastolic function may be influence by afterload. Although the mechanisms underlying this afterload dependence remain to be elucidated, the systolic loading sequence is considered to be an important factor (146).

The timing and magnitude of arterial wave reflection returns during the cardiac cycle may have an important effect on left ventricular relaxation and coronary flow (147). The late systolic pressure rise in the aortic pressure waveform seen as a higher AIx induces a slower relaxation rather than an early systolic pressure rise (147,148). Clinically, Murgo et al (100) have divided human arterial pressure waveforms into three different types (those peaking in early systole, in midsystole and late systole) and examined aortic impedance associated with each wave type. They demonstrated that the occurrence of a pressure rise in late systole was associated with an early return of increased arterial wave reflection and was seen frequently in older people

Experimental studies have shown in an isolated perfused rabbit heart preparation that shortening the reflection time of the wave, the ventricular work shifts from diastole to late systole and decreases coronary perfusion pressure (149). Similarly, Yano et al (147) in a series of elegant experiments in patients with heart disease demonstrated that early return of wave reflection during the cardiac cycle delayed ventricular relaxation in the older patients, while in the younger subjects; diastolic return of the reflected wave (105) accentuated ventricular relaxation. This consistent with our findings that there was an inverse relationship between aortic wave reflection and TDI E`/A`. Furthermore there was a direct relationship between TDI E`/A` and Buckberg ratio, an indirect measure of subendocardial blood supply.

This may suggests a certain sequence of events in the circulation; ventricular ejection generates a forward pressure wave where velocity is measured by PWV. This wave is reflected back from the arterial tree as a wave traveling backwards to the heart. In normal physiological conditions the reflection returns to the ventricle during diastole, after the closure of the aortic valve, minimizing left ventricular afterload and augmenting coronary perfusion pressure. Shortening the reflection time and thereby increasing late systolic augmentation as seen with aortic stiffness, the pressure reflection overlaps the phase of ventricular emptying where the flow is still high, resulting in greater delayed ventricular work.

Based on our study, arterial stiffness as seen in our group of hypertensive subjects leads to a shorter reflection time, consequently a higher late systolic augmentation pressure in the aorta which may be linked to development of impaired relaxation of the left ventricle.

Experimental studies have shown marked relaxation delay when cardiac afterload is increased by partial aortic constriction and have suggested a key role for troponin-I and protein kinase A phosphorylation state as a coupler between afterload and ventricular relaxation (150). Therefore, a high AIx may lead to adaptive changes in the left ventricle, initially there may be only reversible filling abnormalities but as the insult continues, the ventricle may ensue the process of remodelling with enhanced synthesis, degradation and deposition of collagen in the both the interstitial and parivascular myocardial tissue. The resulting myocardial fibrosis may induce myocardial stiffness and diastolic dysfunction, perhaps before the development of LVH. At the same time, arterial stiffening decreases coronary perfusion, further impairing ventricular relaxation and leading to ischaemia. On the other hand, LV

dysfunction and vascular stiffness may be linked as they may share common pathophysiological pathways and may indeed occur in parallel.

In patients with diabetes mellitus, early ventricular dysfunction may relate to both structural and functional intra-myocardial and vascular abnormalities (151). Detection of preclinical heart disease would justify routine screening for presymptomatic ventricular and vascular abnormalities.

A previous study demonstrated that plasma tissue inhibitor of matrix metalloproteinase type-1 (TIMP-1) 100 never treated hypertension correlates with markers of LV diastolic filling (E/A ratio and DT), is predictive of LV dysfunction, and is a potential non-invasive marker of myocardial fibrosis (152). TIMP-1 concentrations are also elevated in never treated hypertensives (153) may facilitate organ fibrosis and development of LVH. Furthermore, it may associate with arterial stiffness in hypertensive patients (154). Recent studies show that plasma levels of glycation end products Ages are associated with increased aortic stiffness in hypertension (155) and LV diastolic dysfunction in type 2 diabetic rats (156).

The prevalence of LV diastolic dysfunction is being increasingly recognized in hypertensive patients in the absence of LVH or reduced ejection fraction (110) and carries prognostic significance (106). On the other hand, the aortic pressure waveform and arterial stiffness provide prognostic information beyond the measurement of blood pressure (96-98) and reducing it provides survival benefit (157,158). Although this study does not answer the question whether arterial stiffness precedes LV diastolic dysfunction or these changes occur in parallel, the coupling of LV diastolic

dysfunction and arterial stiffness in early hypertension may put these patients at increased risk of cardiovascular events by increasing left ventricular afterload and decreasing diastolic coronary perfusion pressure which may progress to left ventricular hypertrophy and subendocardial ischemia. Therefore routine screening for presymptomatic ventricular and vascular abnormalities as well as aggressive BP lowering strategies in newly diagnosed untreated hypertension may help to reduce the risk of early cardiovascular events in hypertension.

Table 4.1 Demographic data in the newly diagnosed hypertensive patients (n=104, mean±SEM).

Parameters	(n=104, mean±SEM)
Age (years)	46±1
Sex (M/F)	104(49/55)
Height (cm)	1.7±0.01
Weight (kg)	83±2
Body mass index (kg/m2)	28.6±0.5
Waist to hip ratio	0.89±0.01
Smokers (%) 23%	23%
Brachial systolic BP (mm Hg)	153±2
Brachial diastolic BP (mm Hg)	90±1
Brachial pulse pressure (mm Hg)	63±1
Mean arterial pressure (mm Hg)	113±1
Heart rate (min-1)	69±1
Aortic systolic BP (mm Hg)	142±2
Aortic diastolic BP (mm Hg)	92±1
Aortic pulse pressure (mm Hg)	50±1
Total cholesterol (mmol/L)	5.1±0.1
HDL cholesterol (mmol/L)	1.4±0.4
Triglycerides (mmol/L)	1.64±0.2
Glucose (mmol/L)	5.3±0.06

Table 4.2 Demographic and haemodynamic data in the newly diagnosed hypertensive patients according to TDI E`/A reversal (n=104, mean±SEM)

Parameters	TDI E`/A` =>1 (n=52)	TDI E`/A`<1 (n=52)	P value
Age (years)	44±1	49±1	<0.01
Male/Female	22/29	27/25	NS
Body mass index (kg/m2)	28.7±0.6	28.6±0.7	NS
Waist/Hip Ratio	0.87±0.01	0.9±0.01	NS
Brachial systolic BP (mm Hg)	148±3	158±2	<0.05
Brachial diastolic BP (mm Hg)	88±1	92±1	<0.05
Brachial pulse pressure (mm Hg)	59±2	66±1	<0.05
Heart rate (beat/min)	67±2	70±1	<0.05
Aortic systolic BP (mm Hg)	136±3	147± 2	<0.01
Aortic diastolic BP (mm Hg)	89±1	94±1	<0.05
Aortic pulse pressure (mm Hg)	47±2	53±1	<0.05

Table 4.3 Arterial stiffness and echocardiographic data in the newly diagnosed hypertensive patients according to TDI E`/A reversal (n=104, mean±SEM)

Parameters	TDI E`/A`=>1 (n=52)	TDI E`/A`<1 (n=52)	P value
Augmentation index (%)	24±2	33±1	<0.0001
Buckberg ratio (%)	158±5	148±3	<0.05
Pulse wave velocity (m/sec)	9.4±0.2	10.4±0.2	<0.001
Relative wall thickness (cm)	0.40±0.01	0.45±0.01	<0.01
Left ventricular mass index (g/m2.7)	32±1	37±1	<0.06
Ejection fraction (%)	62±0.8	62±1	NS
Midwall fractional shortening	14±0.3	13.7±0.3	NS
E/E' ratio	3.4±0.7	3.8±0.5	<0.01

Table 4.4 Correlation coefficients of augmentation index, PWV and TDI E`/A` with clinical and echocardiographic parameters in the newly diagnosed hypertensive patients (n=104, mean±SEM).

Variables AIx PWV E`/A`	Aix	PWV	E`/A`
Age (years)	-0.39 <0.0001	0.46 <0.0001	-0.47 <0.0001
Body mass index (kg/m2)	0.10 NS	0.06 NS	0.10 NS
Waist-Hip Ratio	-0.04 NS	0.19 <0.05	-0.15 NS
Brachial SBP (mmHg)	0.32 <0.001	0.45 <0.0001	-0.18 =0.06
Brachial DBP (mmHg)	0.21 <0.05	0.20 <0.05	-0.21 <0.05
Mean arterial pressure (mmHg)	0.39 <0.0001	0.30 <0.001	-0.25 <0.01
Heart Rate (min-1)	-0.16 NS	0.15 NS	-0.27 <0.01
Aortic systolic BP (mmHg)	0.53 <0.0001	0.46 <0.0001	-0.25 <0.01
Aortic diastolic BP (mmHg)	0.21 <0.05	0.21 <0.05	-0.21 <0.01
Buckberg ratio (%)	-0.15 NS	-0.33 <0.001	0.32 <0.001
Relative wall thickness (cm)	-0.07 NS	0.20 <0.05	-0.36 <0.0001
Left ventricular mass index (kg/m2)	-0.02 NS	0.02 NS	-0.18 =0.06
Deceleration time (msec)	0.27 <0.01	0.29 <0.01	-0.70 <0.0001
Isovolumeic relaxation time (msec)	0.11 NS	0.12 NS	-0.28 <0.01
Midwall fractional shortening (%)	0.04 NS	-0.05 NS	0.00 NS

Table 4.5 Multiple regression analysis with TDI E'/A' as dependent variable with (A) Augmentation Index and (B) Pulse wave velocity as dependent variables.

(A)

Parameters	R_2	β (SE)	P value
Age (years)	0.23	-0.01(0.004)	<0.01
Relative wall thickness	0.33	-2.00 (0.01)	<0.001
Heart rate (beat/min)	0.38	-0.01 (0.003)	<0.001
Alx (%)	0.43	-0.01 (0.003)	0.001
Gender (F)		-0.07 (0.53)	<0.08

(R2=0.45, p<0.0001) Blood pressure, mid-wall fractional shortening, body mass index, smoking status, glucose and cholesterol did not enter the model.

(B)

Parameters	R_2	β (SE)	P value
Age (years)	0.23	-0.02(0.003)	<0.0001
Relative wall thickness	0.32	-1.7(0.58)	<0.0001
Heart rate (min^{-1})	0.37	-0.01(0.004)	<0.0001

(R2=0.37, p<0.0001) Blood pressure, heart rate, gender, body mass index, smoking status, mid-wall fractional shortening, glucose and cholesterol did not enter the model

Figure 4.4 (a,b). Relationship between TDI E`/A` and augmentation index (Top) and pulse wave velocity (bottom) adjusted for age, gender and blood pressure, in newly diagnosed untreated hypertensive patients. Regression lines represent 95% confidence intervals (n=104).

Figure 4.4 (a)

