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The Aging Human Heart. Doppler Echocardiographic Assessment of the Resting Adult Heart Across the Age Bands.

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The Aging Human Heart.

Doppler echocardiographic assessment of the resting adult heart across the age bands.

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Abstract

Objectives: To determine the influence of aging on measured left ventricular (LV) diastolic parameters using healthy subjects aged 40-79 years. To propose age-related reference values for LV filling pressure, LV isovolumic relaxation time (LV IVRT) and myocardial stiffness index for each decade using pulsed waved tissue Doppler.

Background: Pulsed wave tissue Doppler parameters have been used for over a decade in the clinical setting as an aid to the evaluation of diastolic function and filling pressures, however there is limited information on normal reference ranges especially in middle age and the older person.

Methods: Subjects with no known history of cardiovascular disease were selected for this prospective study. All subjects underwent routine 2-dimensional echocardiography and Doppler studies. Pulsed wave tissue Doppler was performed to measure peak S', E' and A' myocardial velocities from both the medial and the lateral mitral annulus. The mean E' peak velocity was (medial E' + lateral E') calculated, and mean E/E' ratios for the two annular sites were then used as an index of left ventricular filling pressure. The study population was divided into four age decades: 40-49, 50-59, 60-69, 70-79 years. The LV filling pressure, isovolumic relaxation time and stiffness index were analysed for each of the four decades to determine normal reference ranges from middle age to the older person.

Results: One hundred and twenty-one healthy subjects (Male, n = 65) aged 40-79 years were included in this study. LV filling pressure ($p = 0.005$), LV IVRT ($p < 0.001$) and myocardial stiffness ($p = 0.003$) significantly increased with age. A trend was observed for the greatest increase to occur in the last two age groups (60-79 years). A reference value table for these three parameters was created.

Conclusions: The results of this study quantify reference values for average diastolic parameters in healthy middle aged and older subjects. This study confirms the independent impact of aging on average diastolic parameters and indices obtained by pulsed tissue Doppler imaging. Age should be taken into account when tissue Doppler is used to assess LV diastolic function.

Declaration

I confirm that this thesis which I now submit for examination for the award of MPhil is entirely my own work and has not been taken from the work of others, save and to the extent that such work has been cited and acknowledged within the text of my work.

This thesis was prepared according to the regulations for graduate study by research of the Dublin Institute of Technology and has not been submitted in whole or in part for another award in any other third level institution.

The work reported on in this thesis conforms to the principles and requirements of the DIT's guidelines for ethics in research.

DIT has permission to keep, lend or copy this thesis in whole or in part, on condition that any such use of the material of the thesis be duly acknowledged.

_____ Date _____

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List of abbreviations

A-late transmitral flow velocity

A'-late diastolic myocardial velocity

AF- atrial fibrillation

ANOVA-analysis of variants

ASE-American Society of Echocardiography

BSA-body surface area

DT-deceleration time

E-transmitral early peak velocity

E'=early diastolic myocardial velocity:

E_m- early myocardial diastolic velocity (also referred to as E')

EACI-European Association of Cardiovascular Imaging

E/A ratio- transmitral early peak velocity / late transmitral flow velocity

E/E' ratio- an index of left ventricular filling pressure it is a ratio of Doppler transmitral E peak velocity and average E' peak velocity.

E/E' = index of LV filling pressure

ECG-electrocardiogram

EDV-end diastolic volume

EDP-end diastolic pressure

EF-ejection fraction

HF-heart failure

HFPEF-heart failure with preserved ejection fraction

HR-heart rate

IHD-ischaeemic heart disease

IVRT-isovolumic relaxation time

LA-left atrial

LAD-left atrial diameter

LAV-left atrial volume

LOLIPOP-London Life Sciences Prospective Population

LV-left ventricle

LVIDd-left ventricular diastolic dimension in diastole

LV IVRT-left ventricular isovolumic relaxation time

LVDD- left ventricular diastolic dysfunction
LVEDD-left ventricular end-diastolic diameter
LVH-left ventricular hypertrophy
LVESD-left ventricular end-systolic diameter
LVEDV-left ventricular end-diastolic volume
LVEF-LV ejection fraction
MHz-Mega-hertz
MVA-Mitral Valve Annulus
MV-mitral valve
M-mode-motion mode
PCWP-pulmonary capillary wedge pressure
RA-right atrial
RV-right ventricular
RWMA-regional wall motion abnormalities
S'-systolic wave corresponds to ventricular ejection
S_m- systolic myocardial velocity, (also referred to as S')

SUH-Sligo University Hospital
TAPSE-tricuspid annular plane systolic excursion
TDE-Tissue Doppler Echocardiography
TDI-Tissue Doppler imaging
TIA-Transient Ischaemic Attack
TVI-Tissue Velocity imaging
2D echo two-dimensional echocardiogram.

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Chapter 1. Introduction

1.1 Introduction

From the moment of conception man is destined to die. All the body's organs appear to participate in the senescence, particularly the heart. Such a time related decay of cardiac function appropriately may be termed presbycardia. Aging heart changes added to covert acquired heart disease may cause overt cardiac malfunction. Hence, what would ordinarily be disregarded as mild acquired disease, or stress in younger adults, should be regarded as serious in the elderly. Therefore, we embark on a quest to define what is normal within a range of time related cardiac changes for a specific decade. To that end, the researcher employed the use of tissue Doppler echocardiography in the evaluation of diastolic parameters in a healthy population of both middle aged and older persons to determine normal age related changes of left ventricular filling pressure and myocardial stiffness.

Middle age is defined for this study as “the period of life between youth and old age, usually (in man) considered occurring approximately between the ages of 40 and 60” (Collins English Dictionary.com).

Death from cardiovascular disease is the leading cause of death in Ireland, such diseases accounted for 8899 deaths in 2014 (CSO.2014). This study investigated the contribution of several advanced cardiac ultrasound investigation techniques to make early diagnosis of cardiac dysfunction and thus early intervention in a group of patients attending Sligo University Hospital (SUH).

Early research of left ventricular fibre architecture in man revealed an interesting article by Greenbaum, (Greenbaum *et al.* (1981)). This group set out to investigate the possibility of regional variation of ventricular structure. Twenty-four normal post-mortem human hearts were studied and inspected for cavity shape and sub-epicardial fibre orientation using dissection and histology of sections in two orthogonal planes. The ventricular architecture was complex. There was a striking variation found in the arrangement of sub-epicardial muscle, the most pronounced being the contrast between the longitudinal arrangements of fibres observed on the oblique margin and the circumferential arrangement of those on the acute margin. On the diaphragmatic surface of the left ventricle, fibres near the crux and apex ran circumferentially while those between ran obliquely; those on the diaphragmatic

surface of the right ventricle also ran circumferentially. Deeper in the myocardium the arrangement was simpler. In the mid-wall of the left ventricle fibres were circumferential, and best developed towards the base and in the upper part of the septum. Near the apex of the left ventricle and in the mid-wall of the right ventricle such fibres were sparse. The sub endocardial region consisted of longitudinally directed fibres forming the trabeculae and papillary muscles, while fibres deep through and between the trabeculae coursed more obliquely. These findings were confirmed by histology. Several research papers in the literature had documented the effects of aging on mean values of myocardial velocities (Henein, (2002); Munagala, (2003); Innelli, (2008)). Pulsed tissue Doppler imaging was used to record these velocity values using the septal and lateral mitral annulus as reference points, in a population of healthy subjects and these are presented in Table 1.1.

Table 1.1 Previously published studies of tissue Doppler velocity measurements at mitral valve annulus sites and reference values for age groups used to determine E/E' as defined in the abbreviations.

Studies	No. of subjects (age range)	Site of Mitral Annulus	Measurements taken
Tighe <i>et al</i> (2002)	103 normal (20-88)	Lateral	E', A', E/E'
Munagala <i>et al</i> (2003)	1012 normal (45-70)	Septal and Lateral (no average)	E', A', E/E'
Yu <i>et al</i> (2005)	138 normal (20-82)	Septal, Lateral, Anterior, Inferior, Posterior. (no average)	E', A' and S
De Sutter <i>et al</i> (2005)	174 normal, 86 hypertensive (21-87)	Septal	E', E/E'
Van de Veire <i>et al</i> (2006)	249 normal (18-82)	Septal	E', E/E'

None of the above previously published studies used mean lateral and septal annular velocities to produce average values pertaining to E/E' for use in clinical practice. Systolic and diastolic velocities have been found to be lower at the septal mitral valve annulus than at the lateral aspect. The proposed research study will focus on obtaining an average value of E' from both the septal and lateral mitral valve annular sites to produce reference values.

Chapter 2. Background.

2.1 Background to the current study.

It is widely known that aging results in diastolic dysfunction (Henein *et al.* (2002)), (Okura *et al.* (2009)). As people age arterial stiffening occurs and this may give rise to a cascade of events leading to increased aortic impedance and left ventricular (LV) loading as well as an increase in LV wall tension. The influence of load-related changes in myocardial diastolic velocities has been documented in several studies (Henein *et al.* (2002); Yalcin *et al.* (2002); Munagala *et al.* (2003); Okura *et al.* (2009)). Mitral Doppler E wave velocity is altered by changes in preload or left atrial pressures. Tissue Doppler recorded at the lateral basal wall does not change significantly and the effects of preload can be corrected by the ratio of mitral E/E' (Nagueh *et al.* (1997)). There are reported normal values for children (Eidem *et al.* (2004)) and the elderly, yet very little data on the middle-aged groups of the population.

2.1.1 Background of Tissue Doppler Imaging (TDI).

Over one hundred and sixty years ago an Austrian Professor of Mathematics, Christian Doppler first described the Doppler principle for light (Doppler. (1842)). This technique has been applied to cardiac ultrasound and has been developed and incorporated as an essential part of routine Echocardiography, providing valuable information for diagnosis of regurgitation, and obstructive as well as shunt lesions. In contrast to two-dimensional Echocardiography, Doppler signals are less affected by tissues between region of interests and the transducer.

Tissue Doppler Imaging (TDI) is a relatively new technique, it provides velocities of normal and pathological myocardial structures during the cardiac cycle. The assessment of myocardial wall velocities with respect to timing and amplitude has been suggested for quantification of global and regional systolic and diastolic function, and additional applications are currently under investigation. Kostis *et al* first described the pulsed wave Doppler technique for investigation of posterior wall velocities (Kostis *et al.* (1973)), and an association was found between low peak systolic velocity and abnormal wall motion (Isaaz *et al.* (1989)). An additional new technique for producing images of the velocity of tissue motion within the myocardium was introduced (McDicken and Sutherland, (1992)). Several studies demonstrated the feasibility and the reliability of colour Doppler M-Mode were undertaken by Sutherland and Fleming *et al.*, (1995). Measurements using a rotating phantom

showed appropriate colour coding to allow velocity assessment. By examining still images of agar and gel blocks adequate axial and lateral resolution of 3 x 3 millimeters was documented, permitting accurate recognition of significant wall motion abnormalities.

Tissue Doppler echocardiography is a real-time ultrasound technique that provides a measure of cardiac wall motion. It offers an objective means to quantify global and regional left and right ventricular function and to improve the accuracy and reproducibility of conventional echocardiography studies. Radial and longitudinal ventricular function can be assessed by the analysis of myocardial wall velocity. A quick and easy assessment of left ventricular ejection fraction is obtained by mitral annular velocity measurement during a routine study (Rodriguez. (1996)) especially in patients with poor endocardial definition or abnormal septal motion. Tissue Doppler echocardiography is also referred to as Tissue Doppler imaging (TDI) or Tissue Velocity imaging (TVI). Tissue Doppler is used in Echocardiography to measure the velocity of the heart muscle throughout the cardiac cycle by use of the Doppler effect. Tissue Doppler signals have higher amplitude and lower velocities compared with standard spectral Doppler measuring blood flow velocities, and signals must be extracted using different filter and gain settings. The velocity curves are recorded from the base of the mitral annulus at the insertion point of the mitral valve leaflets, in the septal and lateral hinge points of the four-chamber view and the inferior and anterior points of the two-chamber view of the heart. Peak velocities are routinely measured at each of the mitral ring sites however the practice of averaging peak velocities from the septal and lateral points has become standard clinical practice. This method measures annular velocities towards and away from the probe during the cardiac cycle. These annular velocities are an indication of the longitudinal contraction of the ventricle during systole its elongation during diastole.

Diastolic function can be reliably evaluated using TDI. The peak mitral annular velocity during early filling (E') is a measurement of left ventricular diastolic function and has been shown to be relatively independent of left ventricular filling pressure. If there is evidence of impaired relaxation (diastolic dysfunction), the E' velocity will be reduced. The late filling phase is represented by the A' velocity which is a passive phase and a function of atrial contractility. The ratio between E' and A' is a measure of diastolic function. Trans-mitral blood flow is represented by early (E) and late (A) blood flow from the atrium into the ventricle which correspond to the annular velocity phases. Blood flow is determined by the pressure difference between the atrium and the ventricle and is related to the pressure drop

during early relaxation and the initial atrial pressure. In mild diastolic dysfunction, the peak mitral inflow velocity E is reduced in proportion to the E' . The ratio of E/E' is related to the atrial pressure, and can indicate increased filling pressure. Tissue Doppler is extremely useful in the diagnosis of heart failure with preserved ejection fraction (HFPEF) which occur in 50% of the total heart failure population.

Pulsed tissue Doppler is available on most modern cardiac ultrasound systems. It is a useful feature that allows us to accurately measure left ventricular myocardial function. Tissue Doppler derived myocardial early diastolic velocity (E_m or also referred to as E') is a reliable index of myocardial relaxation. Some authors and investigators have measured the diastolic parameters at the level of the septal mitral annulus (Srivasatava *et al.* 2004), others have preferred to measure the same parameters at the lateral mitral annulus (Park *et al.* (2006)).