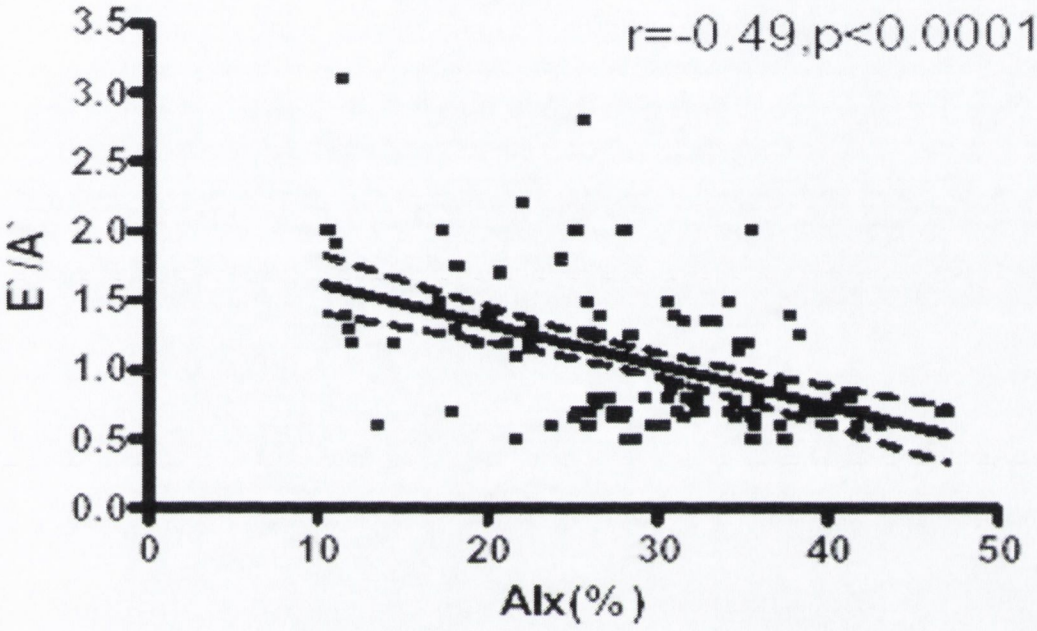
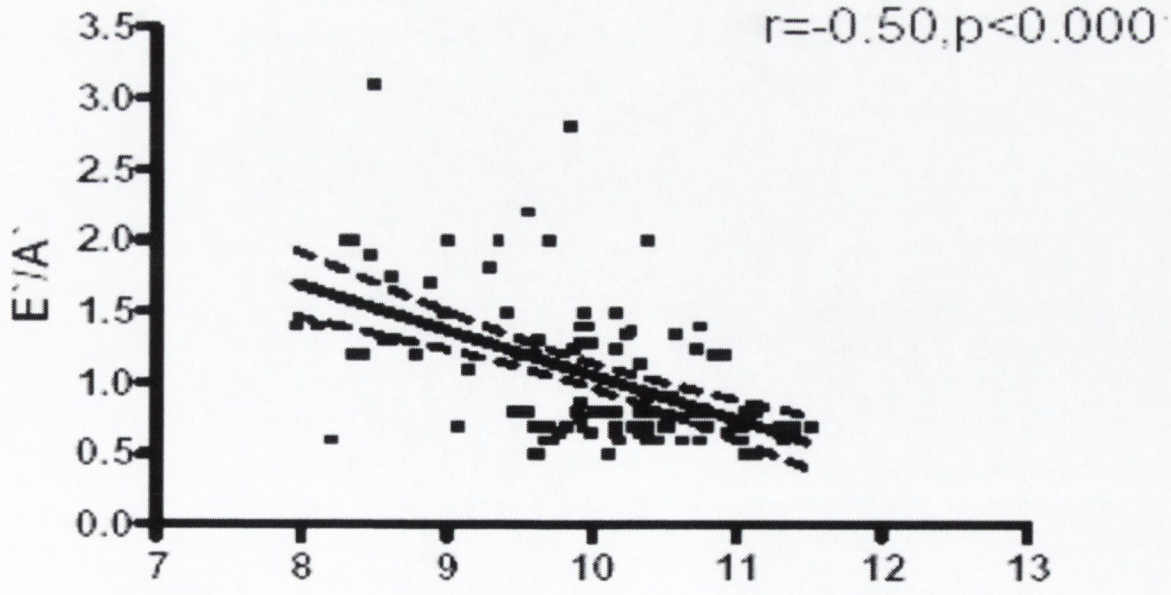
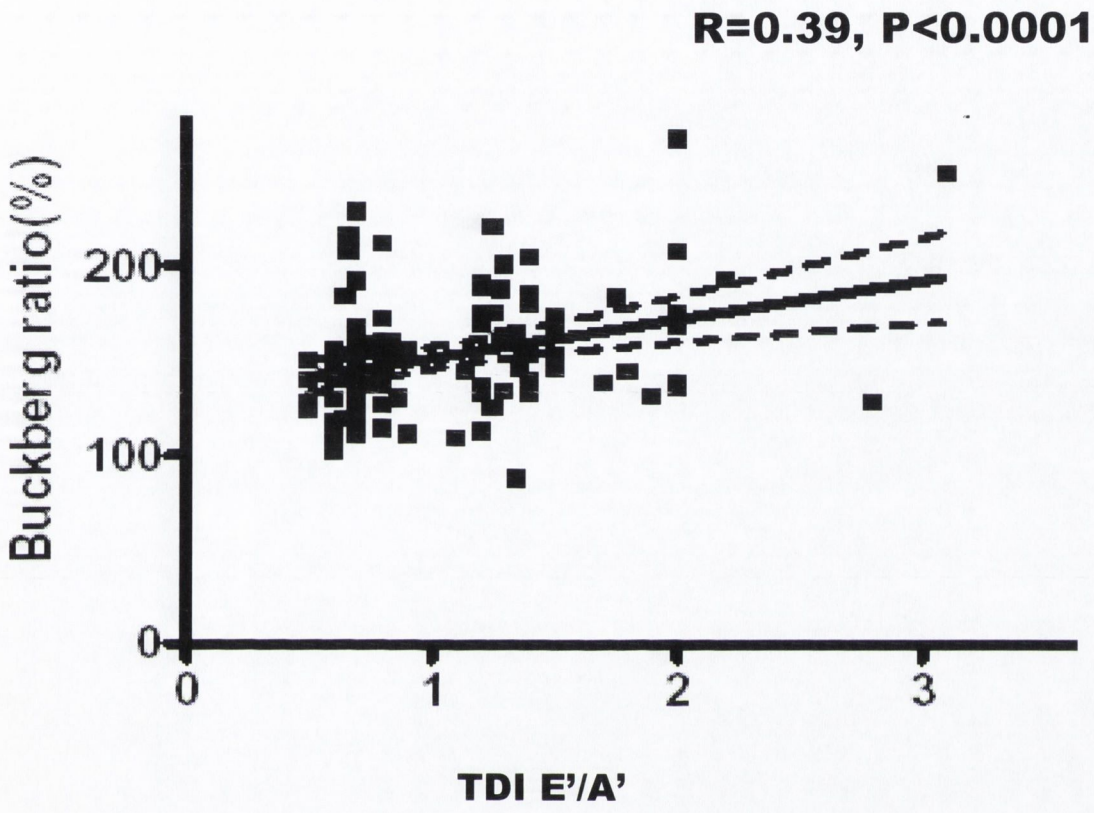


Figure 4.4 (b)



Pulse Wave Velocity m/sec)

Figure 4.5 Relationship between TDI E`/A` and Buckberg ratio, adjusted for age, gender and blood pressure in newly diagnosed untreated hypertensive patients. Regression lines represent 95% confidence intervals (n=104).



CHAPTER 5

Novel Index of Myocardial Stiffness and Myocardial Performance Index in Preclinical Assessment of Diastolic Dysfunction in Early Hypertension

5.1 INTRODUCTION

There is an increasing interest in the concept of diastolic dysfunction (159), which has been facilitated by the availability of non-invasive Doppler methods of characterising diastolic function (160). A recent study (161) showed that subjects with normal ejection fraction (EF) can have moderate or severe diastolic dysfunction, most often without accompanying clinical evidence of heart failure.

Alterations of left ventricular structure and function can be present in wide range of cardiac conditions particularly Systemic Hypertension (HTN) and accurately characterized by echocardiography (162). In patients with HTN and preserved left ventricular (LV) systolic function, HTN has been linked to a gradual development of diastolic LV dysfunction, referred to as diastolic heart failure (163). HTN with LVH is a known risk factor for the development of asymptomatic LV dysfunction and congestive heart failure (164).

A variety of indices derived from Doppler-echocardiography have been used to predict outcome in patients with LV dysfunction including LV cavity dimensions, ejection fraction, and mitral inflow velocities (165). However, the confounding effects of changes in loading conditions can significantly affect the measurements based on Doppler recordings of ventricular filling velocities. Tissue Doppler imaging (TDI) that measures the velocity of the myocardium during the cardiac cycle has been used to assess systolic and diastolic function (166). Tissue Doppler imaging can be used to measure mitral or tricuspid annulus velocities that reflect ventricular function in the long axis (167,168). Several studies have shown that the early mitral annulus velocity is a relatively preload-independent in the assessment of LV relaxation (169,170), and

the ratio of peak early diastolic mitral inflow velocity (E) over the myocardial velocity can be used to estimate LV filling pressure (E/E'), (171--173).

Non-invasive echocardiographic indexes of systolic and diastolic ventricular function are of great clinical importance in the diagnosis and management of patients with heart disease (174). However, there is no universally accepted gold standard to assess overall left ventricular contractility and relaxation.

The Doppler myocardial performance index (MPI) has been proposed as a reflection of overall cardiac function (175-179). The MPI, which combines parameters of both systolic and diastolic ventricular function, is easily obtainable and has been clinically useful in non-invasive assessment of global ventricular function. This index is defined as the sum of isovolumic contraction time (ICT) and isovolumic relaxation time (IRT) divided by ejection time (ET), and reflects overall left ventricular contractility and relaxation (175-179).

Recently a simple index using pressure volume relationships, the left ventricular stiffness index (LVSI), derived by dividing the E/E' by the left ventricular end diastolic dimension (LVEDD) has been shown to differentiate pathological from physiological LVH in athletes (180). Therefore, the aim of the study was to evaluate a novel LVSI together with MPI in preclinical assessment of diastolic dysfunction in early hypertension.

5.2 PATIENTS AND METHODS

5.2.1 Study Population

We recruited 100 consecutive patients (53 men, 47 women; mean age 47.23±1.22) with newly diagnosed untreated hypertension (> 140/90 mmHg clinic or > 135/85 mmHg Ambulatory). Subjects with secondary hypertension, ischemic heart disease, arrhythmia, diabetes mellitus, and valvular heart disease were excluded.

5.2.2 Echocardiographic measurements:

Assessment was done using a commercially available ultrasound system Phillips Sonos 5500 equipped with Tissue Doppler echocardiography capabilities. Baseline echocardiography examinations were done to rule out structural abnormality. M-mode measurements of left atrial (LA) size, aortic root (AR), left ventricular end-diastolic dimension (LVEDD), left ventricular end-systolic dimension (LVESD), septal and posterior wall thickness were recorded. Left ventricular ejection fraction was assessed qualitatively using the modified Simpson's rule. Transmitral Doppler (TMD) peak early diastolic E wave velocity (cm/s), peak late A wave diastolic velocity (cm/s), their ratio E/A, deceleration time (DT) and isovolumic relaxation time (IVRT) were recorded. The same measurements were repeated during phase II of Valsalva maneuver. In keeping with other studies (4) pulmonary vein flow (PVF) Doppler was difficult to obtain and not available in all patients so was not included in the analysis. Furthermore the PVF may sometimes be within normal limits despite other evidence of diastolic dysfunction (4). We therefore chose to use the Valsalva manoeuvre as a method of reducing left atrial pressure, as his technique has been shown to be useful in unmasking pseudonormalization of mitral inflow pattern, particularly when PVF is difficult to obtain (4).

Tissue Doppler imaging (TDI) was measured and an average from four sites (lateral, septal, anterior, and inferior annulus) calculated. The following measurements were recorded: early diastolic velocity (E') and late diastolic velocity (A') and their ratio. The ratio of early diastolic mitral inflow velocity (E) to TDI E' (E/E'), which is a marker of diastolic filling pressure, were calculated. Myocardial stiffness is assessed by the E/E') Pressure/ left ventricular end diastolic diameter (LVEDD) Volume relationship (E/E'/LVEDD ratio) (LVSI) (180) (fig 5.1). Myocardial performance index (MPI), which is defined as the sum of isovolumic contraction time (ICT) and isovolumic relaxation time (IRT) divided by ejection time (ET) reflects overall left ventricular contractility and relaxation (fig 5.2) was recorded (181).

5.3 Statistical Analysis:

Results were analysed with JMPIN version 5.0 (SAS for Windows). Results are expressed as mean±SEM and a $p<0.05$ considered significant. Relationships were analysed using Spearman Rho correlations. Analysis of variance and Wilcoxon Rank Sum Test were used.

5.3 RESULTS:

The clinical characteristics of the patient population are summarised in Table 5.1.

There was a significant difference in age (P<0.001) between patients with normal, pseudonormal and impaired relaxation using the Canadian guidelines. However, there was no significant difference in gender distribution when diastolic dysfunction was classified using Canadian guidelines (table 5.2)

Hypertensive patients with DD have higher values for left atrial dimension, left ventricular mass index, and septal wall thickness compared to subjects with normal diastolic function (P<0.001).

Myocardial performance index showed better correlation with EF% (R=-0.42, P<0.0001) than correlation of LVSI and E/E' with EF% (table 5.4). LVSI and MPI, (Fig 5.6&5.7) are significantly correlated with TD E' (R=-0.91&0.89 respectively) (P<0.0001) compared to LVSI and MPI with TMD E and E/A (R=-0.33 & -0.40 respectively) (P<0.001).

TDI E' and E'/A' were significantly lower in DD (7.4±0.15 & 0.64±0.01 respectively) especially when associated with LVH (7.13±0.31 & 0.62±0.02 respectively) compared to the normal (16.75±0.55 &1.35±0.02) (P<0.0001).

The LVSI and E/E' are impaired in hypertensives with DD (1.9±0.06 & 9.7±0.3) and more prominent in hypertensive with LVH (2±0.13 & 10±0.53) comared to normal (P <0.0001). However, MPI did not show any difference between DD with or without LVH (0.47±0.02 & P<0.0001).

As the severity of DD increased, LVSI and E/E' increased, compared to MPI. LVSI and E/E' were (0.94±0.04 & 4.76±0.2) in normal diastolic function, (1.7±0.05 & 8.48±0.24) in stage I diastolic dysfunction, and (2.2±0.08 & 10.85±0.32) in stage II diastolic dysfunction ($P<0.0001$). On the other hand, MPI value was higher in DD compared to the normal, but it did not show any significant different between stage I and II of DD (0.48±0.01) though levels of significance appear to be similar ($P<0.0001$).

There were stronger positive correlation between the LVSI and E/E' ($R=0.961$ & $P<0.0001$) than correlation of LVSI with MPI ($R= 0.725$ & $P <0.0001$).

5.4 DISCUSSION:

High blood pressure has a high prevalence in the general population and is one of the major risk factors for ischemic heart disease (182). Early detection of changes in cardiac performance, before irreversible damage to the heart has occurred, can contribute substantially to a further decline in hypertension-related death (182).

One of the key distinguishing features of hypertensive with and without LVH is the degree of diastolic dysfunction. The American Heart Association recommends TDI E' as the best measure of diastolic function (183). This report is consistent with our findings that E' was significantly lower in DD especially when associated with LVH compared to the normal.

E', the early diastolic velocity of mitral annulus as obtained by tissue Doppler imaging (TDI) behaves as a pre-load-independent index of LV relaxation (184) and it has been used to differentiation between constrictive and restrictive cardiomyopathy (185). Mitral inflow E velocity as obtained by pulsed-wave (PW) Doppler when corrected for the influence of relaxation by using E/E' ratio correlates well to the mean pulmonary capillary wedge pressure (PCWP) as obtained by invasive measurements. (184)

A recent study reported that the novel non-invasive measurement of LV stiffness could help to differentiate athletic from hypertensive LVH. Myocardial stiffness was assessed by the pressure/volume relationship (E/E'/LVEDD ratio (180). In our study we have further validated this measure. In hypertensive patients with DD compared with normal, however a higher E/E' ratio indicates reduced compliance (increased

stiffness), that accounts for significantly higher E/E'/LVEDD ratios in hypertensive patients with DD compared to normal diastolic function.