Tissue Doppler measurements taken at the medial (septal) annulus tend to overestimate the severity of left ventricular myocardial diastolic dysfunction as measurements at the lateral annulus. Another research group (Munagala *et al.* (2003); Innelli *et al.* (2007)) suggested that the average of both septal and lateral values provides a more comprehensive evaluation of myocardial diastolic function

2.2 Effects of aging and Left ventricular filling pressure

Transmitral inflow velocity, systolic and diastolic TDE velocity measurements vary with age. The influence of aging on systolic left ventricular wall motion velocities along the long and short axes in clinically normal patients determined by pulse tissue Doppler imaging was investigated by a Japanese team lead by Onose *et al.* (1999). Their objective was to evaluate the influence of aging on left ventricular regional systolic function along the long and short axis in clinically normal patients. This group recorded LV wall motion velocity patterns in the mid-wall portion of the middle of the LV posterior wall in the parasternal long axis view (short axis direction) and at the endocardial portion of the middle of the LV posterior wall in the apical long axis view (long axis direction), with pulse Tissue Doppler imaging in 80 normal patients whose ages ranged from 15 to 78 years. These results suggested that shortening of the longitudinal fibres in early systole is impaired with increased age in healthy individuals. This impairment resulted in insufficient spherical change in the LV cavity although global LV pump function and myocardial contractility were maintained.

Normal gender and age related reference values for both E' and A' have been established in several studies comprising subjects free of heart disease, hypertension and diabetes. (Munagala *et al.* (2003); Chahal *et al.* (2009)). These studies showed that E' values declined with age, while A' values increased. The E'/A' ratio dropped below 1 after 60 years of age, like the E/A ratio of mitral inflow. Research to date has indicated that velocities are highest at the lateral wall and lowest at the septum (Park *et al.* (2006)). The E/E' was dependent on the site of E' measurement, and this ratio was also age dependent. The E/E' ratio can be used to determine left ventricular filling pressure in patients who have diastolic and systolic heart failure.

Myocardial relaxation is less complete in the older person (>65 years) which results in a reduction of the early LV filling rate. While LV systolic function is preserved across adult life, LV diastolic performance is markedly altered by aging. This was first documented on M-mode echocardiography which displayed a reduced mitral E-F slope indicating age-related changes in diastolic performance (Alam *et al.* (1992)). Pulse Doppler confirmed that the trans-mitral early diastolic peak filling rate declined by as much as 50% between the ages of 20 and 80 years of age. Late LV filling velocity which is represented by peak A wave velocity increases with age and relies more on atrial contraction. A greater contribution from atrial contraction is required with aging to assist with ventricular filling. This results in a modest increase in left atrial (LA) size which can be seen on routine echocardiography.

Tissue Doppler and M-mode techniques are less influenced by preload and afterload than pulsed Doppler. Preload is the end diastolic volume (EDV) at the beginning of systole. The EDV is directly related to the degree of stretch of the myocardial sarcomeres. Afterload refers to the ventricular pressure at the end of systole (ESP). Both techniques have assisted in demonstrating the effects of age-associated reduction effects on early diastolic ventricular filling rate and increased late filling.

The resting LVEDV is preserved across adult age groups in healthy individuals; the atrial contribution to LV filling in older adults is a result of adaptation to reduced early diastolic filling rates in a thicker and stiffer LV. Therefore, the relative importance of early and late diastolic filling is reversed with advanced age. The impairment of early LV filling with age may be explained in part by reduction of LV compliance resulting from the increased LV wall thickness with advancing age. An age-related reduction in LV compliance has been shown in animal studies (Aronow *et al.* (2013)). Studies in man have shown and confirmed

an age-related reduction in LV compliance which was only minimally changed in older adults even after one year of endurance training as described by Fleg *et al* (2013).

A diminished early diastolic filling rate may not compromise resting EDV or stroke volume. An underlying reduction in LV compliance may cause a greater rise in LV diastolic pressure in older persons. This is especially true during episodes of tachycardia which are stress-induced, thus indicating a lower threshold for dyspnoea than in the young (Aronow *et al.* (2013)).

In atrial fibrillation (AF) there is a loss of atrial contribution to LV filling which can lead to serious deterioration in diastolic performance in older individuals. It is reasonable to speculate that the frequent occurrence of heart failure (HF) in the elderly despite well preserved LV systolic function may be a result of impairment of early diastolic filling. Arterial stiffening in the elderly results in an increase in arterial systolic and pulse pressure (Aronow *et al.* (2013)). There is also an increase in pulse wave velocity and a late peak in systolic pressure. Arterial stiffening causes an increase in aortic wall thickness and in aortic root size. These factors combine to increase aortic impedance and LV loading resulting in increased LV wall tension. This in turn tends to to prolonged myocardial contraction which in turn tends to reduce the early diastolic LV filling rates. An increase in LV wall thickness leads to an increase in LA size and an increase in left atrial (LA) filling; this may result in a slightly increased diastolic volume. With advancing age, the LV becomes thicker and more spherical; in conjunction with this the LV length diminishes (Aronow *et al.* (2013)).

Chapter 3. Literature Review of aging and measured diastolic parameters.

3.1 Search strategy

Databases used in the primary search included PubMed, EBSCOhost Medline and Google Scholar. The following key words were used “aging heart” AND “echocardiography” AND “tissue Doppler” AND “left ventricular filling pressure” OR diastolic dysfunction” OR myocardial stiffness” OR “diastolic dysfunction” OR “isovolumic relaxation time”. MeSH terms used for aging were “aging”, “elderly”, “older”, “geriatric”, “middle age”. Truncated versions of echocardiography included “echo” and “echo Doppler”. Only full text articles written in English were included. Reference lists were hand-searched for additional articles and relevant chapters within text books were consulted. The search yielded 119 articles of which seven were reviewed in detail. The flow chart pertaining to the search strategy is contained in **Appendix 1**.

3.2 Early research

Doppler Tissue imaging (TDI) was originally developed by Karl Isaaz, and his colleagues to measure the velocity of the left ventricular posterior wall (Isaaz *et al.* 1989). Doppler tissue imaging velocities were recorded at the posterior wall of the left ventricle (LV) and were compared with M-mode measurements. A significant linear correlation was found between peak E-wave velocity and M-mode peak diastolic endocardial velocity ($r = 0.90$, $p < 0.001$) and between peak S-wave velocity and M-mode peak systolic endocardial velocity ($r = 0.81$, $p < 0.001$). Tissue Doppler imaging has several advantages over conventional M-mode echocardiography in the assessment of myocardial velocity as demonstrated by Garcia *et al.*, (1996).

Garcia (1996) compared TDI measured velocities with velocities obtained from highly accurate off line digitised M-mode scans. TDI was capable of measuring velocities at multiple sites within the myocardium without been limited to the endocardial surface. Additionally, TDI can measure instantaneous velocity at any stage within the cardiac cycle, and rapidly assessing the mitral valve ring motion on line, whereas M-mode analysis had to be performed off line and was rather time-consuming. Garcia also found that TDI had greater reproducibility of the correlation between velocity components and haemodynamic events measured with standard Doppler flow techniques, when tissue velocity

was measured with TDI ($r = 0.99$) rather than when tissue velocity was measured with M-mode ($r = 0.95$). TDI velocities were classified

these as follows; a negative, early diastolic wave (E-wave), a late diastolic wave (A-wave) and a positive systolic wave (S-wave) as were described (Isaaz *et al.* 1989). This was confirmed by an Italian team in the assessment regional left ventricular diastolic dysfunction in hypertrophic cardiomyopathy using tissue Doppler (Severino *et al.* (1998)).

A Spanish team led Garcia-Fernandez published a paper on the use of tissue Doppler imaging in the assessment of regional diastolic function in Ischaemic heart disease which also validated this (Garcia-Fernandez (1999)). They observed that the early diastolic E wave occurred shortly after the T wave on the electrocardiogram (ECG) and is associated with a rapid filling phase after the opening of the mitral valve. The following phase demonstrates no wall motion, which would correspond to diastole. The end of the P-wave on the ECG, signals the start of the late diastolic A wave, secondary to the late myocardial relaxation after mechanical contraction of the left atrium. The systolic S wave corresponds to ventricular ejection and follows the QRS complex of the ECG, which initiates ventricular depolarization and then contraction.

This novel non-invasive method was used by Isaaz and his team to measure the velocity of the left ventricular posterior wall in control subjects and in patients who had known coronary artery disease to identify and to characterise any regional dysfunction. Isaaz studied 17 normal subjects and 23 patients undergoing cardiac catheterization. It was found that the peak systolic velocity was greater than or equal to 7.5 cm/s in all control subjects and in patients with normal left ventricular posterior wall motion. However, Isaaz found that in ten out of twelve patients with posterior wall dysfunction, the peak systolic velocity was less than 7.5 cm/s, which indicated abnormal left ventricular wall motion. This study TDI demonstrated a sensitivity of 83%, and a specificity and an accuracy of 95%. Garcia *et al.* (1996) also noted abnormalities during diastole with a similar patient group. All patients had a lower peak E wave velocity than the healthy controls and a higher peak A-wave velocity. Garcia performed TDI on 30 normal subjects and 43 patients with ischaemic heart disease (IHD) in each of the 16 segments of the myocardium. This research by Garcia on the assessment of regional diastolic function in IHD using TDI also found that the patients with abnormal left ventricular posterior wall motion had the most severe decreases in peak E-wave velocity and only slight increases in peak A wave velocity, (Garcia-Fernandez *et al.* (1999)).

Garcia reported that patients with abnormal left ventricular posterior wall motion had the most severe decreases in peak E wave velocity and only slight increases in peak A wave velocity. The usefulness of TDI in measuring myocardial velocities in the detection of regional LV dysfunction which was associated with ischemic heart disease (IHD) was described by Garcia-Fernandez *et al.* (1999) in a study that divided the myocardium into 16 segments according to the anatomy of the coronary circulation. Tissue Doppler measurements were performed in each of these segments in the 30 healthy controls and in the 43 ischaemic heart disease patients. Mean segmental peak early diastolic velocity was reduced (mean \pm SD: 6.4 ± 2.1 cm/s vs 8.5 ± 2.8 cm/s; $p < 0.01$); peak early diastolic velocity and the E/A diastolic velocity ratio was reduced in the diseased segments. the E/A diastolic velocity ratio was decreased (0.95 ± 0.3 vs 1.5 ± 0.6 , respectively < 0.01). This clearly indicated the abnormal myocardial relaxation in those effected regions. The isovolumic relaxation time (IVRT), which is defined as the time interval produced by the closing of the aortic and the pulmonary valves at the end of ventricular systole to the onset of the E wave, was prolonged in the IHD group compared to the control group (104 ± 36.7 ms vs 69.6 ± 30 ms; $P < 0.01$). They found no differences in any of these parameters between the normally perfused segments of the ischemic patients and the corresponding segments of the control group. This study added to our knowledge that tissue Doppler can be used to assess regional left ventricular function.

3.3 Left ventricular filling pressure

Doppler tissue imaging has been used as a noninvasive measurement for the evaluation of LV relaxation and the estimation of LV filling pressures. An American group led by Nagueh investigated whether the E' obtained by tissue Doppler imaging at the mitral annulus behaved as a preload-independent index of left ventricular relaxation and to evaluate the relationship of the mitral E/E' ratio to LV filling pressures (Nagueh *et al.* (1997)). A total of 135 subjects were divided into three groups according to mitral E/A ratio, LV ejection fraction (LVEF) and clinical symptoms. There were 34 asymptomatic subjects with a normal LVEF and an E/A ratio ≥ 1 ; a further 40 subjects had a E/A ratio < 1 and no symptoms of heart failure (HF); and an additional 51 subjects with HF symptoms and an E/A ratio > 1 . The E' was recorded at the lateral MV annulus. A subset of 60 patients had invasive pulmonary capillary wedge pressure (PCWP) recorded simultaneously by tissue Doppler recordings. A pulmonary artery balloon-occlusion catheter is an invasive procedure used to acquire the

PCWP. This wedge pressure provides an indirect measurement of left atrial pressure and is considered the gold standard for evaluation of pulmonary oedema. A normal PCWP range is between 2-15 mmHg. The results showed that the E' was reduced in the group with heart failure symptoms of impaired relaxation compared with the group of normal subjects (5.8 ± 1.5 and 5.2 ± 1.4 vs 12 ± 2.8 cm/s, respectively, $p < 0.001$). The E/E' ratio correlated strongly with PCWP ($r = 0.87$; $\text{PCWP} = 1.24 (\text{E/E}') + 1.9$) with a difference between Doppler and catheter measurements of 0.1 ± 3.8 mmHg. Nagueh and his team concluded that the E' behaves as a preload-independent index of LV relaxation. Mitral E velocity, corrected for the influence of relaxation (the E/E' ratio), related well to mean PCWP and may be used as an estimate of LV filling pressures.

Age is thought to be major consideration when defining normal values for mitral inflow velocities and time intervals (Nagueh *et al.* 2009). Increasing age leads to a decline in the mitral E velocity and the E/A ratio also decrease, while MV DT and A velocity increase. There are several factors other than LV diastolic function and filling pressures that affect mitral inflow, including heart rate and rhythm, the PR interval, cardiac output, mitral annulus size and LA function. The age-related changes in diastolic function parameters may represent slowing of myocardial relaxation, which leads to the development of diastolic heart failure in the older person.