In our study we have observed that as the severity of diastolic dysfunction increased based on stages of diastolic function (4), LVSI and E/E' values are increased prticularly in stage II of DD compared to subjects with normal diastolic function. On the other hand, MPI value was higher in DD compared to the normal, but it did not show any significant different between stage I and II of DD. Moreover, LVSI and E/E' are impaired in hypertensives with DD before hypertrophy develops and impairments are more prominent in hypertensive with LVH. However, MPI did not show any difference between DD with or without LVH

The MPI, which defined as the sum of the isovolumic contraction time (ICT) and the IRT divided by the ejection time (ET), enables noninvasive estimation of combined systolic and diastolic function (186). The only diastolic function parameter used in the index is the isovolumic relaxation time (IVRT) (186). It has been reported that the MPI and mitral inflow Doppler-derived parameters are preload dependent, however, the diastolic parameters of TDI were preload independent (187). In acute myocardial infarction (AMI) patients, the MPI detects with reliability milder types of diastolic dysfunction (188). However, because of its pseudonormalisation, the MPI cannot be considered a reliable indicator of more severe patterns of LV diastolic dysfunction in AMI patients (188).

In our study, shortened IVRT in patients with pseudonormal pattern results in reduction of the MPI. Therefore, the MPI may not reflect true level of ventricular dysfunction in these patients.

The results of our study demonstrate a useful application of TDI parameters and LVSI in the assessment of diastolic function. With standard Doppler and 2-D echocardiographic indexes, Doppler myocardial velocities permit the differentiation between normal subjects and patients with different degrees of diastolic dysfunction and this method would be helpful in identifying patients with pseudonormal pattern of DD.

As we demonstrated in chapter 3 there was wide variance in the diagnosis of diastolic dysfunction based on the current standard echocardiographic criteria. Thus current guidelines are of limited value and could be enhanced by the inclusion of TDI. On the other hand, LV diastolic dysfunction may occurs independently of the presence of LVH, demonstrating that TDI and LVSI are capable of detecting diastolic segmental functional changes in non-hypertrophied wall segments in newly diagnosed untreated hypertensive patients. As the IVRT shortens in patients with a pseudonormal mitral inflow pattern resulting in a reduction of the MPI. Therefore, the MPI may not reflect an appropriate level of DD in these patients. Nonetheless, LVSI may provide early detection of diminished myocardial function and may help identify patients requiring aggressive and targeted medical therapy in hypertensive patients but its superiority over existing indices remains to be established.

Table 5.1 Baseline demographic and haemodynamic data in newly diagnosed hypertensive patients.

Variable	(N=100, mean±SEM)
Age (years)	47±1.2
Sex (m/f)	53/47
Height (cm)	172±2
Weight (kg)	85±2
Waist (cm)	93±3
Systolic blood pressure (SBP) mmHg	154±2
Diastolic blood pressure (DBP) mmHg	93±2
Mean arterial pressure (mmHg)	117±1.8
Heart rate (beats/min)	74±2

Table 5.2 Echocardiographic data in all subjects with newly diagnosed hypertensive patients (n=100, mean±SEM)

	Normal	Impaired relaxation (Stage I)	Pseudonormal pattern (Stage II)	P value
No. Of Patients	41	25	34	NA
Age (years)	41.3±1.9	56.8±1.8	47.2±1.6	<0.0001
Gender (M/F)	21/20	15/10	17/17	NA
LA (cm)	3.46±0.04	3.89±0.09	3.8±0.07	<0.0001
IVSD (cm)	0.88±0.01	1.08±0.03	1.02±0.02	<0.0001
LVEDD (CM)	4.9±0.05	4.9±0.07	4.8±0.06	0.21
LV mass index (g/m^2)	77.78±2.69	102.8±5.7	90±4.2	<0.001
TMD E (cm/sec)	80.3±2.8	60.2±2.8	76.7±1.6	<0.0001
TMD A (cm/sec)	61.9±1.6	77.1±2.9	67.2±1.5	<0.0001
TMD E/A ratio	1.28±0.03	0.7±0.02	1.1±0.01	<0.0001
DT ms	172.3±1.4	224.9±2.1	176.6±2.3	<0.0001
IVRT ms	80.5±0.8	115.4±1.2	78.7±1.8	<0.0001
TMD E cm/s Post Valsalva	66.7±3	51.8±2.2	48.7±1.5	<0.0001
TMD A cm/s Post Valsalva	57±1.8	76±2.6	70.2±1.7	<0.0001
TMD E/A Post Valsalva	1.15±0.02	0.66±0.02	0.68±0.01	<0.0001
DT ms Post Valsalva	220.5±1.9	254.3±3	241.8±1.8	<0.0001
TDI E' cm/s	16.7±0.5	7.3±0.2	7.2±0.1	<0.0001
TDI E'/A' ratio	1.35±0.02	0.6±0.01	0.6±0.01	<0.0001
TDI E/E' ratio	4.7±0.2	8.4±0.2	10.8±0.3	<0.0001
LVSI	0.94±0.04	1.7±0.05	2.2±0.08	<0.0001
MPI	0.35±0.01	0.48±0.01	0.47±0.01	<0.0001

Table 5.3 Doppler echocardiographic parameters in subjects with normal diastolic function, diastolic dysfunction (DD) with and without LVH (n=100, mean±SEM)

	Normal	DD without LVH	DD with LVH	P value
No. Of Patients	41	41	18	NA
Age (years)	41.3±1.9	51.9±1.5	49.7±2.8	<0.001
Gender (M/F)	21/20	20/21	12/6	NA
TMD E (cm/sec)	80.3±2.8	72.4±1.9	63.5±3.8	<0.01
TMD A (cm/sec)	61.9±1.6	72.6±2	68.6±2.6	<0.01
TMD E/A ratio	1.28±0.03	0.9±0.02	0.9±0.06	<0.0001
DT ms	172.3±1.4	192.5±4.5	207.5±4.3	<0.0001
IVRT ms	80.5±0.8	93.9±2.9	95.1±5.7	0.02
TMD E cm/s Post Valsalva	66.7±3	50.4±1.5	49.1±2.2	<0.0001
TMD A cm/s Post Valsalva	57±1.8	73.2±1.9	71.3±2.3	<0.0001
TMD E/A Post Valsalva	1.15±0.02	0.6±0.01	0.6±0.02	<0.0001
DT ms Post Valsalva	220.5±1.9	254±3	239±2	<0.0001
TDI E' cm/s	16.7±0.5	7.3±0.1	7.1±0.3	<0.0001
TDI E'/A' ratio	1.35±0.02	0.6±0.01	0.6±0.02	<0.0001
TDI E/E' ratio	4.7±0.2	9.7±0.3	10±0.5	<0.0001
LVSI	0.94±0.04	1.9±0.06	2±0.13	<0.0001
MPI	0.35±0.01	0.47±0.01	0.47±0.01	<0.0001

Table 5.4 Correlation of MPI, LVSI, and E/E' with EF% (Simpson's rule & Teichloz method)

	EF% Teichloz method	P value	EF% Simpson's rule	P value
MPI	R=-0.35	P<0.001	R=-0.42	P<0.0001
E/E'	R=-0.28	P<0.01	R=-0.31	P<0.01
LVSI	R=-0.23	P=0.01	R=-0.29	P<0.01

Fig 5.1 Left ventricular stiffness index (189)

$$\text{LVSI} = \frac{\text{E/E' (Pressure)}}{\text{LVEDD (Volume)}}$$

Figure 5.2 Myocardial performance index (190).

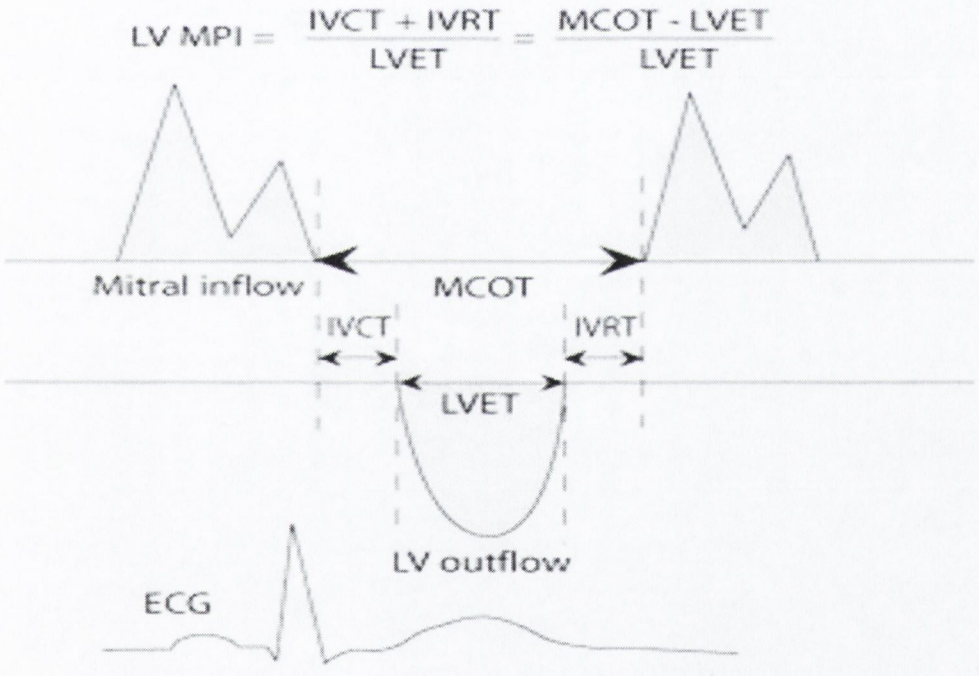


Figure 5.3 Left ventricular stiffness index (LVSI) in stages of diastolic dysfunction (P<0.0001)

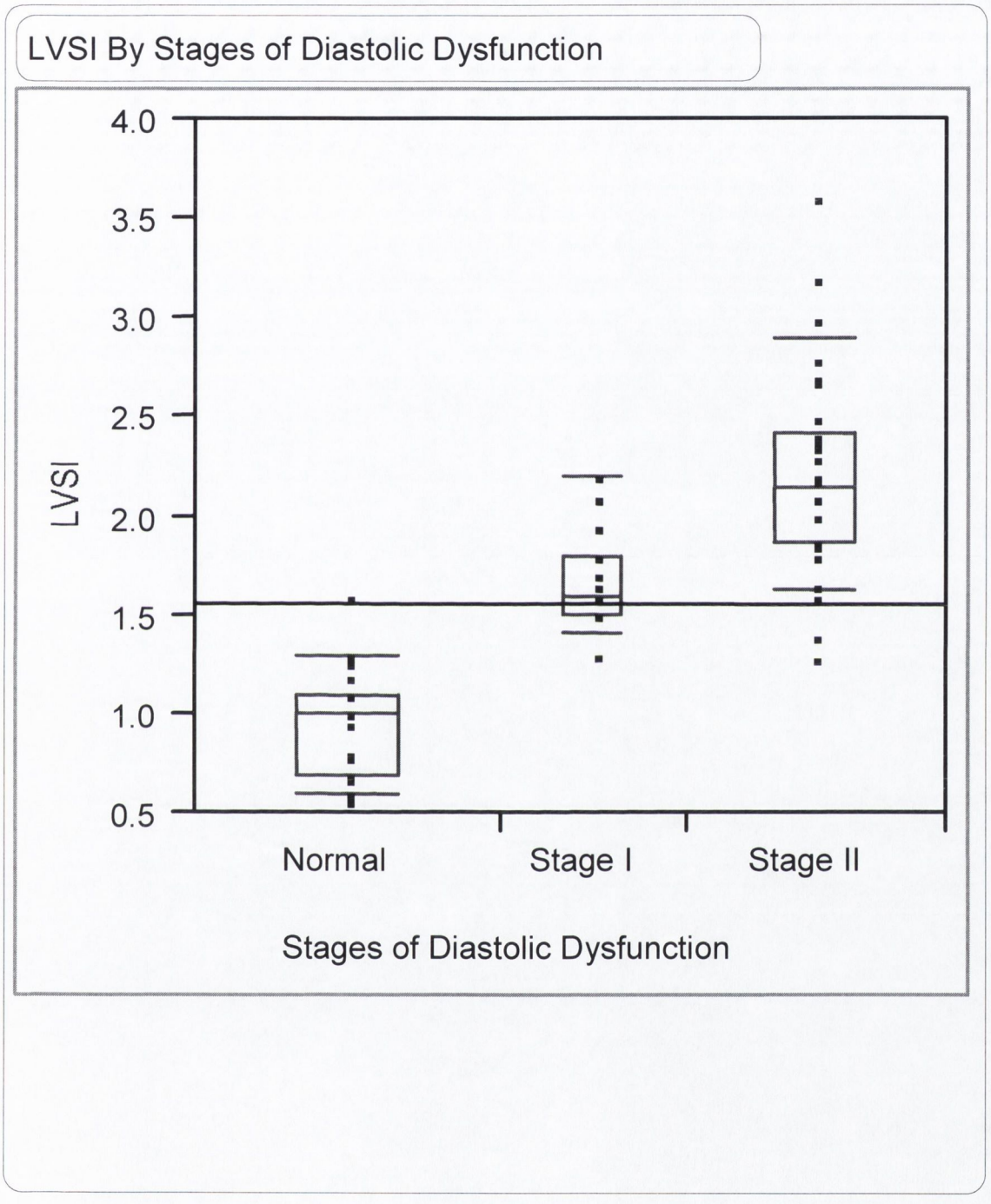


Figure 5.4. E/E' in stages of diastolic dysfunction (P<0.0001)