The characteristics of mitral and tricuspid annular velocities in healthy subjects using pulsed wave tissue Doppler tissue Imaging were identified by a Swedish group (Alam *et al.* (1999)). They felt that generally accepted reference values were still missing. Sixty-two consecutive healthy subjects were examined (with a mean age of 46, range 22 to 82 years). The subjects were divided into three different age groups, Group 1 participants younger than 40 years of age; Group 2, 40 – 59 years of age; and Group 3, were 60 years of age and older. Recordings were made along the long axis in the apical 4 and 2 chamber views by using 4 sites (septal, anterior, lateral and inferior) at the mitral annulus and one site at the tricuspid annulus. Systolic mitral annular velocities (10.3 ± 1.4 cm/s) correlated strongly with global left ventricular function determined by M-mode echocardiography of the mitral annular displacement. The systolic velocity was significantly lower in group 3 than group 1 (9.6 versus 10.8 cm/s, $p < 0.01$). An irregularly weak, but significant, correlation was found between systolic velocity and the age of the subjects ($r = -0.43$, $p < .001$). Systolic and early diastolic mitral annular velocities were found to be lower at the septum than at any other left

ventricular sites. Alam noted that the transmitral flow (E/A) velocity only represented global diastolic function and was preload dependent. The mean value of diastolic parameters used in TDI is representative of global function.

The use of TDI at different sites allows the determination of regional diastolic function, (Alam *et al.* 1999). Alam also observed from previous studies that the mitral annular early diastolic velocity was relatively preload-independent (Sohn *et al.* (1997)). Alam and his co-workers observed that the mitral annular early diastolic velocity to be preload independent thus making TDI a very useful method in the assessment of both regional and global diastolic function in pathological conditions. The mitral annular diastolic parameters in this study also correlated well with MV E deceleration time ($r = 0.62$, $p < .001$) and the isovolumic relaxation time ($r = 0.61$, $p < .001$). Tricuspid annular systolic velocity (15.2 ± 1.9 cm/s) was higher than mitral annular systolic velocity ($p < 0.001$). Alam found that unlike mitral annular velocity, systolic tricuspid annular velocity was not correlated with age. The method of recording the annular velocity was feasible in all subjects, and was simply done and highly reproducible. This paper increased our knowledge base as it linked mitral annular displacement parameters to tissue Doppler velocities.

3.4 Aging and diastolic function

The influence of aging on the assessment of diastolic function was investigated by Tighe *et al.* (2003). One hundred and three healthy men and women were recruited to a cross-sectional study to examine the association between age and TDI parameters of diastolic function with measurements recorded at the lateral mitral valve annulus in these healthy subjects. The mean age was 54 ± 19 years (range 23 to 88). They were divided into seven age decades for the purposes of this study with 40% of the subjects aged over 60 years of age. No differences were found in heart rate, weight and body surface area, the ejection fraction likewise did not vary with age. A decreasing E/A ratio with aging was noted and the E wave deceleration time also slowed with aging. A strong inverse correlation ($r = -0.72$) was noted between E' velocity and age.

A moderately strong direct correlation between the E/E' ratio and age ($r = 0.54$) was found. The E/E' ratio progressively increased with age (**Appendix 2**). This study by Tighe *et al* was one of the first studies to report on the effect of age on the E/E' ratio. Tighe noted that

several of the older subjects had E/E' ratios > 8.0 which would have been previously described as being correlated with raised LV filling pressures, however Tighe considered it very unlikely that these subjects had increased filling pressures. He suggested that the E/E' ratio is less predictive of LV filling pressures when the LV ejection fraction is $> 50\%$ than in other subjects with lower ejection fractions. This was supported by data produced by Ommen *et al.* (2000) in a study involving patients referred for cardiac catheterisation.

While Tighe *et al* only used the lateral mitral valve annulus to sample TDI velocities, they considered that this location was the most accessible and the most reproducible. Their study demonstrated the significant influence of aging on TDI parameters and highlighted that age should be taken into consideration when using TDI to assess LV diastolic function.

A tissue Doppler study on the impact of aging on left ventricular longitudinal function in healthy subjects was published by Innelli and his Italian co-workers in 2008. This group evaluated the influence of aging on average values of pulsed tissue Doppler recorded at the septal and lateral mitral valve annulus, in a healthy population and it proposed reference values according to different age decades, (Innelli *et al.* (2008)), (Appendix 2). A total of 246 healthy subjects were recruited (male/female = 160/86, mean age 40.9 years). The S', E' and A' tissue Doppler peak velocities were recorded. The ratio of transmitral E peak velocity and average E' peak velocity ($\text{lateral E}' + \text{septal E}'/2$) was calculated as an index of LV filling pressure. The population was divided into 7 groups according to decades from age 10 to >70 years. Innelli *et al* concluded that E' was progressively reduced and A' increased with advancing age at both the MV annular sites and the averaged values. The average E/E' ratio was higher in the last three age decades. By statistical analysis they concluded that age was the main independent predictor of average E', A' and the E/E' ratio. This paper highlighted how aging has an independent impact on average tissue Doppler indices of the septal and lateral mitral annulus in normal subjects and it also provided reference values of tissue Doppler average values for each of the age decades.

3.5 Left ventricular filling pressure and aging

An analysis of age dependency of diastolic ventricular behavior and filling using tissue Doppler in healthy hearts was published by Henein in 2002. This was a cross-sectional study of healthy hearts in the Umea region of Sweden (Henein *et al.* 2002). Diagnosis of diastolic ventricular dysfunction is dependent upon the filling pattern and on the fact that most patients

diagnosed with diastolic heart failure are elderly. Data from healthy asymptomatic patients across a range of ages is rare. The aim of that study was to investigate any age-related variation in normal diastolic physiology the filling pattern and the segmental myocardial longitudinal velocities.

Myocardial shortening and lengthening velocities were studied by Henein *et al.*, using TDI in 60 healthy randomly selected subjects. The subjects ranged in age from 22 to 88 years. Myocardial velocities were recorded at four left ventricular sites and at 3 levels (basal, mid cavity and apical). It was noted that while systolic myocardial velocities were conserved across the age groups, there was a marked decrease in early diastolic velocities with age (from 16cm/s at age 30 years to 9cm/s at 80 years of age), ($r = -0.63$, $p < .0001$) and a corresponding significant increase in late diastolic velocities (from 10 to 16cm/s). Myocardial lengthening velocities were related to trans-mitral flow velocities, showing a correlation of 0.64 ($p < 0.0001$) in early diastole and 0.68 ($p < 0.0001$) in late diastole. They concluded that normal aging causes a decrease in early diastolic velocities and a substantial increase in late diastolic myocardial lengthening velocities. This would also explain the known trends in the trans-mitral flow pattern with age. Systolic myocardial velocities do not change significantly with age. The results showed that systolic segmental velocities are independent of age as is the overall left ventricular function as assessed by the shortening fraction. They observed that early diastolic velocities were strongly related to age, with left free wall early diastolic velocity decreasing with age. Early diastolic velocities correlated directly with transmitral flow velocities. Normal aging caused a decrease in early diastolic velocities and an increase in late diastolic myocardial lengthening velocities. In summary, these findings should be considered when evaluating diastolic function in the elderly. A small population sample of 60 subjects may be an area of weakness in this study for this reason the results should be interpreted with caution due to the small sample size.

A prospective population study by Munagala *et al.* (2003) set out to determine if newer diastolic function parameters were associated with age and to define reference ranges for these parameters. The group randomly selected 2042 individuals aged over the age of 45 years in Olmsted County in Minnesota, USA. A total of 1012 randomly selected subjects met the inclusion criteria as they had no history of heart disease and had a normal 2D echocardiogram.

Measurements were taken of trans mitral E and A filling velocities at rest and with the Valsalva manoeuvre.

Lateral and septal mitral annular velocities, E/lateral and E/septal early diastolic mitral annular velocities were recorded and the index of left ventricular myocardial performance index (MPI) was also recorded. The E/A ratio at peak Valsalva correlated with age ($r = -0.54$, $p < 0.001$). Both E/ lateral ($r = 0.39$, $p < 0.001$) and E/septal ($r = 0.27$, $p < 0.001$) increased with age. LV MPI showed a marginal correlation with age ($r = 0.08$, $p = 0.014$). Age specific reference ranges were also provided, (**Appendix 3**). The strength of this study was that it was a large cross-sectional sample of middle aged to older persons with no cardiac disease. Munagala observed that E' at both the septal and lateral MV annular sites declined with age which was reflective of age related LV impairment to relaxation. Munagala also noted that E' at the lateral MV site was higher than the E' recorded at the septal annular site and that E/E' recorded at both septal and lateral sites increased significantly with age. They also observed that the 95th percentile values for both E/E' at septal and lateral MV annular sites were greater than 10 in almost all age groups whereas E/E' at the septal annulus exceeded 15 only in those greater than 70 years of age. Munagala stated that there are implications when interpretation is carried out on normal subjects as the E/E' at both septal and lateral sites often exceeds 10. A weakness in this study was that reference values for myocardial S' were not recorded for this large population based study. Munagala concluded that these newer Doppler derived diastolic parameters of diastolic function showed a variable but significant correlation with age and that these age specific reference ranges increased our knowledge and understanding in the interpretation of results.

3.6 Age and gender

Age and gender related differences in the TDI parameters of left ventricular diastolic dysfunction were also investigated in New York, USA, by Park *et al.* (2007). This team recruited 276 outpatients and studied the effects of age and gender in relation to left atrial (LA) size, LA volume, mitral Doppler E/A, and E/E' ratio by TDI and to evaluate left ventricular diastolic dysfunction (LVDD) using TDI. The patients were selected regardless of indications or congestive heart failure status. The patients were placed in four age groups: < 45 years of age, 46-60 years of age, 60-69 years of age and those > 70 years of age. The mean age was 56 years and the study took place at a university private practice over a six-month period. The exclusion criteria were the presence of moderate to severe valvular disease, any prior valve surgery, severe mitral annular calcification, atrial fibrillation and those patients with permanent pacemakers and implantable defibrillators were also excluded.

Echocardiography measurements of left atrial size and volume as well as transmitral Doppler velocities in addition to tissue Doppler velocities at the mitral septal and lateral annular sites were all recorded. They also observed that in the group of patients < 70 years of age there was a statistical significant increase in left atrial size with age. The mean LA size was 4.0 ± 0.51 cm for men and 3.65 ± 0.47 cm for women ($p < 0.0001$). However, the main limitation to this study was that the left atrial volume index was not measured because the body surface area was not available in all patients. Also, this group did not consider systolic dysfunction and co-morbidities and the status of congestive heart failure.

They also stated that there was no statistically significant difference between men and women when looking at mitral E/A inflow and mitral septal or lateral mitral annular E/E' ratio. The mean mitral E/A for the four different age groups was 1.49, 1.17, 1.03 and 0.89 ($p < .0001$). There was and no difference in TDI measurements between men and women. This study concluded that in patients aged greater than 70 years of age the LV diastolic dysfunction was mild to moderate in severity when using the lateral or the mean of septal and lateral MV annular measurements.

Age and gender specific changes in left ventricular relaxation were also investigated by the Japanese team of Okura *et al.* (2009). This group studied 1333 healthy individuals with no known history of heart disease or hypertension (mean age 55 years). Peak E' and A' were measured. E/E' was used as an index of left ventricular filling pressure. Diastolic indices correlated well with age, E' correlated negatively and significantly with age ($r = 0.75$, $p < .0001$). Likewise, A' ($r = 0.36$; $p < .0001$) correlated positively and significantly with age. They noted that in the age groups 30-39 and 40-49 years that the E' was significantly lower in males than in females. In the groups 50-59 and 60-69 years, E' was similar for both males and females. However, it was noted for those aged 70-79 and 80-89 years, E' was significantly lower in females than males, E' correlated negatively and significantly with age in both male ($r = 0.70$; $p < .0001$) and female ($r = 0.78$; $p < .0001$). Age related changes in diastolic indices were gender specific, and that diastolic function declined more significantly in females ($p < 0.01$) than in males. In the older person, diastolic function declined more significantly in females. They concluded that this could explain the higher incidence of diastolic dysfunction and higher mortality from cardiovascular causes in the elderly female population. The one major limitation to this study was its methodology, in that the investigators only measured the septal mitral annular velocities. The velocity of the E'

obtained from the lateral mitral valve annulus was higher than that obtained from the septal annulus and the E/E' tends to be lower there than that of the septal mitral annulus. For this reason, averaging of the septal and lateral mitral annular velocities is now deemed best practice. The authors of this paper acknowledged that while the subjects had no known history of heart disease or hypertension, subclinical conditions such as impaired glucose tolerance may be related to LV relaxation abnormalities in middle aged subjects as noted by Okura *et al.* (2000).

A study of normative reference values for tissue Doppler imaging parameters of left ventricular function was published by Chahal *et al.* (2009). This was a population based study from the London Life Sciences Prospective Population (LOLIPOP), which stated that there was a lack of percentile-based normative reference values for tissue Doppler which are clinically important parameters (Chahal *et al.* (2009)). A total of 453 subjects (age range of 35-75 years) were included in this study. Subjects were free of any manifest cardiac disease and any significant coronary artery disease as determined by electron beam computed tomography. They underwent 2D and Doppler echocardiography where measurements were obtained on-line from both annular site segments and the transmitral E-wave to E_m ratios were calculated (E/E'). Mean velocities and E/E_m ratios of the two annular sites were then derived for the four age groups (35-44, 45-54, 55-64, 65-75). The biplane Simpsons method was used to quantify ejection fraction. The left atrial volume was calculated and indexed to body surface area to obtain a left atrial volume index. Myocardial velocities were measured online using pulse wave Doppler. Mean velocities and E/E' ratios of the two MV annular sites were calculated. Average E/E_m ratio increased significantly with advancing age ($p < 0.001$). This was the first study to report percentile based values for both systolic and diastolic TDI measured parameters of LV function. As previously described in this study by Munagala *et al* reference values for myocardial S' were not recorded. This paper by Chahal produced standardized values across different age groups from middle aged to the older person in the clinical use of tissue Doppler imaging (**Appendix 4**). Chahal concluded that increasing age was associated with a significant attenuation in myocardial velocity when averaged from both the septal and lateral mitral annulus. The strength of this study is that it proposed age specific reference values for the important TDI parameters of LV function. The values were based upon a large multi-ethnic group comprising Indian, Asian and European Caucasian males and females who were recruited from a list of 58 General Practitioners in West London.