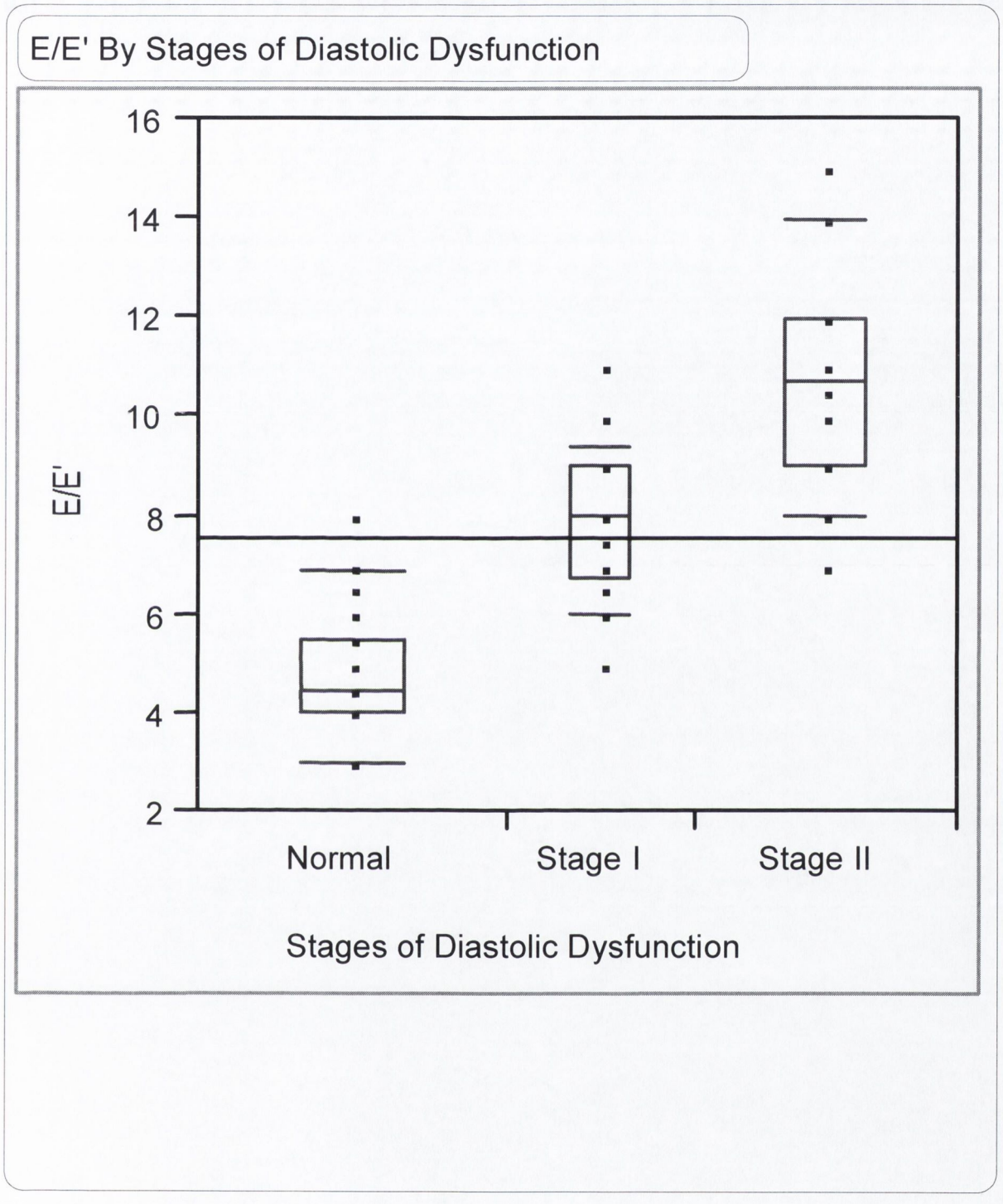


Figure 5.5 Myocardial performance index in stages of diastolic dysfunction (P<0.0001).

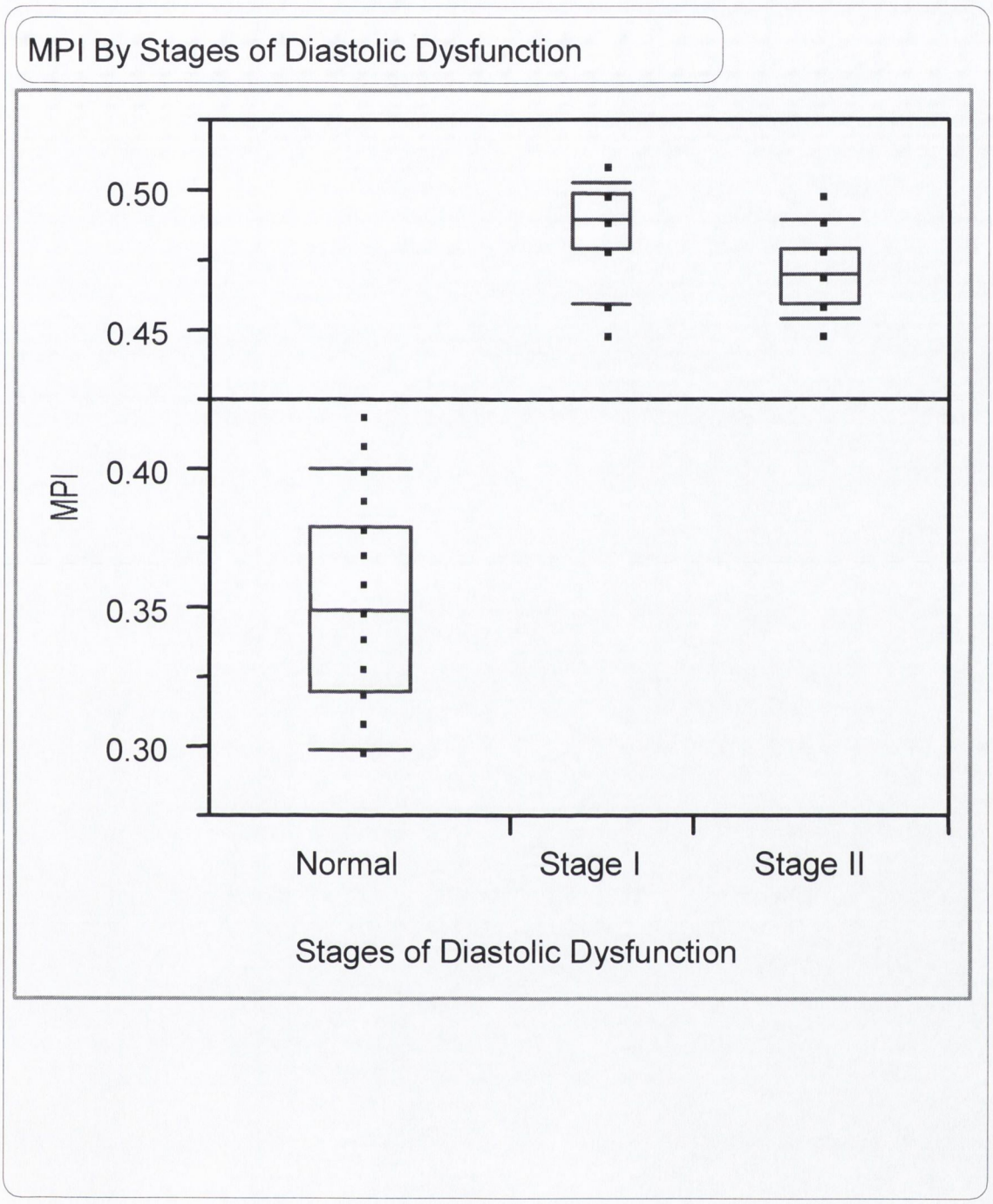


Figure 5.6 Correlation of LVSI and E' TDI (R=-0.91 & P<0.0001)

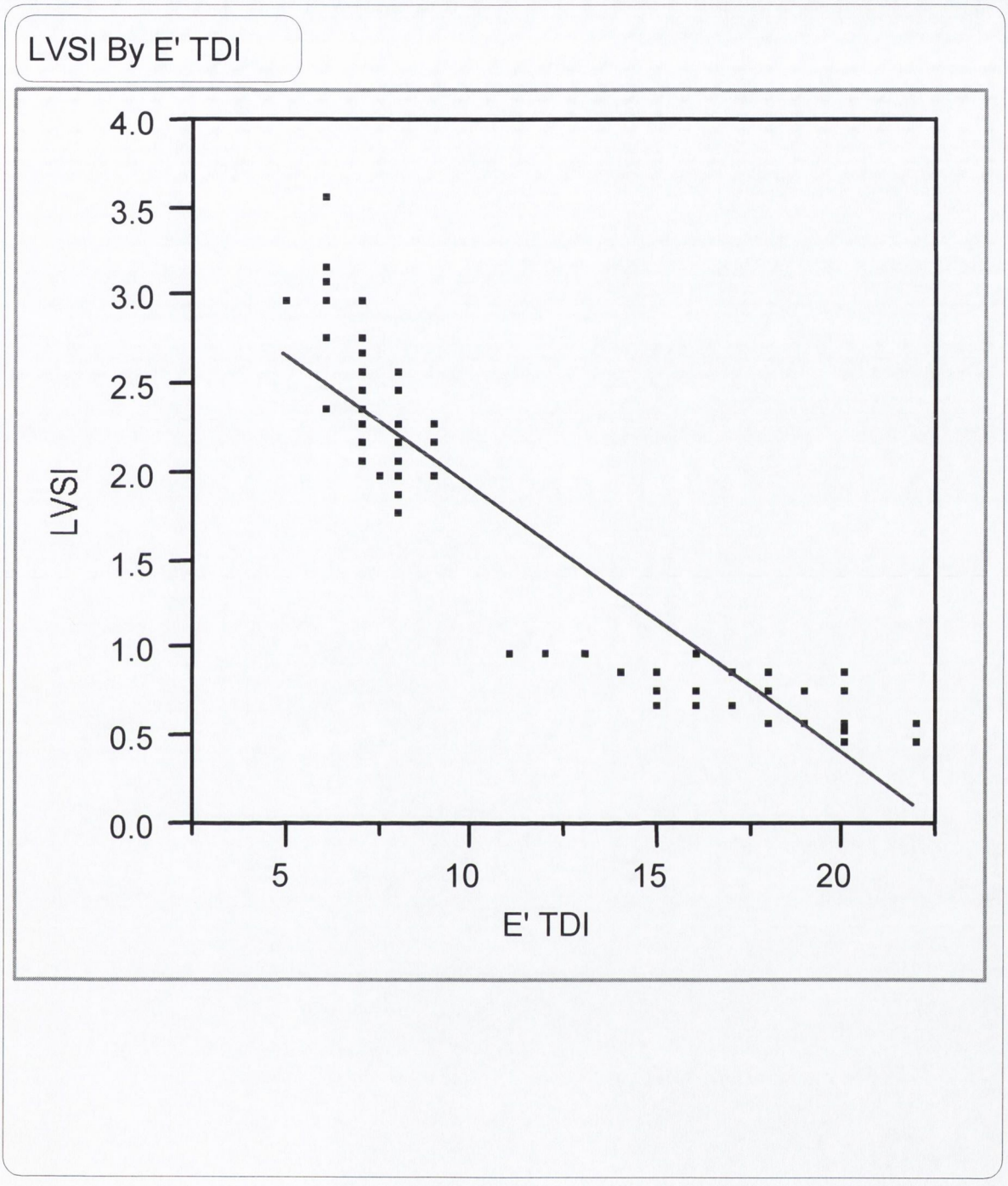
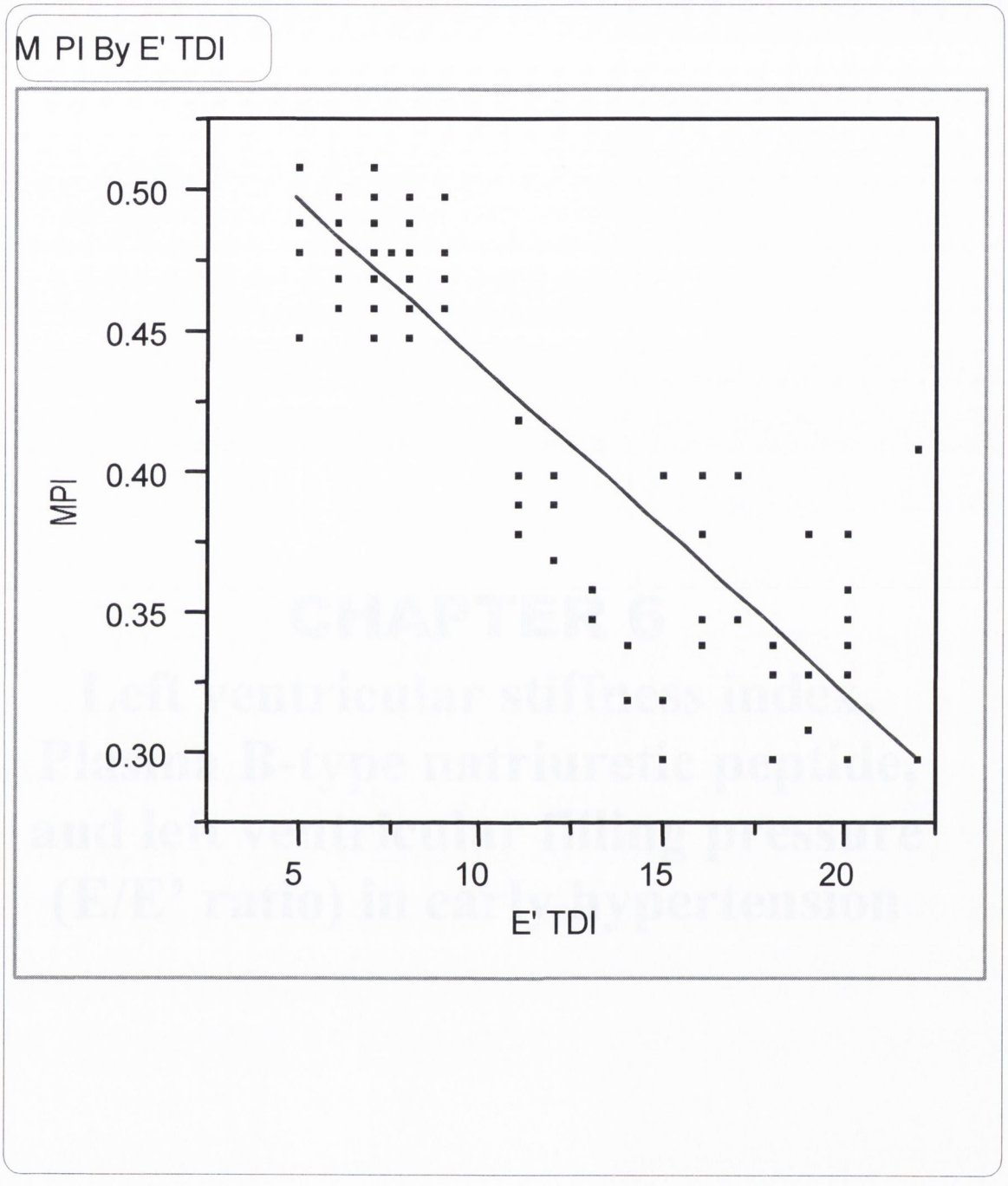