3.7 Myocardial Stiffness

Myocardial stiffness and LV function in patients with dilated cardiomyopathy in conjunction with altered titin expression, was discussed in a paper published by Nagueh *et al* (2004). In this paper three different echocardiographic methods were used to assess LV stiffness.

- mitral early diastolic velocity (peak velocity of mitral inflow in early diastole after MV opening), and the MV deceleration time (DT of E wave),
- A velocity transit time from LV inflow to LV outflow (A wave transit time: time taken for A velocity to propagate from LV inflow to LV outflow which relates inversely to late diastolic LV stiffness). A higher LV stiffness is associated with a shorter A transit time.
- the ratio of end diastolic volume (EDV) to end diastolic pressure (EDP). A higher ratio EDV/EDP was found in more compliant ventricles.

Myocardial stiffness and tissue Doppler imaging were investigated in a study published by King *et al.* (2006). King and his co-workers investigated the timing difference between tissue Doppler E' and peak MV opening to distinguish physiological hypertrophy in athletes from hypertrophic cardiomyopathy. They derived indices of end diastolic stiffness: E/E' could be used to estimate LA pressure, and LVEDD was used to estimate LV end-diastolic volume. The ratio (E/E')/LVEDD was used as an estimated index of end-diastolic stiffness. The control group had an index of 1.5 while the athletic group had an index of 1.2. In athletes, the LVEDD was larger than the controls and the E/E' was normal, which would indicate a compliant ventricle. However, the hypertrophic cardiomyopathy group had an index as high as 2.2, despite a normal LVEDD but with a higher E/E' which indicated increased stiffness due to a reduction in LV compliance. Myocardial stiffness can be calculated by using Doppler parameters and LV volume. King *et al.* (2008), stated that by using E, E' and the LV end diastolic dimension (LVEDD) a new novel index of diastolic stiffness can be derived. The E/E' ratio is an index of LV filling pressure (Nagueh *et al.* (1997)) and the LVEDD is an index of LV volume. The ratio (E/E')/LVEDD is therefore used as a measurement tool to provide a novel index of diastolic stiffness. The pressure volume relationship as a measure of diastolic stiffness in detecting cardiac adaptation in elite rowers was investigated by King *et al.* This study recruited 36 international rowers and 30 sedentary subjects, which were matched for age and gender. Chamber size, transmitral peak

early (E) and late (A) diastolic filling velocities and isovolumic relaxation times (IVRT) were recorded. Tissue Doppler echocardiograms were also measured from four sites at the mitral annulus and the diastolic stiffness was then derived using the three measured parameters E, E' and LVEDD. The rowers were sub-divided into two groups based on the presence or absence of left ventricular hypertrophy (LVH).

This study showed no difference in E' between the two groups. However, there was a difference in the stiffness index (controls 1.48 (0.3) vs elite rowers 1.17 (0.34), $p = 0.016$). Furthermore, there was no difference in the stiffness index between the rowers with LVH (1.11 (0.32) or without LVH (1.17 (0.34), $p = 0.68$). The authors of this paper acknowledge that a study limitation was the use of M-Mode measurements which uses geometric assumptions such as ellipsoid shape rather than volumetric quantification to accurately assess the LVEDD measurement.

The number of sedentary subjects was also quite small and was age matched which may identify future research as to normal reference values for myocardial stiffness in healthy individuals from middle age to the older person.

3.8 Left Ventricular Isovolumic Relation Time (LV IVRT)

Normal aging results in changes in Doppler measures of ventricular filling and relaxation, including the early and late mitral inflow velocities and the prolongation of the isovolumic relaxation time (IVRT) (Bryg, *et al.* (1987)). The effects of aging and physical activity on these Doppler measures of diastolic function were studied by Prasad *et al.* (2007). This group hypothesized that healthy aging would result in slowing of ventricular diastolic filling and myocardial relaxation, whereas lifelong endurance training would prevent these changes. They recruited 13 sedentary but healthy (70 ± 4 years) and 12 fit veteran athletes (68 ± 3 years). Additionally, they recruited 12 young healthy subjects (32 ± 9 years) for comparison. Both pulmonary wedge pressure and Doppler measurements were recorded at 6 different loading conditions, cardiac filling was decreased by using lower body negative pressure at -15 and -30mmHg immediately followed by Doppler measurements. When negative pressure was released and pressures returned to baseline cardiac filling was increased by using a rapid warm (37°C) isotonic saline solution at 100 ml/min. They noted that like E/A ratio, IVRT was also preload dependent. The IVRT at baseline was significantly longer in the sedentary seniors compared with the young subjects and this relationship was maintained during

cardiac unloading ($p < .0001$). The sedentary seniors could shorten the IVRT (from 144.91 ± 5.44 ms at baseline to 114.38 ± 4.45 ms at maximal saline infusion). The young subjects retained shorter IVRTs at higher filling pressures (90.98 ± 2.93 ms, $p < .001$). The IVRT was longer in fit seniors than in the young subjects across all the filling conditions ($p < .001$). There were no significant effects of training noted at any filling pressure ($p < 0.546$). Just like the sedentary

seniors the fit subjects were also able to shorten the IVRT during cardiac loading. The fit subjects were unable to normalize the relaxation time in comparison to the young during maximal saline infusion ($p < .001$). Lifelong endurance training did not completely prevent the changes in E/A ratio ($p < 0.212$) and IVRT ($p < 0.546$). The fit seniors could achieve an E/A ratio of 1.0 during baseline and saline solution infusion. It should be noted that the E/A ratio is a combination measurement of both early and late transmitral filling and is a relatively non-specific measure which is influenced by early diastolic mechanics, ventricular stiffness, LA pressure and atrial systole. Direct catheter derived measurements of Tau correlated closely with non-invasive Doppler measurement of IVRT and this has been proven in both human and animal studies (Thomas *et al.* (1992)).

In the study by Prasad *et al.* (2007) there was prolongation of the IVRT across a broad range of filling pressures in healthy sedentary subjects, and lifelong training did not alter this finding. The IVRT in the older subjects was considerably longer than in the younger subjects at baseline. This would suggest that normal aging leads to a decrease in the rate of left ventricular relaxation occurring before the mitral valve opens. Both fit and sedentary older persons had IVRTs that were identical despite marked differences in static LV compliance. Prasad concluded that the ‘mechanical processes occurring during IVRT take place during the earliest portion of diastole before the influx of blood into the ventricle and therefore appear to be independent of static myocardial stiffness’.

Table 3.1. Previously published papers for peak diastolic velocities of longitudinal motion for the basal LV myocardial segments from apical 4 chamber (cm/s).

Author	N	Age (yrs)	Variable	Lateral velocity (cm/s)	Septal velocity (cm/s)
Isaaz- 1993	17	31 \pm 13	E'	16.3 \pm 2.1	12.3 \pm 2.1
			A'	7.8 \pm 3.0	8.9 \pm 2.4
Pai-1998	20	44 \pm 16	E'	16.7 \pm 4.3	12.1 \pm 2.6
			A'	11.7 \pm 2.8	12.6 \pm 2.3
Galiuto-1998	27	24 \pm 10	E'	17.3 \pm 4.4	12.6 \pm 2.8
			A'	6.9 \pm 1.6	7.4 \pm 2.2
Kukulski-2000	25	33 (16-68)	E'	14.9 \pm 3.5	11.2 \pm 1.9
			A'	6.6 \pm 2.4	7.8 \pm 2.0
Edner-2000	88	51 (20-81)	E'	12.8 \pm 4.3	9.7 \pm 2.8
			A'	9.2 \pm 2.9	9.2 \pm 2.3

3.9 Gap in Literature

Following review of the current literature it emerged that there is a paucity of research pertaining to reference values for myocardial stiffness in the middle aged to older person in the general population.

3.10 Aims and objectives of the current study

3.10.1 Aims

To ascertain if Tissue Doppler imaging (TDI) used as part of routine echocardiography has a role in determining normal reference values for left ventricular diastolic function and to establish normative reference values of E and E', A', E/E' for middle aged (40-64 years) and for older persons (> 65 years) in the north-west region of Ireland.

To determine if these normal parameters are age related and thus to assist in differentiating pathological patients from normal healthy individuals when performing tissue Doppler evaluation in this population.

3.10.2 Objectives

The aim of the current study was met using the following objectives:

- Tissue Doppler imaging was used to determine diastolic parameters including LV filling pressure, myocardial Stiffness Index and LV IVRT to determine if filling pressure and the myocardial Stiffness Index increase with aging.
- To use the E/E' ratio as a reliable expression of left ventricular filling pressure.
- To derive a value for the myocardial Stiffness Index by using the equation $\text{Stiffness Index} = E/E' \div LVEDD$.
- To derive normal reference values for each of the above parameters across four decades from middle age to the older person (40-79 years).

Chapter 4. Methodology.

4.1 Introduction.

The purpose of the study was to determine if a relatively new imaging technique called Tissue Doppler Imaging (TDI) has a role in evaluating heart function. A primary aim of the current study was to determine normative reference values of TDI indices of diastolic dysfunction in middle aged and older persons and to determine normal age of these indices for specific decades. While it is acknowledged that reference values exist for different age groups both in the European and American context, this study is unique in that it is the first Irish study to compare TDI measured diastolic parameters of LV filling pressures and myocardial stiffness subjects from each decade from middle age to the old age.

4.2 Ethical Consideration

Ethical approval was granted by the Research Ethics Committee at Sligo University Hospital (SUH) (**Appendix 5**). All data collected during the research was kept strictly confidential in accordance with the Data Protection Act 1998.

4.3 Study Design

This was a single site prospective cross-sectional study. Data were collected from patients who were referred to the cardiac investigations department of SUH by a General Practitioner (GP) or a medical consultant.

4.4 Recruitment

All patients who were referred by a GP or medical consultant for echocardiography and who met the inclusion and exclusion criteria were considered for eligibility. Patients had no known previous cardiac history. Inclusion and exclusion criteria are contained in Table 4.1.

Table 4.1 Inclusion and exclusion criteria for current study.

	Criteria
Inclusion Criteria	age 40 to 79 years normal cardiac anatomy optimal echocardiographic images clear acoustic windows no clinical or echocardiographic evidence of cardiovascular disease normotensive and normal sinus rhythm
Exclusion Criteria	subjects aged <40 years and >79 years poor echocardiographic windows (suboptimal endocardial definition) global left ventricular hypokinesis mitral valvular disease hypertrophic, dilated or restrictive cardiomyopathy congestive heart failure

4.5 Group Allocation

Subjects were allocated by age to one of four age categories: Group 1, 40 - 49 years; Group 2, 50 - 59 years; Group 3, 60 - 69 years; Group 4, 70 - 79 years.

4.6 Study Procedure

All patients initially underwent routine standard 2-D echocardiography. If the subject and their images met the inclusion criteria additional measurements were taken using pulsed TDI. All recordings were performed from the apical 4-chamber view, apical 2 chamber view with the participants resting in the left lateral position. Full patient preparation is given in **Appendix 6**.

Pulsed wave Tissue Doppler was used as a non-invasive imaging modality to assess the systolic motion of the mitral annulus to derive a mean value for mitral valve annular displacement velocity. Tissue Doppler signals of systolic velocity were recorded from the

Mitral Valve Annulus (MVA) from the apical four-chamber view. A mean systolic velocity (S') was derived from the following sites of interrogation; Apical 4 chamber view, medial mitral valve annulus (MVA) and Lateral MVA. Medial and Lateral sites of the Mitral annulus were investigated using Tissue Doppler to evaluate diastolic parameters (E' , A'). The mean value of these two sites was obtained to calculate average E/E' to derive left ventricular filling pressures.

Measurements were made at the lateral and medial aspects of the MV annulus to derive an average value for mitral annular displacement velocity. A mean velocity was more likely to reflect global left ventricular function. The sector angle was adjusted to ensure the highest possible sampling frequency. This measurement was relatively easy to obtain in difficult to image patients and tissue velocity images of the mitral annular region can almost always be obtained from the apical window. The pulsed wave Tissue Doppler sample was placed over the mitral annulus and the software allowed real time display of velocity changes in the region under interrogation.

A bi-plane modified Simpson's method was used to trace the endocardium in diastole and systole to ascertain the Ejection Fraction. This method required cardiac imaging in the apical 4 chamber and 2 chamber views.

4.7 Sample size

4.7.1 Minimum required sample size.

Sample size was based on other published papers. Regarding their sample size, Innelli (2007) recruited 246 subjects, Henein *et al.*, (2001) had 60 subjects in the age range 23 to 88 years and Chahal *et al.* (2009) 453 subjects. An online calculator was also used to determine an ideal sample size, this was from the National Statistical Service (NSS) of Australia, (**Appendix 7**). Sligo University Hospital serves a population of 260,000 and performs 5200 echocardiograms per year. This study and data collection took place over a six-month period. The NSS online calculator determined that a sample size of 246 subjects would be required. A total of 121 patients met the inclusion criteria and were recruited to this study over the six-month period. They comprised of four groups and represented both genders in the 40 to 79 age bands.

4.8 Data Management

4.8.1 Data collection and storage

All participants were imaged using a Philips IE33, (Philips Medical Systems, Bothell WA, USA)) ultrasound system providing tissue velocity imaging facilities. A standard phased array S5-1 MHz multifrequency transducer, serial number 032FR5 was used. For general cardiac imaging the frequency range was 1.7 to 3.4 MHz, while in TDI mode with image sector reduced the probe frequency was 2.2 to 3.4 MHz. This ultrasound system is equipped with 2D, steerable colour, and pulsed waved TDI. All echocardiographic measurements were obtained from frozen images and measurements recorded during the scan. Timing was facilitated by ECG monitoring. Images were stored off line on a Horizon Cardiology workstation (McKesson) system, software version 13.1.2 (McKesson). Long term storage of images was facilitated using Horizon cardiology / NIMIS. Data were protected by password protection to ensure patient confidentiality and each patient was assigned an identification number ranging from 1 to 121. Where possible the echocardiographic imaging controls were set to “standard” values but due to variation in size between subjects, it was sometimes necessary to adjust these parameters during examinations to optimize image quality.