Figure 5.7 Correlation of MPI and E' TDI (R=-0.89 & P<0.0001)



CHAPTER 6

Left ventricular stiffness index, Plasma B-type natriuretic peptide, and left ventricular filling pressure (E/E' ratio) in early hypertension

6.1 INTRODUCTION

Doppler-echocardiography has been used to predict outcome in patients with LV dysfunction including LV cavity dimensions, ejection fraction, and mitral inflow velocities (189). Shortening of the early diastolic deceleration time (DT) of the mitral E-wave suggests impaired LV filling and increased left atrial (LA) pressure and has been shown to be a strong predictor of an adverse outcome in symptomatic and asymptomatic individuals with LV dysfunction (190,192). However, the confounding effects of changes in loading conditions can significantly affect the measurements based on Doppler recordings of ventricular filling velocities. Recently, TDI that measures the velocity of the myocardium during the cardiac cycle has been used to assess systolic and diastolic function (193). Tissue Doppler imaging can be used to measure mitral or tricuspid annulus velocities that reflect ventricular function in the long axis (194,195). Several studies have shown that the early mitral annulus velocity is a relatively preload-independent assessment of LV relaxation (196,197), and the ratio of peak early diastolic mitral inflow velocity (E) over the myocardial velocity can be used to estimate LV filling pressure (E/E'), (197-200). Recently a simple index using pressure volume relationships, the left ventricular stiffness index (LVSI), derived by dividing the E/E' by the left ventricular end diastolic dimension (LVEDD) has been shown to differentiate pathological from physiological LVH in athletes (201).

Increasingly B-type natriuretic peptide (BNP), a neurohormone secreted from the cardiac ventricles in response to myocyte stretch (200), has been incorporated in algorithms to assess diastolic and systolic heart failure and the response to treatment.

The early recognition and treatment of diastolic dysfunction as well as differentiation of pathological and physiological LVH remains a crucial part of patient assessment. The aim of the study was to further validate the new left ventricular stiffness index (LVSI) with plasma BNP, as well as with LV filling pressure obtained by E/E' ratio in patients with early hypertension and hypertrophic cardiomyopathy (HCM), and to evaluate whether the LVSI may help to demonstrate early diastolic dysfunction in patients with newly diagnosed hypertension.

6.2 METHODS

6.2.1 Study population:

10 asymptomatic patients with characteristics of mild hypertrophic cardiomyopathy (HCM) (LVSD > 1.3 cm) without LV outflow tract obstruction. The patients were recruited from cardiology out patients department with a clinical diagnosis of HCM based on clinical presentation (chest pain, dyspnea, family history of HCM), examination findings, and the presence of significant LVH in the absence of an identifiable cause of the LVH. Five had strong family history of HCM, arrhythmias, dyspnoea, and serial echoes over previous years showed progressive left ventricular thickness.

10 newly diagnosed untreated hypertensive patients (mean age 46.9±2.1 years, 58 women), with elevated blood pressure (clinic > 140/90 mmHg and daytime ambulatory > 135/85mmHg). 10 normal age matched control group were recruited from hospital staff. Subjects with secondary hypertension, ischemic heart disease, arrhythmia, diabetes mellitus, and valvular heart disease were excluded.

6.2.2 Echocardiographic measurements:

Assessment was done using a commercially available ultrasound system Phillips Sonos 5500 equipped with Tissue Doppler echocardiography capabilities. Baseline echocardiography examinations were done to rule out structural abnormality. M-mode measurements of left atrial (LA) size, aortic root (AR), left ventricular end-diastolic dimension (LVEDD), left ventricular end-systolic dimension (LVESD), septal and posterior wall thickness were recorded. Left ventricular ejection fraction was assessed qualitatively using the modified Simpson's rule. Transmitral Doppler (TMD) peak early diastolic E wave velocity (cm/s), peak late A wave diastolic velocity (cm/s), their ratio E/A, deceleration time (DT) and isovolumic relaxation

time (IVRT) were recorded. Tissue Doppler imaging (TDI) was measured and an average from four sites (lateral, septal, anterior, and inferior annulus) calculated. The following measurements were recorded: early diastolic velocity (E') and late diastolic velocity (A') and their ratio. Myocardial stiffness is assessed by the pressure/volume relationship (E/E'/LVEDD ratio) (LVSI) (201)

6.2.3 BNP Analysis:

Blood for BNP was collected on the same day as the echocardiogram in the fasting state. Samples were processed and analysed using the Biosite fluorescence immunoassay system

6.2.4 Statistical Analysis:

Results are presented as mean± standard deviation for continuous variables, and medians. Analysis of variance and Wilcoxon Rank Sum Test were used. For correlation spearman rho test was used. Analysis was done using the JMP version 5.0 (SAS for Windows). A p value <0.05 was considered statistically significant.

6.3 RESULTS

Table 6.1 shows no significant difference in demographic details between groups.

Table 6.2 showed that HCM patients have significantly higher values for left atrial dimensions, septal and posterior wall thickness (P= 0.001) compared to hypertensive and control groups.

E/E' ratio, LVSI and BNP were higher in HCM compared to hypertensive and control groups (P = <0.001 for all three parameters). The hypertensive group had a significantly higher LVEDD compared to HCM (P=0.018). TDI E' wave was significantly lower in HCM and Hypertensive patients compared to normal group (P=0.001).

The IVRT, E/A and DT were not significantly different among the three groups.

BNP values are significantly higher in HCM compared to hypertensive and control groups. This parameter was also higher in hypertensive compared to controls (P < 0.000) (fig 6.1).

Figure 6.2 and 6.3 showed that the LVSI and E/E' were significantly higher in the HCM group compared to hypertensive and control groups (P<0.000 & P=0.003) respectively and higher in Hypertensive compared to the control group (P<0.001& P=0.003) respectively.

Figure 6.4a showed that there was a positive correlation between BNP and LVSI (r= o.875) as well as with E/E' ratio (r= 0.805) (Figure 6.4b). Though levels of significance appear to be similar (P<0.0001).

6.4 DISCUSSION

Although mitral inflow Doppler echocardiography provides an assessment of abnormal left ventricular (LV) diastolic filling dynamics, its inherent limitations suggest the need for additional measures of diastolic dysfunction (202). The ratio of mitral inflow velocity to early diastolic velocity of the mitral annulus (E/E') derived from tissue Doppler imaging has been shown to be associated with the mean LV end diastolic pressure (LVEDP) measured on invasive testing, this is currently felt to be the gold standard.

Mak et al (202), suggest that BNP reflects ventricular pressure. Lubien et al (203) found that, in the absence of left ventricular (LV) systolic dysfunction, BNP levels were significantly higher in patients with LV diastolic dysfunction as assessed with echocardiography than in subjects without LV diastolic dysfunction. It has been reported that increased BNP concentrations in subjects with diastolic dysfunction are strongly related to LVH (204).

Recent study (201) reported that a new left ventricular stiffness index (LVSI), derived by dividing the E/Ea by the left ventricular end diastolic dimension (LVEDD) has been shown to differentiate pathological from physiological LVH in athletes. Therefore, we evaluated the relationship of this new LVSI to plasma BNP and the LV filling pressure obtained by E/E' ratio in patients with early hypertension and hypertrophy cardiomypathy (HCM), compared to controls.

One of the key distinguishing features of both Hypertensive LVH and HCM is the degree of diastolic dysfunction. Studies done by Ho et al (205) and Nagueh et al

(206) suggest that TDI can be used to identify a group of individuals with HCM with or without the presence of LVH. The American Heart Association recommends TDI E' as the best measure of diastolic function (207). This report is consistent with our findings that E' was significantly lower in HCM and Hypertensive groups with diastolic dysfunction compared to control group. However there remains no consensus as to the appropriate normal range. E', the early diastolic velocity of mitral annulus as obtained by tissue Doppler imaging (TDI) of the lateral mitral annulus behaves as a pre-load-independent index of LV relaxation (208). Mitral inflow E velocity as obtained by pulsed-wave (PW) Doppler when corrected for the influence of relaxation by using E/Ea ratio correlates well to the mean pulmonary capillary wedge pressure (PCWP) as obtained by simultaneous catheter measurements (208).

Recent studies have addressed the prognostic implication of TDI E' or E/E' in patients with various cardiac diseases (209-212). Hillis et al (211) reported that E/E' > 15 predict poor outcome in patients with acute myocardial infarction. More recently, McMahon and colleagues (212) showed that E/E' predicts adverse clinical outcome in children with hypertrophy cardiomyopathy. On the other hand, Nagueh et al (208) reported that E/E' ratio <8 is very specific for a PCWP <15 mmHg while a ratio >15 is very specific for elevated pressures >15 mmHg. Between 8 and 15, there is a gray zone with overlapping of values for PCWP. These suggest the need for additional measures of diastolic dysfunction (208).

It has been suggested that novel non-invasive measurement of LV stiffness could help to differentiate athletic from hypertensive LVH. Myocardial stiffness was

assessed by the pressure/volume relationship (E/E'/LVEDD ratio (201). In this study we have further validated this measure. In patients with HCM, LVEDD is lower compared with hypertensive and control group, however a higher E/E' ratio indicates reduced compliance (increased stiffness), that accounts for significantly higher E/E'/LVEDD ratios in HCM compared to Hypertensive and control group. LVSI was significantly higher in the HCM compared to hypertensive and control and higher in hypertensive compared to control group. On the other hand, BNP values are significantly higher in HCM compared to hypertensive and in hypertensives compared to controls. Moreover, BNP showed a positive correlation with both LVSI and E/E' ratio.

6.5 STUDY LIMITATION

The group size is small. Our study group included only patients in sinus rhythm; we do not looked at patients in AF

6.6 CONCLUSION

The Left ventricular stiffness index is a simple, non-invasive test providing a good correlation with BNP, suggesting it may give additional information on LV diastolic function. This index may be useful in distinguishing physiological from pathological hypertrophy, but larger studies are indicated.

Table 6.1 Demographic data in hypertrophic cardiomyopathy (HCM), hypertensive, and control groups.

	HCM (n=10)	Hypertension (n=10)	Control group (n=10)	P value
Age (years)	37.8	38.1	38.0	0.99
Men/women	8/2	6/4	5/5	0.36

Table 6.2 Comparison of echocardiographic data, new Left ventricular stiffness index (LVSI), and Brain natriuretic peptide (BNP) in HCM, hypertensive, and control groups.

	HCM (n=10)	Hypertension (n=10)	Control group (n=10)	P value
Systolic/diastolic BP	114±2/65±2	158±2/96±3	110±2/62±3	0.016
LA (cm)	4.7±0.6	3.9±0.4	3.5±0.4	0.001
IVSD (cm)	1.6±0.4	1.26±0.17	0.86±0.67	0.001
LVPWD (cm)	1.2±0.14	1.1±0.17	0.85±0.84	0.001
LVEDD (cm)	4.5±0.42	4.94±0.43	4.7±0.29	0.018
EF %	63.4±8	67.1±7.7	70.3±4.2	0.1
IVRT (ms)	84.5±17.6	82±9.2	82±7.9	0.87
TMD E/A ratio	1.58±1.28	1.25±0.27	1.28±0.18	0.54
TDI E' (cm)	8.2±1.5	7.6±0.09	17.9±3	0.001
E/E' ratio	11.39±3.99	6.89±2.7	5.3±2.7	0.000
LVSI (E/e'/LVEDD) ratio	2.6±0.81	1.55±0.56	1.05±0.18	0.000
BNP	2234.4±1583	125.5±57.9	72.3±23.8	0.000

Figure 6.1 Brain natriuretic peptide level in HCM, hypertensive, and control groups (P<0.001).