4.8.2 Statistical Analysis

Data for each variable were transposed from the Horizon cardiology system into Microsoft™ Excel™ spreadsheets, using separate spreadsheets for each age group category. The frequency of each variable was reported using means and standard deviation (SD) for normally distributed numeric data and reported as frequency tables. Categorical data were expressed as numbers and percentages and displayed in side-by-side bar charts.

Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS®, Version 24, IBM, Armonk, NY, USA). The between group differences were analysed using student’s t-test, analysis of variance (ANOVA). Correlations between primary outcome measures were examined using Pearson’s Linear Correlation Analysis. All results were displayed as graphs, frequency tables or side-by-side bar charts. Statistical significance was set at $p \leq 0.05$. Descriptive data was analysed using Chi-squared test (categorised data).

Chapter 5. Results

The aim of the study was to collect and quantify TDI echocardiography measurement data related to filling pressures, LV IVRT and Stiffness Index and from a sample of the population across four decades (40 years to 79 years of age). There were 30 subjects in each age groups 40-49 years, 50-59 years and 70-79 years, and 31 subjects in the age group 60-69 years, a total of 121 subjects. The results are presented in this chapter.

5.1 Demographics

Recruitment took place in Sligo University Hospital between December 2015 and June 2016. The data from the 121 subjects were collected and summary baseline data are presented in Table 5.1

Table 5.1 Demographics and baseline characteristics of the study groups.

	Group 1 40-49yrs (n=30)	Group 2 50-59yrs (n=30)	Group 3 60-69yrs (n=31)	Group 4 70-79yrs (n=30)	Significance p value
Age (yrs) †	44 (3.4)	55 (2.7)	65 (2.7)	75 (2.8)	Not Relevant
Male n (%) †	11 (36.7)	22 (73.3)	14 (45.2)	18 (60)	0.023
Female (%)†	19 (63.3)	8 (26.7)	17 (54.8)	12 (40)	0.023
HR (bpm) †	73 (14.8)	69 (9.1)	72 (11.6)	70 (8.8)	0.437
BSA (M²) †	1.9 (0.22)	1.9 (0.17)	1.89 (0.25)	1.9 (0.2)	0.685

Key: † Mean (SD), BSA=body surface area: HR= heart rate: yrs.= years.

5.2 Baseline echocardiography measurements

The echocardiography measurements performed on each study participant are given in Table 5.2. There was a significant difference in the Stiffness Index, IVRT, E/A ratio, E/E' ratio and MV E across the groups.

Table 5.2 Echocardiography measurements at baseline

	Group 1	Group 2	Group 3	Group 4	Significance
	40-49yrs	50-59yrs	60-69yrs	70-79yrs	p value
EF (%)†	58.2 (7.43)	60 (7.50)	58.6 (5.72)	56 (4.84)	0.128
MV E †	66.8 (13.87)	65.9 (12.73)	68.8 (16.82)	55.9 (14.48)	0.004
LVEDD (cm) †	4.95 (0.66)	5.09 (0.58)	4.73 (0.53)	4.97 (0.53)	0.121
E/E' ratio †	6.39 (1.69)	6.11 (1.32)	7.21 (2.25)	7.63 (1.89)	0.005
E/A ratio †	1.13 (0.31)	1.10 (0.28)	1.0 (0.28)	0.7 (0.21)	< 0.001
LV IVRT (ms) †	78.13 (7.15)	84.37 (4.63)	89.29 (9.48)	96.20 (9.59)	< 0.001
LA Volume †*	24.96 (7.17)	24.07 (7.04)	25.16 (8.51)	29.37 (11.15)	0.096
Stiffness index †	1.33 (0.40)	1.20 (0.24)	1.53 (0.53)	1.55 (0.46)	0.003

Key:† Mean (SD), *= (ml/M²), Bold Type = significant value, A, late transmitral filling velocity: E, early transmitral filling velocity: E', early diastolic velocity, calculated as the mean of E' measurements at two sites (septal and lateral) around the mitral annulus: EF= Ejection Fraction: LV IVRT=Left ventricular isovolumic relaxation time: Stiffness index = a measure of myocardial stiffness based on the pressure volume relationship: LA=left atrium: LVEDD=left ventricular end-diastolic diameter:

5.3 Primary outcomes

5.3.1 Primary outcome measures

There was a significant difference between the age group categories in mean E/E' ratio (p = 0.005), myocardial Stiffness index (p = 0.003), and LV IVRT (p < 0.001).

All results are presented in Table 5.3.

Table 5.3 Measurement reference values for diastolic parameters for E/E', Stiffness Index, and IVRT in the current study

Measured variable	Group 1 (40-49 yrs)	Group 2 (50-59 yrs)	Group 3 (60-69 yrs)	Group 4 (70-79 yrs)
E/E'				
Mean	6.39	6.11	7.21	7.63
SD	1.68	1.32	2.25	1.89
Min – Max	3.60 – 10.12	4.48 – 10.37	4.44 – 14.87	5.50 – 12.87
Range	6.5	5.89	10.43	7.36
Stiffness Index				
Mean	1.33	1.20	1.53	1.55
SD	0.40	0.24	0.55	0.46
Min – Max	0.63 – 2.38	0.82 – 1.75	0.90 – 3.52	0.96 -2.92
Range	1.75	0.93	2.62	1.96
LV IVRT				
Mean	78.13	84.37	89.29	96.20
SD	7.15	4.63	9.48	9.59
Min – Max	67 – 88	74 – 94	74 – 116	85 – 123
Range	21	20	42	38

Table 5.4 Analysis of the primary outcome measures

	Group 1 (40-49 yrs)	Group 2 (50-59 yrs)	Group 3 (60-69 yrs)	Group 4 (70-79 yrs)	Significance p value
E/E' †	6.39 (1.69)	6.11 (1.32)	7.21 (2.25)	7.63 (1.89)	0.005
LV IVRT †	78.13 (7.15)	84.37 (4.63)	89.29 (9.48)	96.20 (9.59)	< 0.001
Stiffness Index †	1.33 (0.40)	1.20 (0.24)	1.53 (0.53)	1.55 (0.46)	0.003

Key: † = mean (SD), E/E' = index of LV filling pressure, LV IVRT = Left ventricular isovolumic relaxation time, Stiffness index = a measure of myocardial stiffness based on the pressure volume

relationship. The p value represents the variance of each independent measured variable between the four age groups.

5.3.2 Calculation of E/E'

Calculation of E/E' in the current study was determined using the average value of septal E' and medial E'. Baseline values for these echocardiographic measurements are given in Table 5.5 below.

Table 5.5 Tissue Doppler measurements of mitral annulus according to age groups

	Group 1 (40-49 yrs)	Group 2 (50-59 yrs)	Group 3 (60-69 yrs)	Group 4 (70-79 yrs)	Significance p value
Septal annulus					
Septal E'	12.21 (15.06)	9.25 (2.28)	7.97 (2.37)	6.82 (2.07)	0.049
Septal A'	10.14 (1.65)	11.20 (2.25)	11.21 (2.79)	10.64 (1.76)	0.216
Septal E/E' ratio	7.80 (3.01)	7.49 (2.13)	9.47 (4.57)	8.83 (2.59)	0.066
Lateral annulus					
Lateral E'	12.22 (2.52)	12.22 (2.23)	11.45 (2.88)	8.21 (1.98)	0.014
Lateral A'	11.13 (2.20)	12.21 (2.93)	13.12 (3.21)	12.50 (2.59)	0.046
Lateral E/E' ratio	5.76 (1.62)	5.59 (1.40)	6.30 (2.13)	7.04 (2.13)	0.014
Average of septal and lateral annuli					
Average E/E'	6.39 (1.69)	6.11 (1.32)	7.21 (2.25)	7.63 (1.89)	0.005

All values are reported as means (SD)

Key: Avg = average: A'= late diastolic myocardial diastolic velocity: E'= early diastolic myocardial velocity: E/E' = index of LV filling pressure, the ratio of Doppler transmitral E peak velocity and average E' peak velocity. The p value represents the variance of each independent variable between the four age groups.

5.4 Associations between primary outcome variables with age

Pearson correlation analyses were performed to determine the strength of association between the primary outcome variables with age.

5.4.1 LV Filling pressure with age

Sub analysis of the data revealed a small correlation between mean E/E' ratio and increasing age ($r = 0.269$, $p = 0.003$) (Figure 5.1).

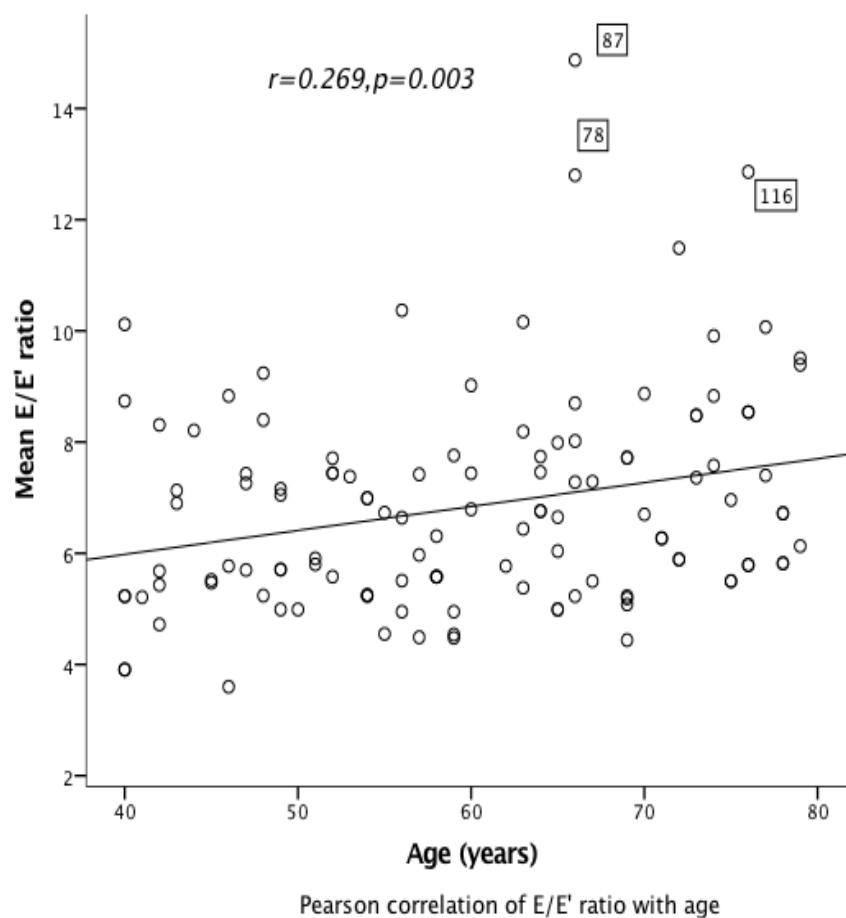


Figure 5.1 Scatterplot of association of mean E/E' with age.

The outliers are identified by identification number for later discussion.

5.4.2 Stiffness Index with age

There was also a small correlation between stiffness index and age ($r = 0.237$, $p = 0.001$) (Figure 5.2).

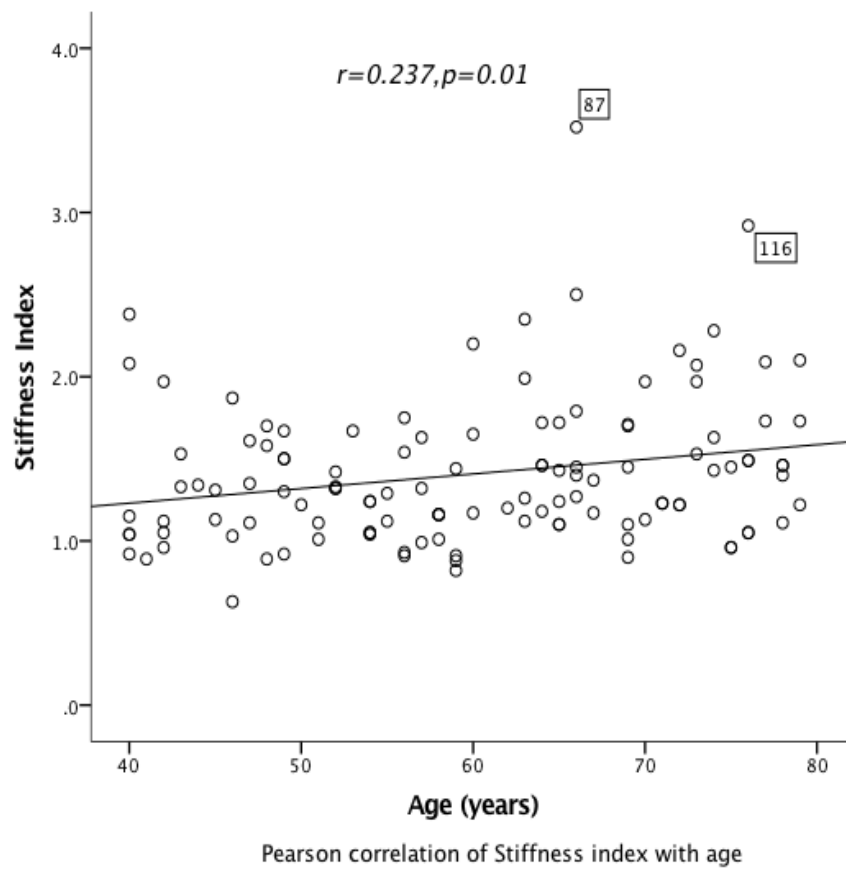
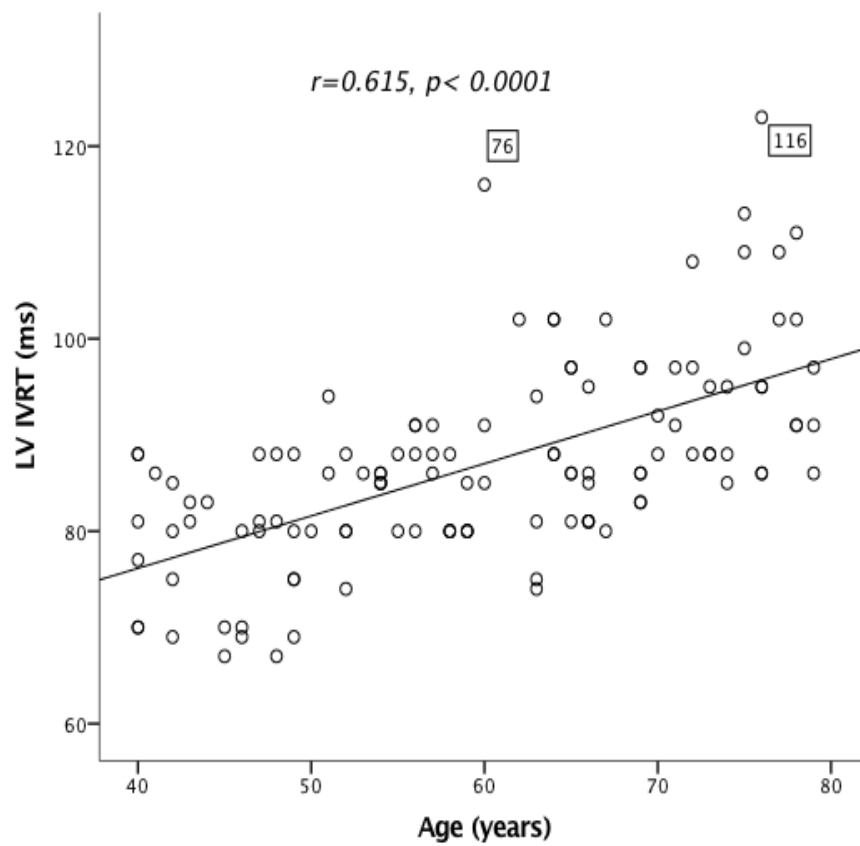