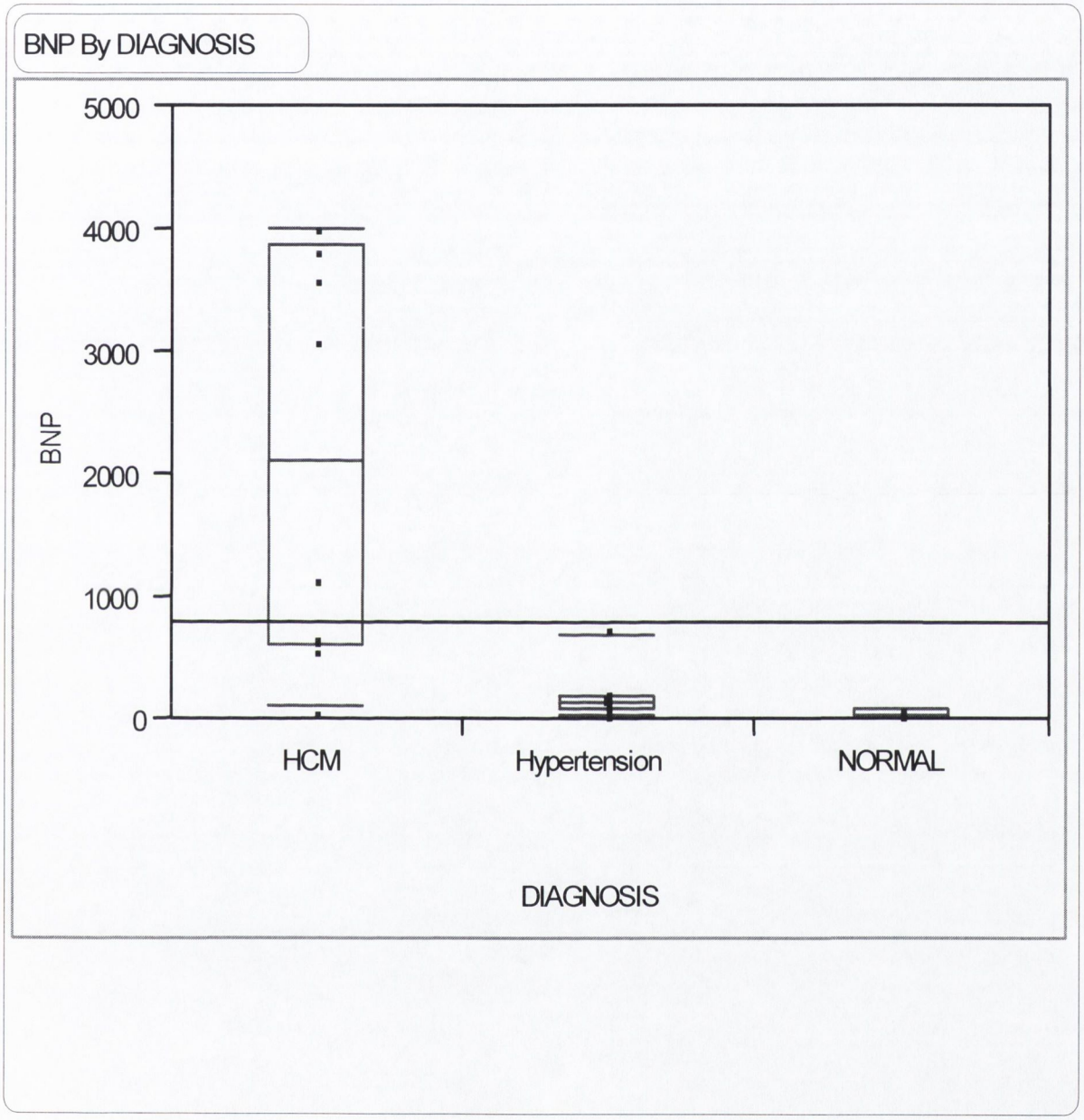


Figure 6.2 Left ventricular stiffness index in HCM, hypertensive, and control groups (P=0.001).

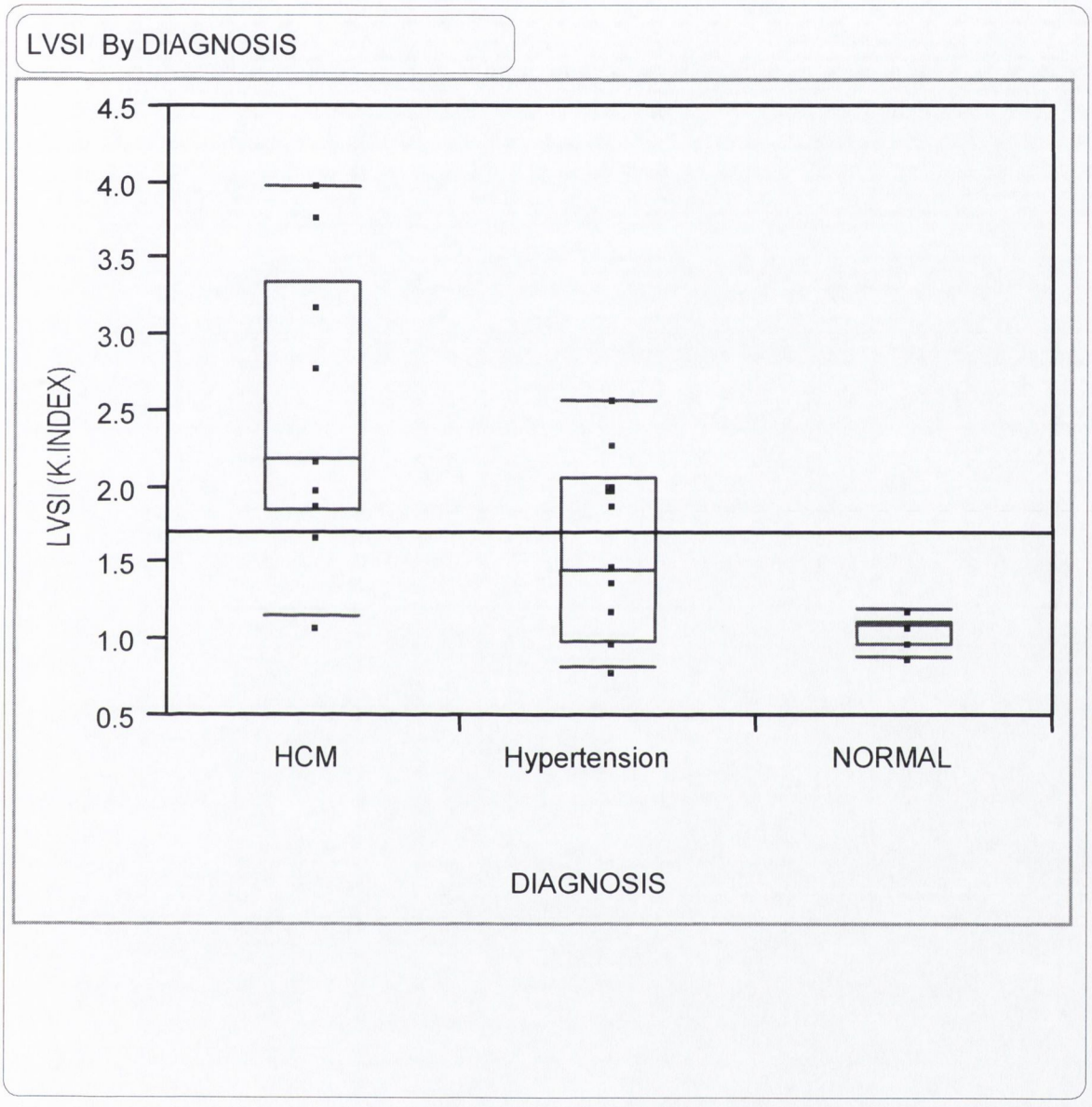


Figure 6.3 E/E' in hypertrophic cardiomyopathy (HCM), hypertensive, and control groups (P=0.003).

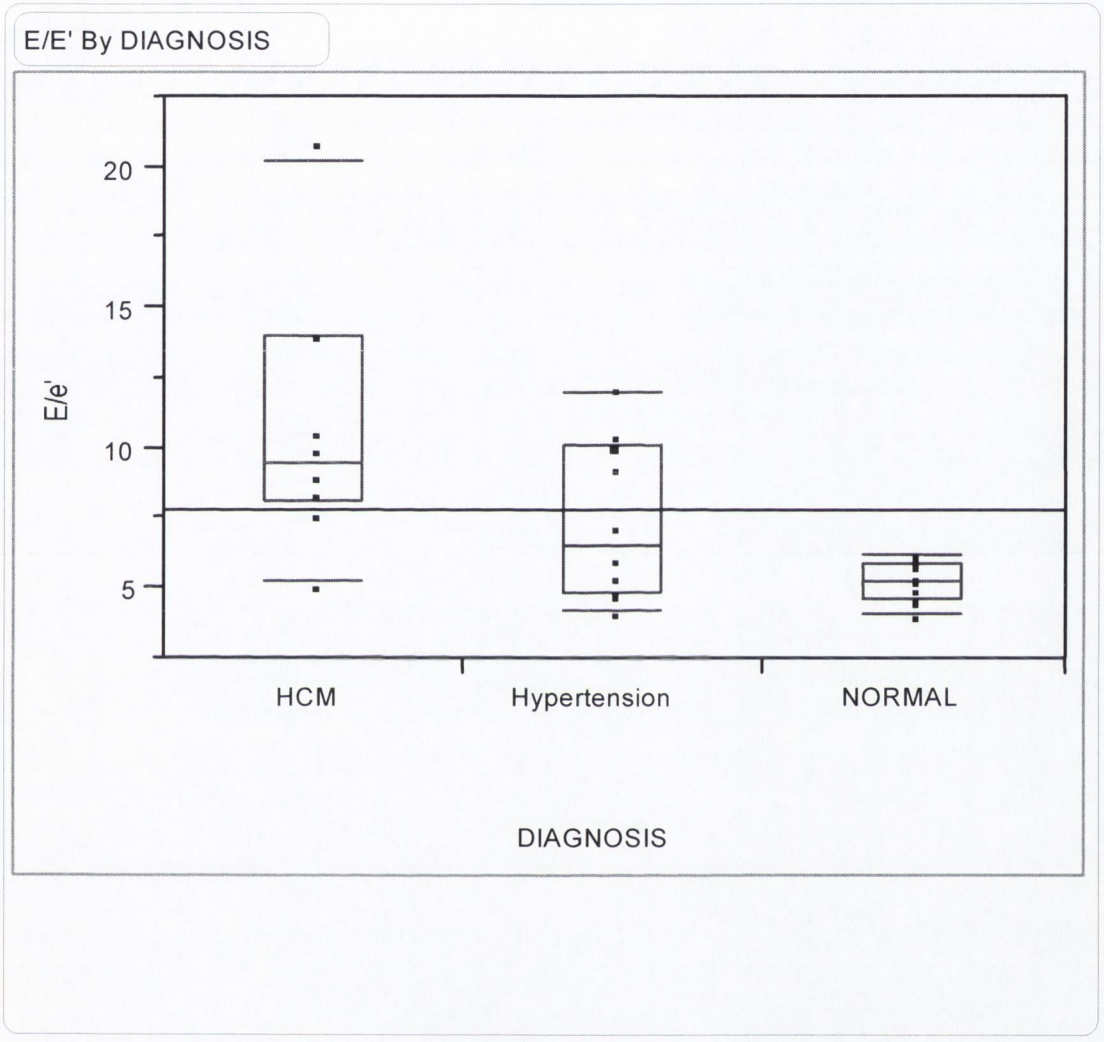


Figure 6.4A & 6.4B.Correlation of LVSI, E/E' Ratio and BNP

Figure 6.4A: Correlation of LVSI and BNP (P<0.0001) (r= o.875).