Figure 5.2 Scatterplot of association of Stiffness Index with age.

5.4.3 LV IVRT with age

There was a strong correlation between LV IVRT and age ($r = 0.615$, $p < 0.0001$) (Figure 5.3).



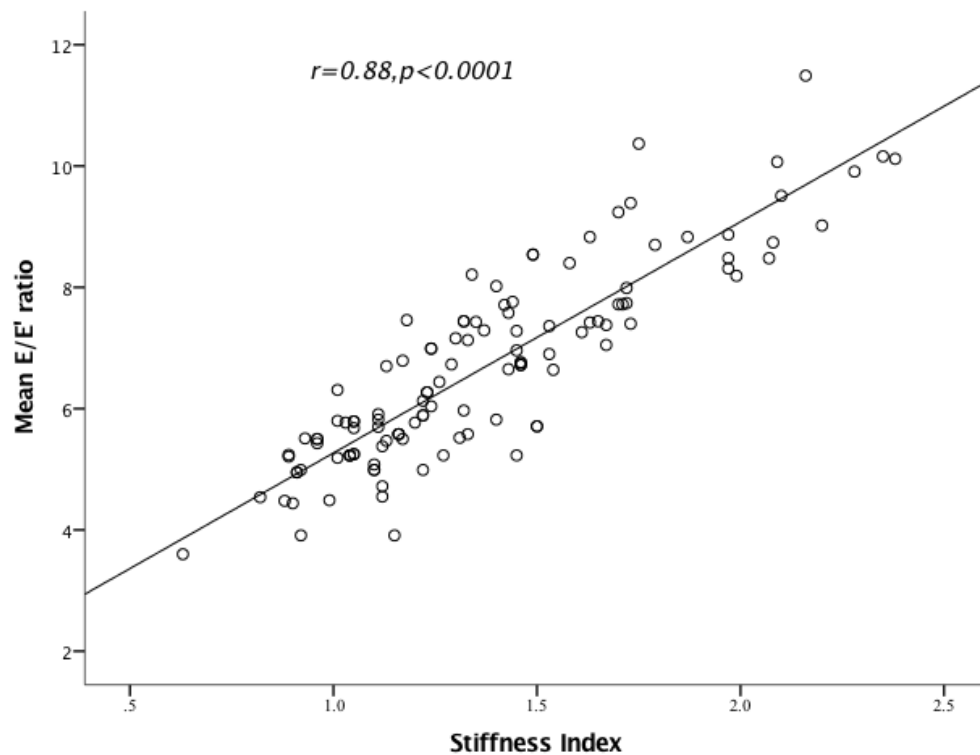
Pearson Correlation between LV IVRT and Age

Figure 5.3 Scatterplot of association of LV IVRT and age.

5.5 Levels of association between primary outcome variables

In the following graphs the relationship between primary outcome variables were investigated using the Pearson correlation coefficient. Both a correlation coefficient (r value) and a statistical significant (p value) are given. The strength and direction of association between the variables is also given.

Analyses of the data indicated a large positive correlation between the mean E/E' ratio and Stiffness index ($r = 0.882$, $p < 0.0001$) (Figure 5.4).



Scatterplot of association of Stiffness index with mean E/E' ratio

Figure 5.4 Scatterplot of association of mean E/E' ratio with Stiffness Index (E/E'/LVEDD).

LV filling pressure was highly correlated with Stiffness Index ($r = 0.882$, $p < .0001$).

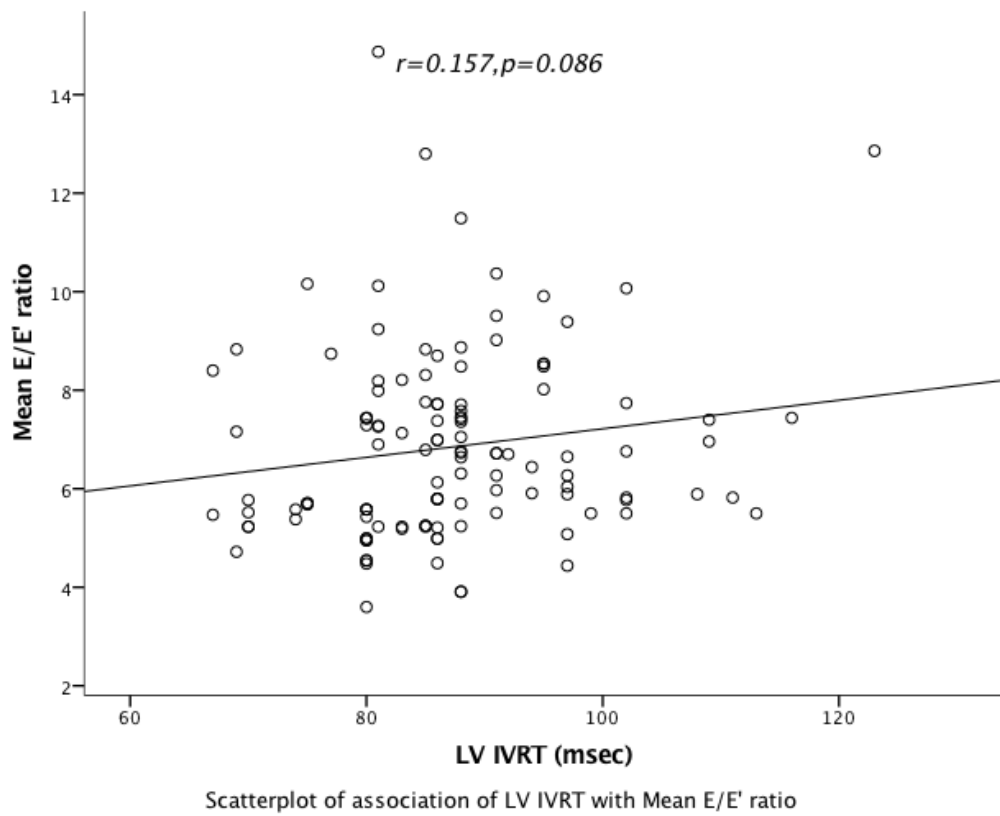


Figure 5.5 Scatterplot, association between mean E/E' and LV IVRT. ($r = 0.157$, $p = 0.086$).

There was a non-significant low correlation between LV Filling pressure and LV IVRT

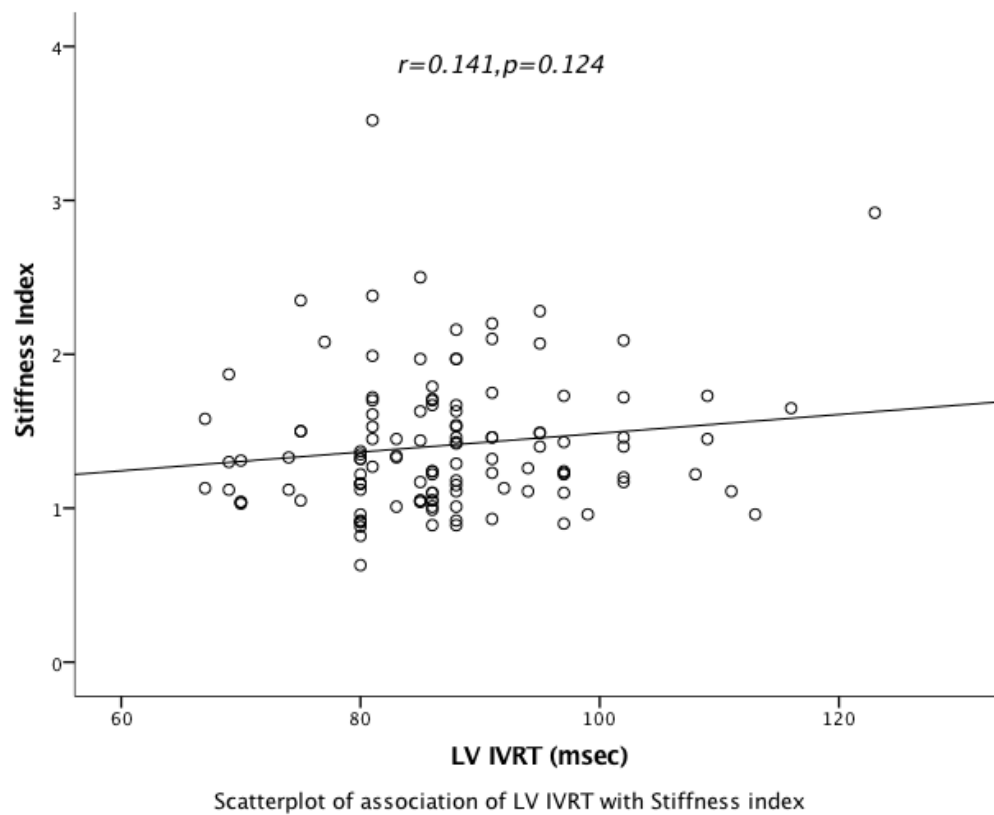


Figure 5.6 Scatterplot of association of stiffness index with LV IVRT ($r = 0.141$, $p = 0.124$)

There was a non-significant low correlation between Stiffness Index and LV IVRT.

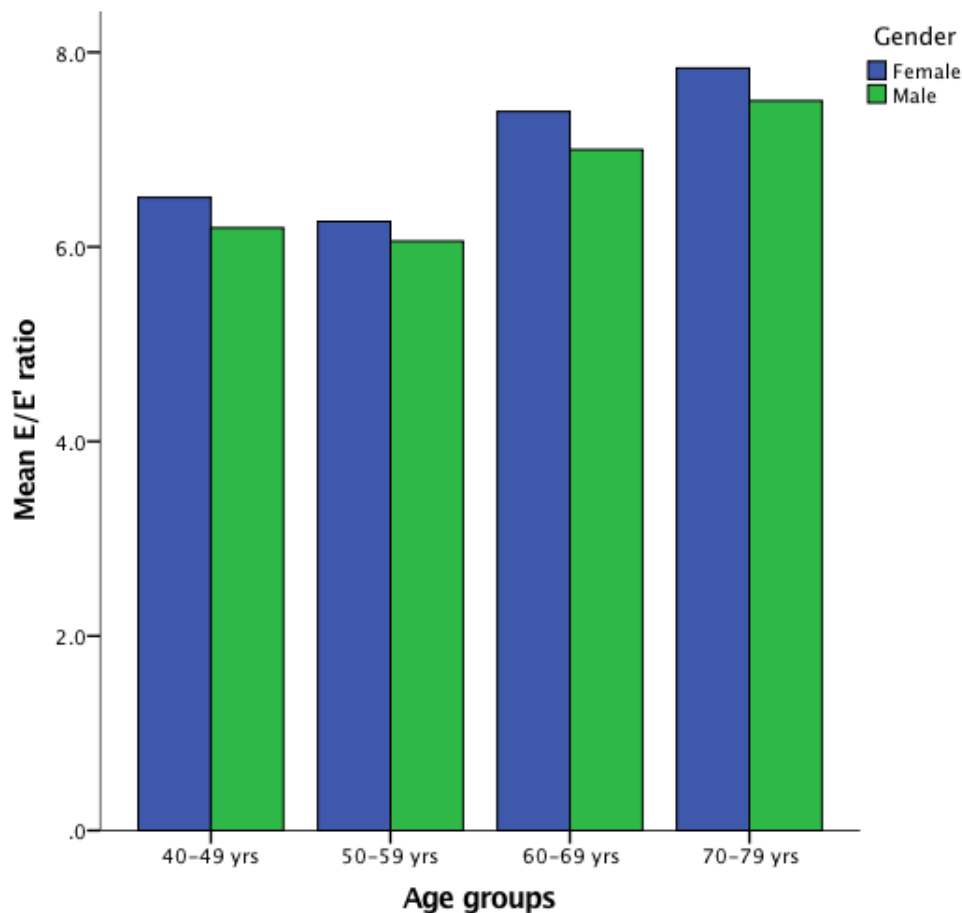


Figure 5.7 Females had higher filling pressures in all four age groups and that filling pressure increased with advancing age. Average E/E' ratio increased over the four decades in the study group.