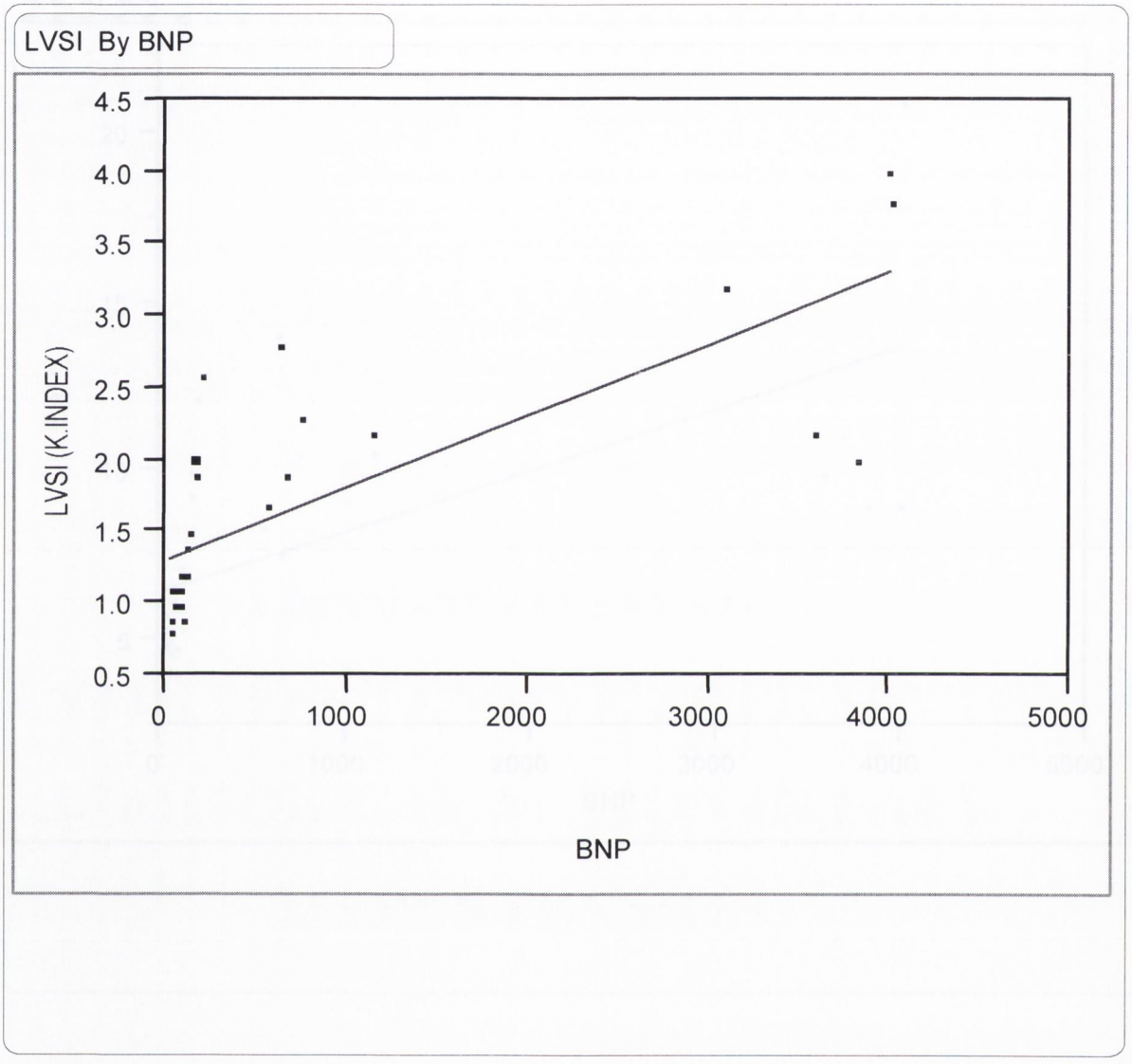
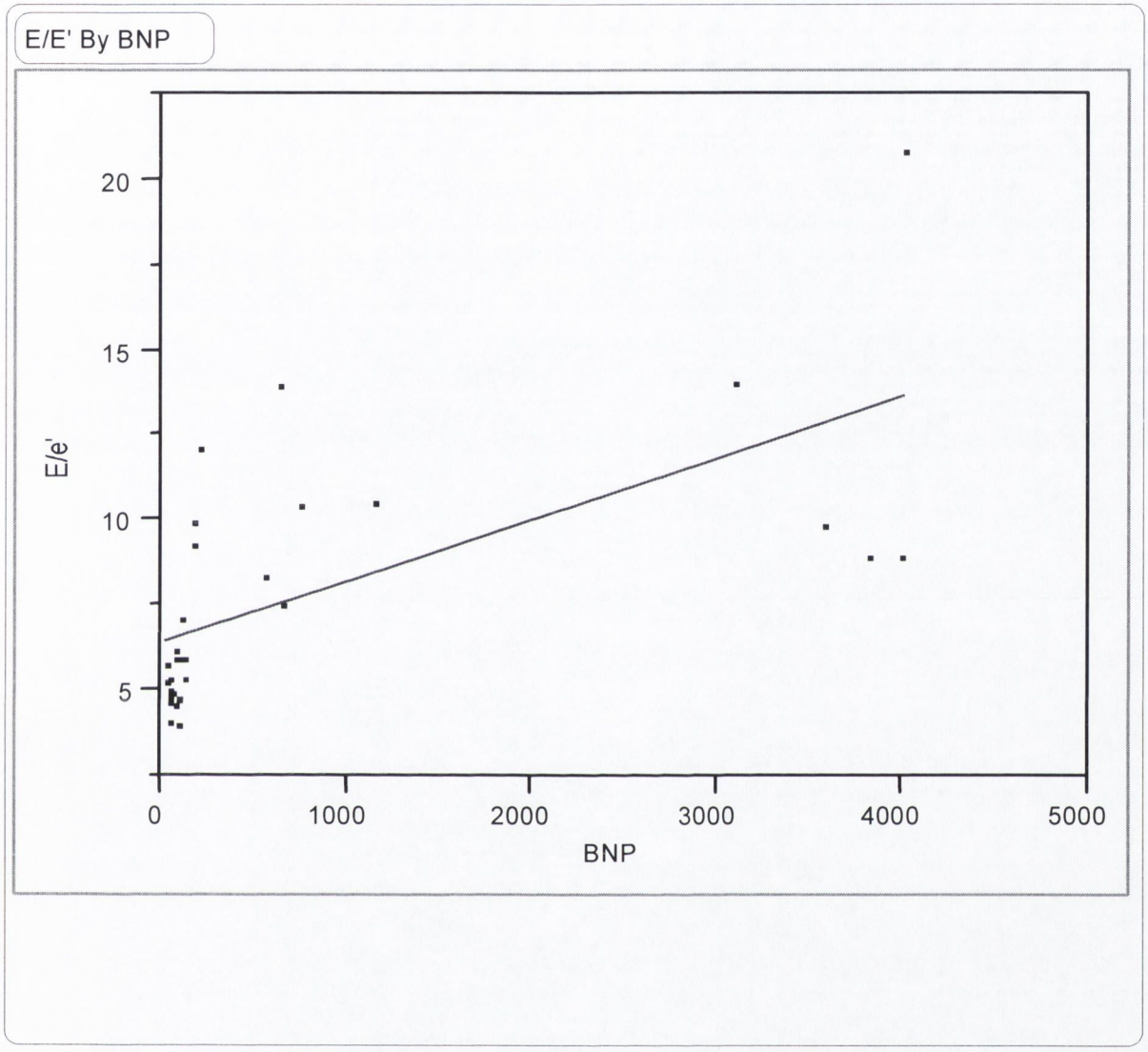


Figure 6.4B: Correlation of E/E' and brain natriuretic` peptide (BNP) (P<0.0001) (r= 0.805).



CHAPTER 7

ASSESSMENT OF ANTIHYPERTENSIVE THERAPY ON DIASTOLIC FUNCTION IN EALY HYPERTENSION

7.1 INTRODUCTION

Approximately one-third of the adult population has hypertension. Large-scale clinical trials have convincingly demonstrated that the treatment of hypertension reduces rates of total mortality, cardiovascular mortality, and stroke particularly in older adults (213). The goal of antihypertensive treatment, in addition to lowering blood pressure, is to reduce the risk of cardiovascular events (214). However, the choice of antihypertensive therapy in the treatment of diastolic dysfunction is less clear.

A previous study showed that antihypertensive therapy could induce regression of LVH in Hypertensive subjects (215). A clinical study showed that ACE inhibitors could induce LV hypertrophy regression and improvement of diastolic function in patients with essential hypertension (216). It has been reported that Valsartan Angiotensin II type 1 receptor blocker (ARB) in patients with hypertension and evidence of diastolic dysfunction may provide clinically useful data on whether such therapy can directly improve diastolic function in patients with hypertension (217).

Hypertensive patients have a 2 to 3 fold higher risk of development of CHF than normotensive adults (218). Furthermore, patients with CHF and normal LV ejection fraction have a 4-fold increase in mortality rate (219). Study showed that ARB provides beneficial effects in hypertensive diastolic heart failure (DHF) independent of its antihypertensive effects even if initiated at an advanced stage (220). Several animal and small human studies examining regression of LV hypertrophy and diastolic dysfunction in hypertensive patients showed that treatment induced

regression of LV hypertrophy did not decrease myocardial collagen levels or reduce the abnormal LV diastolic stiffness and hence improve LV diastolic filling (221-226).

Small studies show improvement of diastolic filling parameters along with systolic and diastolic BP and /or LV mass reduction (227-229). Furthermore, studies in patients with diastolic dysfunction without concomitant LV hypertrophy have either shown no improvement (230) or improvement after multiyear antihypertensive treatment (231). This might be a result of simultaneously changes in active LV relaxation and passive LV chamber stiffness (232).

Aim:

To evaluate whether Candesartan (ARB) or Centyl (bendroflumethiazide) could influence left ventricular (LV) morphofunctional characteristics (induce LV hypertrophy regression and improvement of diastolic function) in newly diagnosed untreated hypertensive patients.

7.2 METHODS

7.2.1 Study Population:

Of total 120 newly diagnosed untreated Hypertensive subjects referred to the hypertension clinic and echocardiography at St. James Hospital for assessment of raised BP and cardiac function, thirty subjects of the hypertensive study population was observed after one and three months of blinded treatment with Candesartan (8mg in 1st month, increased to 16mg in 2nd and 3rd months) or bendroflumethiazide (2.5mg in 1st month, increased to 5mg in 2nd and 3rd months) based regimen. The exclusion criteria were patients with secondary hypertension, coronary heart disease, congestive heart failure, diabetes mellitus, atrial fibrillation & and severe valvular heart disease.

7.2.2 Echocardiographic Measurements:

Assessment was done using a commercially available ultrasound system Phillips Sonos 5500 equipped with Doppler tissue echocardiography capabilities. Baseline echocardiography examinations were done to rule out structural abnormality. M-mode measurements of LA size, AR, LVEDD, LVESD, IVSD, and PWD were recorded. Left ventricular ejection fraction was assessed qualitatively using the Simpson's rule. We examined diastolic function using criteria provided by the Canadian consensus guidelines using mitral inflow Doppler with and without valsalva manoeuvre and included the additional measurement of TDI E'/A' from four sites (lateral, septal, anterior, and inferior annulus).

7.3 RESULTS

7.3.1 Clinical characteristics:

Table 7.1 shows the demographic and haemodynamic variables of the follow-up Hypertensive patients.

7.3.2 Blood pressure and echocardiographic Measurements (2D and M-mode)

Table 2 shows the changes in blood pressure and left ventricular structure after one and three months of antihypertensive treatment. As shown in table 2, systolic BP was reduced by 11% in one month and 13% in three months (P=0.05). However, diastolic BP was reduced by 9% in one month and 11% in three months (P<0.001). There was no significant different in reduction of systolic and diastolic BP between Candesartan and bendroflumethiazide after one and three months.

As shown in table 7.2, left ventricular mass index was reduced by 8% in one-month follow up and 12% in three months (P<0.000). The reduction of LV mass was due to reduction of left ventricular septal diameter (LVSD) 8% in one month and 9% in three months, left ventricular posterior wall diameter (LVPD) 6.5% in one month and 8% in three months, and left ventricular diameter during diastole (LVEDD) 1% in one and three months. Furthermore, we found a 2% reduction in LA size in one month and 3% months as well as aortic root diameter (P<0.000). IVRT shortened by 1% in on month and 4% in three months follow up (P<0.000).

7.3.3 Changes in left ventricular Structure and diastolic filling parameters.

Table 7.3 shows the left ventricular diastolic filling parameters after one and three months of antihypertensive treatment. There were significant increases in the Doppler echocardiographic parameters after three months antihypertensive medication compared to one month follow up. The TMD E wave showed no significant change in one-month duration; however, it was increased by 3% (P<0.000) in three months

follow up; and E/A ratio by 3.5% in one month and significantly increased to 6% in three months (P<0.000). On the other hand, TDI e' wave was increased 9% in one month and significantly increased by 16% in three months (p<0.001), whereas TDI e'/a' ratio was significantly increased by 21% (P<0.001) in three months compared to 14% in one month (P<0.001).

7.3.4 Change in Left Ventricular Filling Patterns.

Of total 30 subjects with newly diagnosed untreated hypertension, at baseline, 56.7% (n=17) had impaired relaxation pattern, whereas 43.3% (n=13) had a pseudonormal pattern. After 1 one month of treatment, the prevalence of the abnormal relaxation decreased to 53.3% (n=16) and a pseudonormal pattern to 33.3% (n=10). On the other hand, after three months of treatment, there was no change in the prevalence of impaired relaxation pattern, whereas a pseudonormal pattern showed more reduction in the prevalence to 30% (n=9) (P<0.001) (fig 7.1).

There was no significant different in left ventricular structures and filling patterns in the hypertensive subjects after one and three months of antihypertensive treatment with candesartan or bendroflumethiazide (table 7.4&7.5).

7.4 DISCUSSION

Hypertension is a major underlying disease that may cause LV diastolic dysfunction, even without LV systolic dysfunction (233). Although 50% of hypertensive patients in the community are estimated to have diastolic dysfunction, there is no specific guideline for diastolic dysfunction therapy at present despite the condition's clear association with increased cardiovascular risk (234).

Preclinical hypertension is considered a precursor of stage 1 hypertension and a predictor of excessive cardiovascular risk. It has been reported that over a period of four years, untreated preclinical hypertensive patients developed untreated stage 1 hypertension. However, antihypertensive treatment of preclinical hypertension with candesartan appeared to be well tolerated and reduced the risk of incident hypertension during the study period (235).

Our study examined the changes in LV geometry and LV diastolic function in 30 subjects during one and three months of antihypertensive treatment. Antihypertensive treatment resulting in significant reduction in left ventricular structures in three months compared to one month follow up, 8 to 12% reduction in LV mass index, 2 to 3% in left atrial size and aortic root diameter, 1 to 4% shortened IVRT. On the other hand it results in 3.5 to 6% increases in TMD E/A ratio, 9 to 16% in TDI E', and 14 to 21% in TDI E'/A ratio.

Our results support the finding by Yalcin et al (236) that 6 months antihypertensive treatment with perindopril led to reduction in LV mass and left atrial size and increased E/A ratio. However, our study contrasts with a study by Cuspidi et al (237)

in a smaller population (n=39) in which 6 months of antihypertensive treatment had no significant effect on LV diastolic filling parameters.

Changes in LV geometry and echocardiographic Doppler parameters are associated with an increase in the proportion of the patients with normal TMD flow pattern by 16%, reduction of abnormal relaxation by 5% and of the pseudonormal pattern by 36%. The antihypertensive treatment normalized E/E' (estimation of left ventricular filling pressures) (238) in 87% of patients.

A Previous study (239) showed that treatment of hypertension greatly attenuates the development of LVH and significantly decreases the incidence of heart failure. In patients with established LVH, regression is both possible and desirable and results in a significant reduction in adverse clinical endpoints (239). A previous study (240) examined the ability of antihypertensive drugs on the reversal of LVH showed the superiority of angiotensin receptor blockers Losartan against b-blockers in a large-scale prospective trial. It also proves for the first time that regression of LVH is associated with better cardiovascular outcome (240). Furthermore, Losartan induced a normalization of LVH and more importantly caused an almost complete regression of concentric LVH, in unsatisfactorily treated hypertensive patients (241). In our study, improvement of diastolic dysfunction parameters may related to reduction in LV mass index (12%), shortening the IVRT (4%), and reduction in left atrial size (3%), therefore increases in TMD E/A ratio and TDI E' wave and E'/A' ratio. This may highlights the role of antihypertensive therapy in primary prevention of hypertensive complication such as congestive heart failure.