5.6 Outliers

Further analysis of figure 5.1 demonstrates three outliers in the study comprising of two subjects in the age group three (60-69 years) and one subject in group four aged over 70. In group three there was one female and one male both aged 66 years. The male subject in this group was had a BSA of 2.2 M^2 , while the female had a very low BSA of 1.4 M^2 .

The male subject had a high LV filling pressure, E/E' ratio of 12.8 and a very high myocardial stiffness index of 2.5. This patient also demonstrated a dilated LA with mild diastolic dysfunction and was taking medication prescribed by a consultant haematologist.

The female subject also had a high LV filling pressure E/E' ratio of 14.87, an extremely high myocardial stiffness index of 3.52 and the echo report highlighted mild aortic valve stenosis and aortic regurgitation as well as a dilated aortic root. The referral request had no documented murmurs or history of cardiovascular disease and stated, “query TIA”, with episodes of dizziness, and this patient had a normal exercise stress test.

The oldest outlier was from group four and was a female aged 76 years, and in this case a high E/E' ratio of 12.86 and a raised myocardial stiffness index of 2.92 were recorded. This patient had a severely dilated left atrium with mild aortic valve stenosis and aortic regurgitation. The referral request for echo once again stated no known cardiovascular disease but a previous history of cancer.

5.7 Summary of findings

The results of the current study highlighted the following.

- LV Filling pressure, Stiffness Index and LV IVRT significantly increased with age.
- LV filling pressure was highly correlated with Stiffness Index.
- There were non-significant low correlations between LV Filling pressure and LV IVRT and between Stiffness Index and LV IVRT.

Chapter 6. Discussion

6.1 Primary outcome

The aim of the current study was to determine the effects of aging on three diastolic parameters and to determine reference values for these variables. This is the first study of its kind to determine the stiffness index from middle age to the older person. The results of the current study demonstrate that aging produce a significant increase in average left ventricular filling pressure (E/E' ratio, $p = 0.005$). The results also highlighted a significant increase in the myocardial Stiffness Index ($p = 0.003$) and in LV IVRT ($p < 0.001$) over the four decades. Of these TDI measurement variables, only LV filling pressure was highly correlated with the Stiffness index ($r = 0.882$, $p < .0001$).

These results will now be discussed in greater detail. This study confirmed previously published data on the impact of age on pulse tissue Doppler diastolic measurements of left ventricular mitral annulus and of E/E' ratio. Table 1.1 provides a summary of the main findings of previous reports which analysed measurements of either the septal or lateral mitral annulus. Only two of these published papers sampled both septal and lateral sites and no group published E/E' averages. Four of the authors of these papers published reference values for E/E' for age decades. This study set out to obtain mean E/E' from two mitral valve annular sites namely septal and lateral, and to obtain reference values for the four decades from middle age to the older person.

6.2 Demographics

Baseline data collected was similar to previous studies in the literature including demographic variables and 2D echocardiography measurements (Innelli *et al.* (2007); Chahal *et al.* (2009)).

6.3 Effects of age on LV Filling pressure

In the current study the average E/E' ratio was determined using the average value of septal E' and lateral E'. The hypothesis behind averaging the septal and lateral velocities is that septal velocities tend to overestimate and lateral velocities tend to underestimate values (Park, (2006). It had been previously noted that E' velocities were greater at the lateral location than at the septal placement of the mitral annulus in healthy subjects (Alam *et al.*

(1999)). For this reason in this study the average pulsed tissue Doppler values of diastolic velocities were used and recorded at the septal and lateral side of the mitral annulus. This methodology follows recommendations and best practice of the American Society of Echocardiography (ASE) and the European Association of Cardiovascular Imaging (EACI) (Nagueh *et al.*, (2009) ; (2016))

There was a small correlation between mean E/E' ratio and increasing age ($r = 0.269$, $p = 0.003$). As was the case with normal spectral Doppler measurement values, tissue Doppler E' was progressively reduced and A' increased with advancing age at both the annular sites as well as the average values. The average E/E' ratio was significantly higher in the age groups 60-69 years and 70-79 years, ($p < 0.005$). Of note, the LV filling pressures of females was higher in all four age groups. An E/E' ratio > 10 is associated with a mean capillary wedge pressure $> 15\text{mmHg}$ with 97% sensitivity and 78% specificity. An E/E' ratio > 10 has been postulated as the cut-off value between normal and abnormal LV filling pressures (Nagueh *et al.* (1997)). In later studies this cut-off value was challenged (Ommen *et al.* (2000)). The patients in the Ommen study were healthy subjects with no cardiac history and had normal left ventricular systolic function. An E/E' value of > 15 was identified to detect abnormally increased left ventricular filling pressure (Ommen *et al.* 2000). In the current study the mean E/E' ratio was >10 in 8 out of the total 121 healthy subjects (6.6%). None had a ratio > 15 . The majority of subjects with E/E' ratio > 10 had a transmitral pattern of left ventricular abnormal relaxation. Of note there was one subject (3.3%) in the decade 40-49 years, one subject (3.3%) in the decade 50-59 years, three subjects (9.6%) in the decade 60-69 years and three (10%) in the decade 70-79 years had an E/E' ratio greater than 10. Transmitral E peak velocity showed a progressive reduction with advancing age. The E/E' ratio increased while the E/A ratio decreased with advancing years.

6.4 Myocardial stiffness index with age

There was a small correlation between stiffness index and age ($r = 0.237$, $p = 0.001$). These results are similar to those of Hussein *et al.* (2014). Hussein studied patients with hypertension and a control group of normal subjects that were divided into two age groups (20-49) and (50-80) years. This aided in determining if the stiffness originated from the disease or was influenced by aging. The LV Stiffness Index and E/E' were significantly higher in hypertensive subjects compared with controls ($p < 0.05$).

It is known that a change in myocardial stiffness and performance caused by overload can be related to fibrosis due to increased collagen in the muscle, which can be attributed to increased stiffness (Kannel *et al.*(1961)). This group used the same equation (E/E') / LVIDd) as King *et al.* (2006). Hussein *et al.* observed that the change in the LVIDd chamber size was very small and insignificant for both groups of young and old patients. Therefore the changes in the stiffness index are the result of the change in the E/E' which represents the change in transmitral pressure as opposed to the change in LVIDd. There was no significant change in LV internal dimensions across the four age decades in the current study, similarly both the LA Volume and the Stiffness Index also increased with aging.

To estimate left ventricular stiffness, a surrogate measurement such as MV deceleration time (MVDt) can be used. Subjects with increased LV stiffness have more rapid rates of deceleration of early LV filling and shorter deceleration times.

6.5 LV IVRT with age

This study also demonstrates that with increasing age, the isovolumic relaxation time is prolonged and there is also a loss of left ventricular compliance which leads to a reduction in the efficiency of myocardial early diastolic activity. The IVRT is a measure of LV relaxation and when the IVRT is prolonged, mitral valve opening is delayed and IVRT is increased. IVRT increases with age and is influenced by heart rate and systolic function, while impaired relaxation lengthens the IVRT.

When myocardial relaxation is impaired, the LV pressure falls slowly during the isovolumic relaxation period resulting in a longer time interval before it drops below LA pressure and thus MV opening is delayed resulting in a prolonged IVRT. Measurement of the IVRT is affected by preload which opposes LV relaxation and this can lead to inaccuracy of measurements.

6.6 Correlation between LV filling pressure (mean E/E') and Stiffness Index

This was the first study to determine the Stiffness Index from middle age to the older person. The results of this study highlight that LV filling pressure is highly correlated with the Stiffness Index with advancing years ($r = 0.882$, $p < 0.0001$). Previous published papers

have used multiple linear regression analyses to demonstrate that age is the single strongest contributor to average E' reduction and of A' and E/E' ratio increase (Innelli *et al.* 2007).

In the past some researchers have preferred to use the septal side of the mitral valve annulus as it moves parallel to the ultrasound beam and is less influenced by the translation (Sohn *et al.* 1997). But septal velocities may be influenced by right ventricular interaction. There was no patients noted to have regional wall motion abnormalities (RWMA) or any evidence of significant valvular heart disease. **Table 5.5** displays tissue Doppler measurements of mitral annulus according to age group. It Demonstrates that like standard spectral Doppler measurements, E' was progressively reduced and A' increased as age increased, this was observed at both annular interrogation sites as well as the average values.

6.7 Strengths of this study

The major strength of the current study was that all measurements were taken by the same cardiac physiologist (lead researcher) helping to ensure the quality of all measurements taken. Similarly the same ultrasound system (Philip IE 33, Philips Healthcare, Bothell, WA, USA) was used to perform echocardiography, thereby insuring consistency and repeatability of the data collected. In keeping with other studies in the literature study subjects were only selected in the absence of known cardiovascular disease and patients with a high body mass index ($BSA > 2.2 \text{ m}^2$) were excluded (Innelli *et al.* (2007). Another strength of this study is that the average values of both medial and lateral mitral annular velocities were recorded.

6.8 Limitations of this study

A limitation of this study is that the population sample is low at 121 subjects as the optimal study design would be 246 subjects as determined by the sample size calculator. A further limitation is that the population ethnicity which was entirely Caucasian.

6.9 Recommendations for future research

This study highlighted that females had higher filling pressures in all four age groups and that the LV filling pressure increased with advancing age. Future research is warranted to determine the effects of hormonal changes on LV filling pressures which may contribute to a higher proportion of females over 60 years having diastolic heart failure.

Chapter 7. Conclusion and future direction of research

We conclude that the findings of this study show an independent impact of aging on average diastolic parameters and indexes obtained by pulsed tissue Doppler obtained from two sites, septal and lateral annular locations each side of the mitral annulus in a group of healthy subjects over four decades from middle age to old age. The reference values obtained in this study can be generalised to other patient cohorts of similar ethnicity.

- Data obtained during this study can also be used as reference data for the quantitative assessment of longitudinal left ventricular function.
- It should be noted, that as is the case with spectral Doppler inflow patterns across the mitral valve, one must be aware when analysing data in patients with cardiovascular disease, that the physiological influence of aging on pulsed tissue Doppler should be considered.
- Future research could involve multiple linear regression analysis to predict if the female gender is an independent predictor of higher raised filling pressures over their male counterparts and why.

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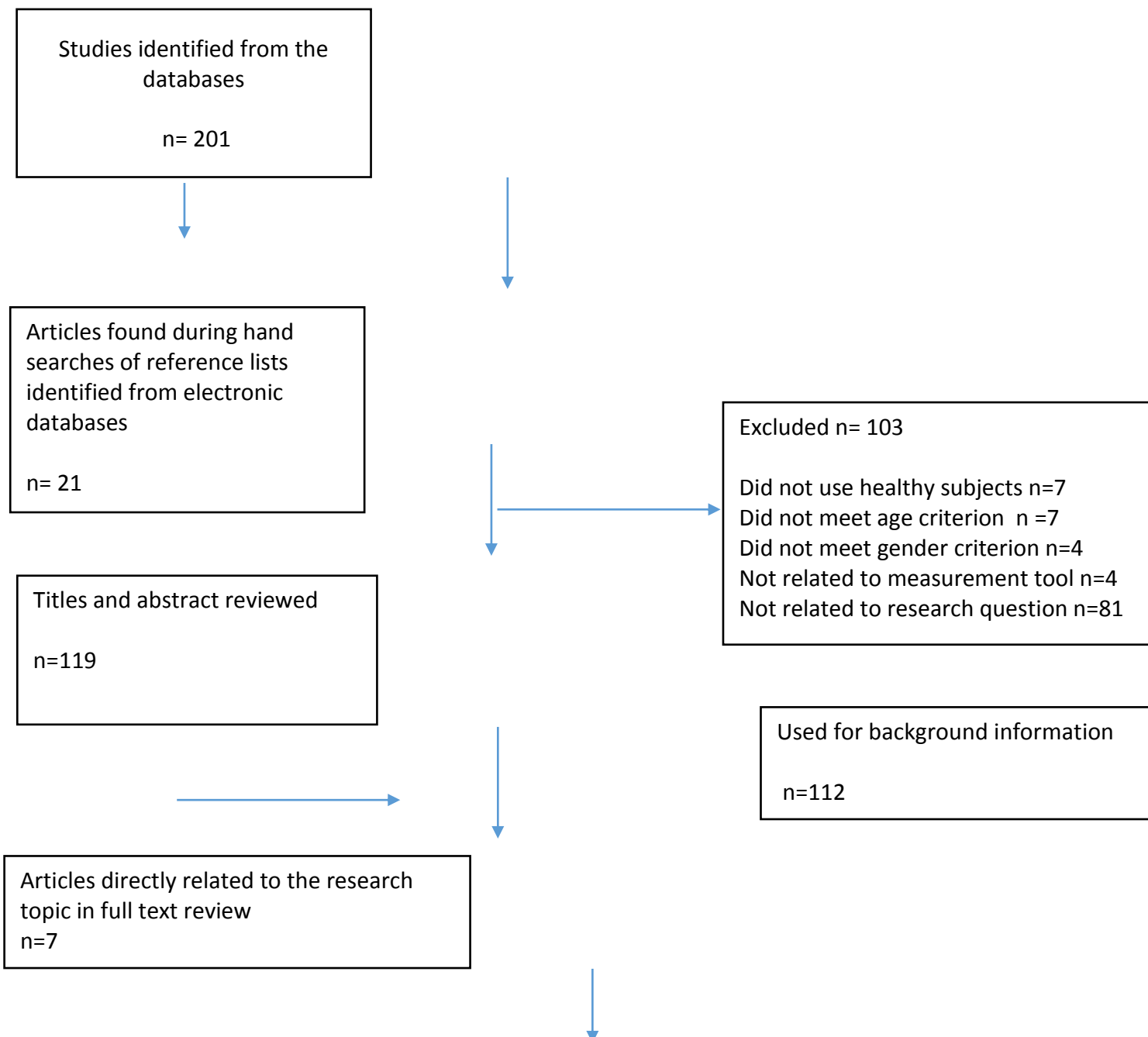
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Appendices

Appendix 1. Flow diagram of search strategy for literature review.