In our study, the prevalence of impaired relaxation and pseudonormal patterns were decreased after one month and three months of monotherapy of antihypertensive treatment (Candesartan or Centyl). However, Candesartan or Centyl did not show any significant different in the left ventricular structures and filling patterns after one and three months.

A previous study evaluated the effect of monotherapy and different combination therapies on cardiovascular target organ damage and metabolic profile in 520 hypertensive patients (242). This study suggests that a combination of agents may be required to get optimal regression or changes both in relaxation and in left ventricular structure and filling patterns. Recent study investigated whether a capsule containing a quarter of the standard dose of 4 antihypertensive agents has greater efficacy than the standard dose of each individually. A low-dose combination of 4 agents (amlodipine atenolol, bendroflumethiazide, and captopril) representing 4 classes of standard antihypertensive agents was more efficacious than a standard single dose of each agent individually (243). These warrant further study.

In conclusion, in patients with newly diagnosed hypertension, Candesartan or Centyl may induce a significant improvement in LV diastolic function. However, large studies may need it to assess overall cardiac function in long period with mono and combination therapy.

Table 7.1 Demographic and haemodynamic variables of the follow-up hypertensive patients.

Variable	(No.=30,mean±SEM)
Age (years)	52.68±8
Sex (m/f)	18/12
Height (cm)	170±7.8
Weight (kg)	80.8±14.2
Waist (cm)	93±2
Hip (cm)	103±1.5
Brachial SBP (mm Hg)	155±2
Brachial DBP (mm Hg)	92±1
Mean arterial pressure (mm Hg)	113±1
Heart rate (beat/min)	70±1.4

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Table 7.2 Blood pressure and left ventricular structures after one and three months of antihypertensive treatment.

Left ventricular structure	**Baseline**	**First month**	**P Value**	**Three months**	**P Value**
No. of patients	30	30	NA	30	NA
Systolic blood pressure (mm Hg)	168.53±2.1	150.03±1.8	P=0.05	146.96±3	P=0.05
Diastolic blood pressure (mm Hg)	96.7±1.23	88.2±1.33	P<0.001	86.76±1.61	P<0.001
Left Atrium (cm)	3.75±0.41	3.68±0.36	P<0.000	3.64±0.31	P<0.000
Aortic root (cm)	3.17±0.34	3.09±0.29	P<0.000	3.05±0.28	P<0.000
Intreventricular septal diameter (cm)	1.01±0.11	0.94±0.12	P<0.000	0.92±0.12	P<0.000
Posterior wall diameter (cm)	0.95±0.12	0.89±0.13	P<0.000	0.88±0.13	P<0.000
Left ventricular diastole diameter (cm)	4.87±0.36	4.84±0.30	P<0.000	4.85±0.26	P<0.001
Ejection fraction %	61.6±3.4	64.5±3.8	P<0.000	65.9±4.2	P<0.000
Left ventricular mass index (g/m^2)	89±17.06	82.13±19.4	P<0.000	78.6±19.4	P<0.000
Isovolumic relaxation time (m/sec)	102.6±19.4	101.6±17.4	P<0.000	98.6±17.5	P<0.000
Deceleration time (m/sec)	203.6±33.2	209±29.2	P<0.000	202.3±25.6	P<0.001

Table 7.3 Left ventricular diastolic filling parameters after one and three months of antihypertensive treatment

Left ventricular diastolic filling parameters	**Baseline**	**First month**	**P value**	**Three months**	**P value**
No. of patients	30	30	NA	30	NA
TMD E (cm)	68.0±15.1	66.4±14.2	P<0.001	69.8±11.9	P<0.000
TMD E/A ratio	0.91±0.19	0.94±0.22	P<0.000	0.96±0.23	P<0.000
TMD E post valsalva (cm)	53.1±9.0	54.5±11.9	P=0.06	55.7±10.8	P<0.001
TMD E/A ratio post valsalva	0.73±0.07	0.8±0.15	P<0.001	0.82±0.14	P<0.001
TDI e'	7.73±1.01	8.5±1.79	P<0.001	9.2±2.26	P<0.001
TDI e'/a' ratio	0.65±0.07	0.75±0.2	P<0.001	0.82±0.21	P<0.001
E/e' ratio	8.43±1.65	7.38±1.65	P<0.000	6.91±1.59	P<0.000

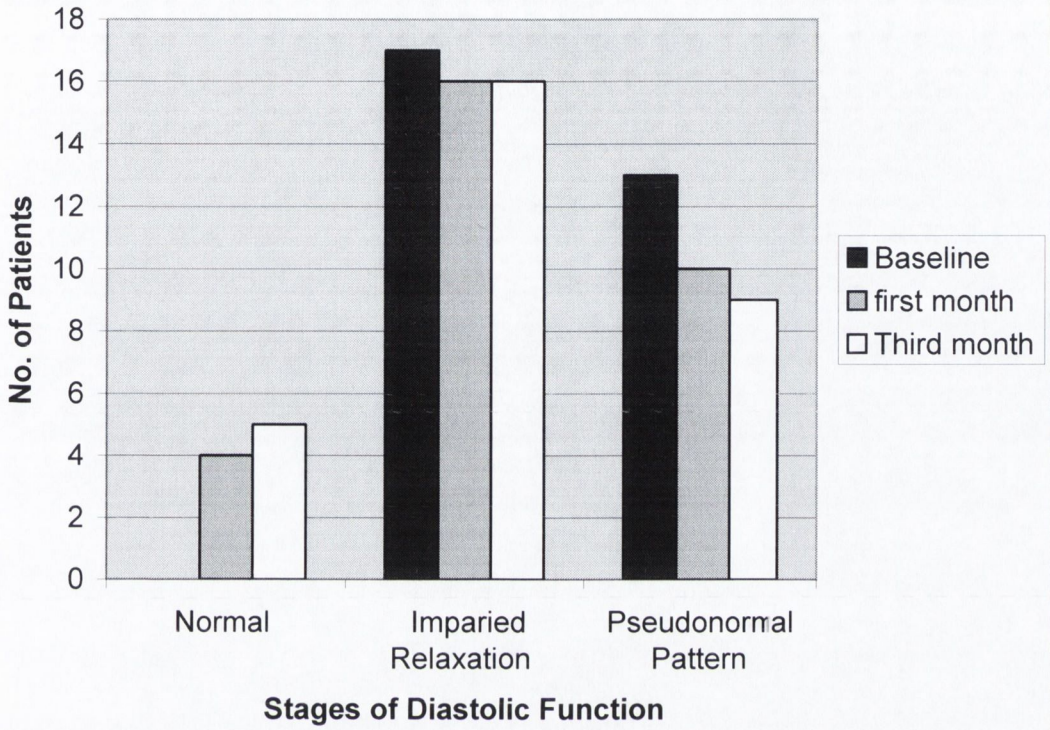
Table 7.4 A comparison of values obtained after 1 and 3 months therapy with candesartan & bendroflumethiazide.

Left ventricular structure	**Candesartan 1st month**	**Bendroflumethiazide 1st month**	**P Value**	**Candesartan 3rd month**	**Bendroflumethiazide 3rd month**	**P Value**
No. of patients	15	15	NA	15	15	NA
Systolic blood pressure (mm Hg)	149.53±3	151±2.4	P=0.23	146.8±4.2	149.9±4.9	P=0.56
Diastolic blood pressure (mm Hg)	88.7±1.23	93.2±1.33	P=0.36	84.7±2.2	91.1±2	P=0.4
Left Atrium (cm)	3.7±0.06	3.5±0.14	P=0.19	3.7±0.06	3.5±0.31	P=0.059
Aortic root (cm)	3.0±0.06	3.1±0.09	P=0.68	3.04±0.06	3.07±0.09	P=0.83
Intreventricular septal diameter (cm)	0.9±0.02	0.9±0.05	P=0.032	0.92±0.02	0.91±0.04	P=0.74
Posterior wall diameter (cm)	0.9±0.02	0.84±0.04	P=0.054	0.89±0.02	0.85±0.05	P=0.23
Left ventricular diastole diameter (cm)	4.8±0.06	4.9±0.1	P=0.36	4.8±0.06	4.8±0.08	P=0.39
Ejection fraction %	64.3±0.82	65.1±1.3	P=0.63	65.8±0.9	66±1.5	P=0.96
Left ventricular mass index (g/m^2)	82.9±3.1	83.5±7.5	P=0.49	78.4±3.4	79±8.4	P=0.69
Isovolumic relaxation time (m/sec)	101.5±3.9	102±5.53	P=5.5	97.5±3.8	101±6	P=0.47
Deceleration time (m/sec)	209±6.9	209±8.3	P=0.89	201±5.7	205±8.3	P=0.77

Table 7.5 A comparison of Doppler values obtained after 1 and 3 months therapy with candesartan & bendroflumethiazide.

Left ventricular diastolic filling parameters	**Candesartan 1st month**	**Bendroflumethiazide 1st month**	**P Value**	**Candesartan 3rd month**	**Bendroflumethiazide 3rd month**	**P Value**
No. of patients	15	15	NA	15	15	NA
TMD E (cm)	67.4±3.4	64.4±3.7	P=0.69	71.5±2.9	66.6±2.9	P=0.21
TMD E/A ratio	0.93±0.04	0.95±0.09	P=0.78	0.97±0.04	0.95±0.08	P=0.58
TMD E post valsalva (cm)	55±2.3	54±3.6	P=0.69	56.9±2.3	53.5±3.6	P=0.34
TMD E/A ratio post valsalva	0.78±0.02	0.8±0.07	P=0.90	0.8±0.03	0.8±0.05	P=0.92
TDI E'	8.3±0.39	8.8±0.7	P=0.61	9.1±0.5	9.4±0.7	P=0.66
TDI E'/A' ratio	0.73±0.04	0.8±0.07	P=0.40	0.8±0.04	0.87±0.07	P=0.25
E/E' ratio	7.4±0.41	7.2±0.38	P=0.77	7±0.37	6.5±0.33	P=0.62

Figure 7.1 Change in the diastolic filling pattern in one and three months of anthihypertensive treatment



CHAPTER 8

CONCLUSION

CONCLUSION

This thesis presents the development of clinical applications of the relatively new ultrasound modality, TDI in conjunction with the earlier more established modalities of echocardiography. The contents of this thesis outline the investigations leading up to the recognition of the early diastolic dysfunction in hypertension. From there we examine the usefulness of a new timing parameter of diastole, which allows us to measure the diastolic function in newly diagnosed hypertensive patients.

Doppler-echocardiography has been used to predict outcome in patients with LV diastolic dysfunction (7). However, measurements based on Doppler recordings of ventricular filling velocities are subject to variation depending on preload. TDI E' has shown to be free of such limitations. The American Heart Association recommends TDI E' as the best measure of diastolic function (26). This report is consistent with our findings that E' was significantly lower in DD especially when associated with LVH compared to the normal. The prevalence of LV diastolic dysfunction is being increasingly recognized in hypertensive patients in the absence of LVH or reduced ejection fraction. In our study, LV diastolic dysfunction is quite prevalent in patients with newly diagnosed hypertension 59 % based on Canadian guidelines and separately by measuring the TDI parameter E'/A' (<1) (64). Our findings demonstrate the wide variance in the diagnosis of diastolic dysfunction based on the current standard echocardiographic criteria. Thus current guidelines are of limited value and could be enhanced by the inclusion of TDI. Physicians, in particular non-cardiac imaging specialists, should be cautious about echocardiographic reports describing diastolic dysfunction and ensure that the assessment of diastolic function is based on a

comprehensive echocardiographic study integrating all available two dimensional, Doppler flow data and TDI.

We have also shown that LV diastolic dysfunction occurs independently of the presence of LVH. TDI indices and a novel index of myocardial stiffness are capable of detecting diastolic segmental functional changes in non-hypertrophied wall segments in newly diagnosed untreated hypertensive patients. Furthermore, this index of myocardial stiffness correlates significantly with BNP in hypertensive patients. Therefore, LVSI is an important addition to the echocardiographic evaluation of hypertensive patients, which may provide early detection of diminished myocardial function and may help identify patients requiring aggressive and targeted medical therapy.

Our study on arterial stiffness showed that there was an inverse relationship between aortic wave reflection and TDI E`/A`. Furthermore there was a direct relationship between TDI E`/A` and Buckberg ratio, an indirect measure of subendocardial blood supply. Although this study does not answer the question whether arterial stiffness precedes LV diastolic dysfunction or these changes occur in parallel the coupling of LV diastolic dysfunction and arterial stiffness in early hypertension may put these patients at increased risk of cardiovascular events. Therefore routine screening for presymptomatic ventricular and vascular abnormalities as well as aggressive BP lowering strategies in newly diagnosed untreated hypertension may help to reduce the risk of early cardiovascular events in hypertension. Furthermore, we evaluated whether Candesartan (ARB) or Centyl (bendroflumethiazide) could influence left ventricular (LV) morphofunctional characteristics (induce LV hypertrophy regression

and improvement of diastolic function) in newly diagnosed untreated hypertensive patients. Our finding showed that antihypertensive treatment may induce a significant improvement in LV diastolic function. However, Candesartan or Centyl did not show any significant different in the left ventricular structures and filling patterns after one and three months.

The simultaneous use of TDI to measure tissue dynamics, and pulsed Doppler to measure hemodynamics, allows the relationships of these vital cardiac functions to be described in time and space. This opens an exciting vista of diagnostic measurements, hitherto available in highly invasive situations, using mild and noninvasive procedures.

The general applicability of our findings will have to be confirmed and deepened in future studies, with larger number of subjects with different races. However this work has contributed to the strong potential of TDI and other echocardiographic techniques and indices that hopefully will contribute to the understanding and prevention of early complications related to hypertensive heart disease.

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