Articles included in final analysis of literature

n=7

Appendix 2.

Literary Review of previously published Reference Values for LV filling pressure and current study values obtained

Author	Variable	40-49 years	50-59 years	60-69 years	70-79 years	p value
Innelli <i>et al.</i> (2007).	E/E' ratio Avg	6.9 ± 1.5	7.7 ± 2.2	8.6 ± 2.4	8.7 ± 2.3	< 0.0001
Tighe <i>et al.</i> (2003)	E/E' ratio Lateral	5.2 ± 1.2	5.7 ± 1.4	6.2 ± 1.8	7.2 ± 3.2	< 0.0001
Current study	E/E' ratio Avg	6.39 ± 1.69	6.11 ± 1.32	7.21 ± 2.25	7.63 ± 1.89	< 0.005

Appendix 3. E/E' values and range for MV septal and lateral leaflets and Tei index from Munagala study (2003)

Author	Variable	45-49 yrs	50-54 yrs	55-59 yrs	60-64 yrs	65-69 yrs	> 70 yrs
Munagala <i>et al.</i> (2003)	E/E' Septal	6.67 (4.6-11.2)	7.00 (4.5-11.6)	7.78 (4.6-13.3)	7.64 (5.0-12.0)	8.57 (5.4-13.3)	8.57 (4.5-16.6)
	E/E' Lateral	5.38 (3.7-7.7)	5.45 (3.7-8.8)	6.0 (3.8-10)	6.67 (4.6-8.9)	7.0 (4.1-11)	7.78 (5-14)
	Tei index		0.30 (0.1-0.5)	0.30 (0.2-0.6)	0.30 (0.2-0.6)	0.40 (0.2-0.6)	0.40 (0.2-0.6)

Appendix 4. E/E' ratio values obtained in the LOLLIPOP study

Author	Variable	35-44 years	45-54 years	55-64 years	65-75 years	p value
Navtej <i>et al.</i> (2009). LOLLIPOP	E/E' ratio Avg	6.9 ± 1.5 (4.5-9.7)	7.3 ± 1.6 (5.1-10.4)	8.4 ± 2.4 (5.5-12.0)	7.6 ± 1.8 (5.2-12.0)	< 0.001

Appendix 5. Research Ethics application approval letter.

Mr Anthony Ryan
Chief Cardiac Physiologist
Sligo University Hospital

January 27 2016

Re. Research Ethics Application

Dear Mr. Ryan,

The Research Ethics Committee (REC) at Sligo Regional Hospital has received your submission for ethical review of the study "*Changes in the Ageing Heart in middle age and geriatric years; a comparison of filling pressures in the left ventricle between these populations using Tissue Doppler*".

The study underwent expedited review and the REC Chairman has given a **favourable ethical opinion** for the study for Sligo Regional Hospital.

Documents reviewed:

- Application Form
- PI CV

The REC requires that approved studies submit an annual report to the REC. The annual report for the above study is due on January 27 2017.

Yours sincerely,



Dr. John Williams
REC Chairperson

Mission Statement

Sligo University Hospital is committed to the delivery of a high quality, patient centred service in a safe, equitable and efficient manner. We recognise and value the contribution of each staff member and endeavour to support them in their ongoing development.

Appendix 6. Procedure in obtaining Doppler and Tissue Doppler imaging data.

Medial and lateral sites of the mitral annulus were investigated using Tissue Doppler. The average value from these two sites was then be obtained to calculate average E/E' to derive

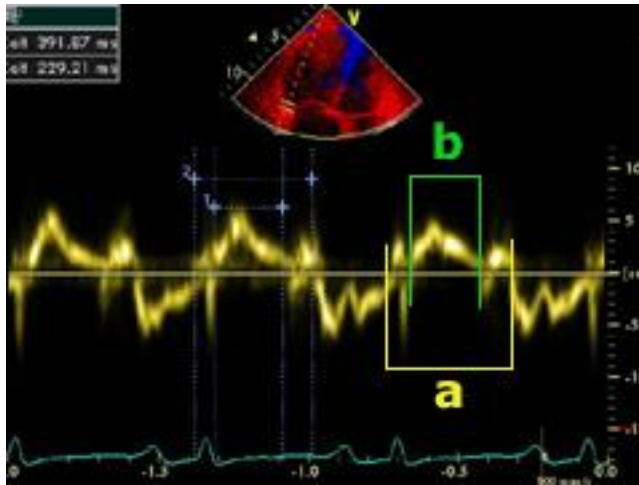
LV filling pressure. All measurements were recorded on line. When acquiring the image, the frame rate was optimised by using an image sector sufficiently narrow to increase the frame rate as near to 100 frames per second as possible and to select the appropriate velocity scale of +20 cm/s to -20 cm/s. These parameters were optimised at the time of imaging, as it was not feasible or possible to modify the frame rate and the velocity scale during post-processing image analysis. Tissue Doppler imaging methods have required modifications in signal processing of returning Doppler signals. The high-pass wall filters, which are used to eliminate the low-velocity and high-amplitude signals of myocardial walls for detection of blood flow velocities in conventional spectral Doppler are bypassed for TDI. Gain amplification is also used to enhance low-velocity myocardial signals and to eliminate the blood flow signals within the cardiac chambers. When pulsed TDI was performed, spectral gain settings had to be reduced to record the low-velocity and high-intensity signals from the myocardial walls. Because the myocardial velocities are low ($< 25\text{cm/s}$), the velocity scale was adjusted to obtain proper displays characteristics and to provide accurate measurements. Pulse wave TDI has the advantage of providing real time velocity information with improved temporal resolution and provides instantaneous temporal display of the Doppler spectral information.

The disadvantages of PW TDI is that only regional quantification of myocardial velocities can be done at selected sites reducing spatial resolution. Sampling cannot be localised to the endocardial or epicardial layers. The alignment of the ultrasound beam parallel to the heart muscle movement may be difficult in some patients. There is also no correction for normal cardiac translation and rotation during sampling. Recording of tissue Doppler signals at end expiration was performed as a routine practice.

A transducer (2.5-4 MHz) was used for imaging, and a sample volume (3.0 mm axial length) was used for accurate placement within the boundaries of the endocardium and epicardium. The sample gate was placed at sites within the 2-dimensional image in either parasternal or apical windows. The myocardial area to be assessed was placed in the centre of the ultrasound beam to allow parallel alignment of the sampling cursor.

The Nyquist limit was then set to a range between -20 to 30 cm/s, with minimal gain and low wall filter settings. The monitor sweep speed was adjusted to allow a sweep speed of 50-100 mm/s to optimise the spectral display of the myocardial velocities.

The apical imaging approach is feasible in most patients and allows a method for the assessment of LV long axis shortening and lengthening. Pulse Doppler sampling was performed in the basal region of the left ventricle close to the mitral annulus. This allowed for the assessment of regional systolic and diastolic myocardial velocities in the lateral, septal anterior and inferior walls and the anteroseptal and postero-inferior segments (Rodriguez *et al* (1996) and Gulati *et al.* (1996)). The motion of the mitral annulus can be assessed with TDI for determination of global LV systolic function in a similar way to where conventional 2-dimensional or M-mode imaging provides measurements of the descent of the base (Simonson *et al.* (1989); Nagueh *et al.* (1997)). There were three main components of myocardial velocities recorded using pulsed TDI. These were the systolic, early diastolic, and late diastolic velocities. The systolic myocardial velocity (S_m) may comprise of 2 components in some patients, representing isovolumic contraction and the systolic ejection phase. The diastolic components are very like mitral flow velocities obtained with conventional spectral pulsed Doppler. The early diastolic myocardial velocity (E_m), and a late diastolic myocardial velocity (A_m) at the time of atrial contraction, can be seen in normal sinus rhythm (NSR), while A_m may be absent during atrial fibrillation or during a tachycardia. Measurements recorded include S_m , E_m , and A_m and the ratio of E_m/A_m . The effects of cardiac translation are reduced using the apical windows. The LV IVRT was calculated as part of the myocardial performance index (Tei index), which is a valuable tool for the calculation of true myocardial performance as it incorporates both diastolic and systolic indices to determine overall left ventricular function. The method for the calculation of this index is outlined as follows; Tissue Doppler measurement of IVRT and IVCT and ejection time to derive the Tei index of myocardial performance. The IVRT is measured from the end of the S' wave to the beginning of the E' wave. The IVCT is measured from the end of the A' wave to onset of the S' wave.



A 3mm sample volume was used, the sample volume was placed at the medial mitral annulus. The tissue Doppler intervals were recorded as follows:

Interval (a) was measured from the end of the A' negative wave and is equal to the sum of IVCT, ET, and IVRT. To the start of E' negative velocity.

The ejection time (ET) (b) corresponds to the duration of the systolic ejection (S').

The sum of IVCT + IVRT is obtained by subtracting (b) from (a).

The myocardial performance index (MPI) is calculated as $(a-b)/b$.

Two-dimensional imaging is used to calculate LV volume.

An apical 4 chamber view (AP4ch) and apical 2 chamber view (AP2ch) were obtained to calculate Left Ventricular volume using a modified Simpson's rule (method of discs) to calculate the Ejection Fraction (EF). The left ventricle is traced carefully to draw the endocardial borders at both end systole and end diastole. The papillary muscles should be excluded from the cavity in the tracing.

Obtaining an Apical Imaging Window.

As the heart lies within the rib cage, and is located between the air-filled lungs, it is effectively shielded from the ultrasound beam. Therefore, it may only be viewed through one of a small number of echocardiographic windows through which the ultrasound may travel unimpeded. Ultrasound gel (Parker) was applied to the chest wall for acoustic matching with the transducer, which was then positioned to view the heart through the apical imaging window as shown in **Diagram 1**. This echocardiographic window is located on the

anterior chest wall, over the palpable apex beat of the heart. The transducer was therefore placed between the sixth and seventh ribs, slightly lateral and inferior to the left nipple. However, it was often necessary to move the transducer slightly away from this position because the position of the heart within the thorax may vary to a small degree between individuals.

Apical Imaging Planes.

Once the apical window is obtained, it should be possible to visualize the heart in three standard apical two dimensional views by altering the orientation of the transducer. A four-chamber view can be produced by directing the transducer superiorly and medially towards the right scapula, parallel to the major axis of the heart and shown in **Diagram 1** below.

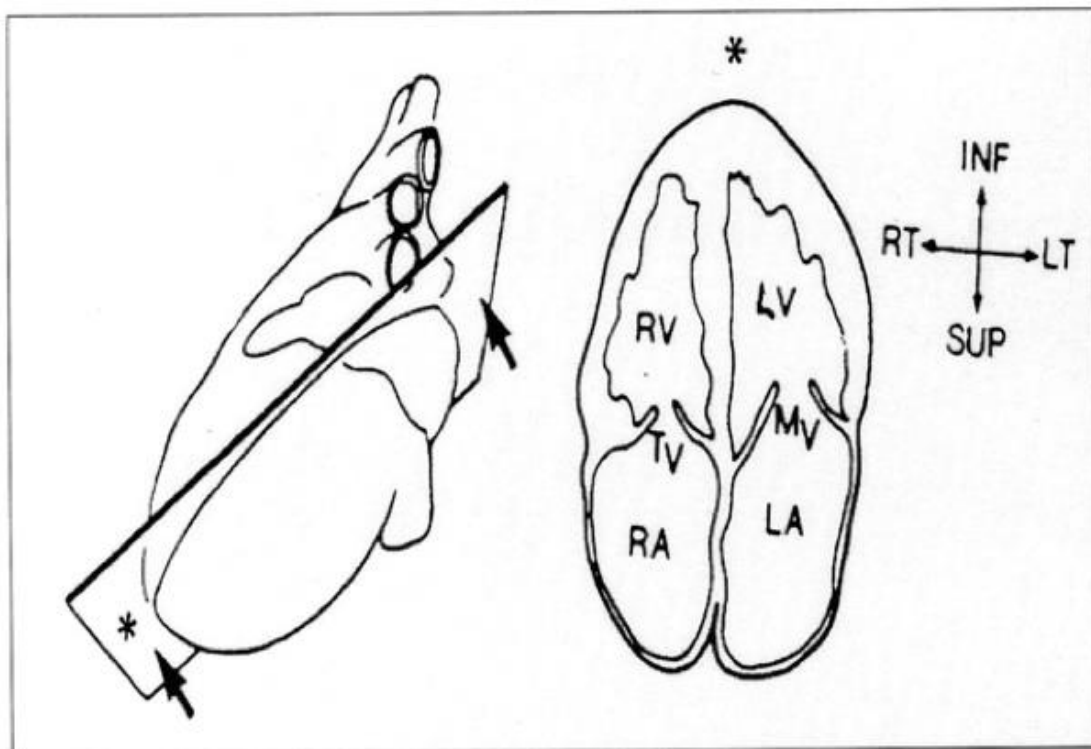


Diagram 1. Apical 4 Chamber View. (Walsh & Wilde, (1999)).

The heart is divided into four chambers by the inter-atrial and inter-ventricular septa and by the atrioventricular valves. The ultrasound beam therefore will section the heart from apex to base along the septum. This should allow simultaneous visualization of all four cardiac chambers demarcated by the mitral and tricuspid valves, and the intra-atrial and intra-ventricular septa. In this view, the left ventricle is bounded by the lateral and posterior septal

walls. By rotating the transducer 60-90 degrees counter-clockwise and moving the transducer more laterally the apical two chamber view is obtained displaying the inferior and anterior walls of the left ventricle as seen in **Diagram 2**.

TDI Sampling sites.

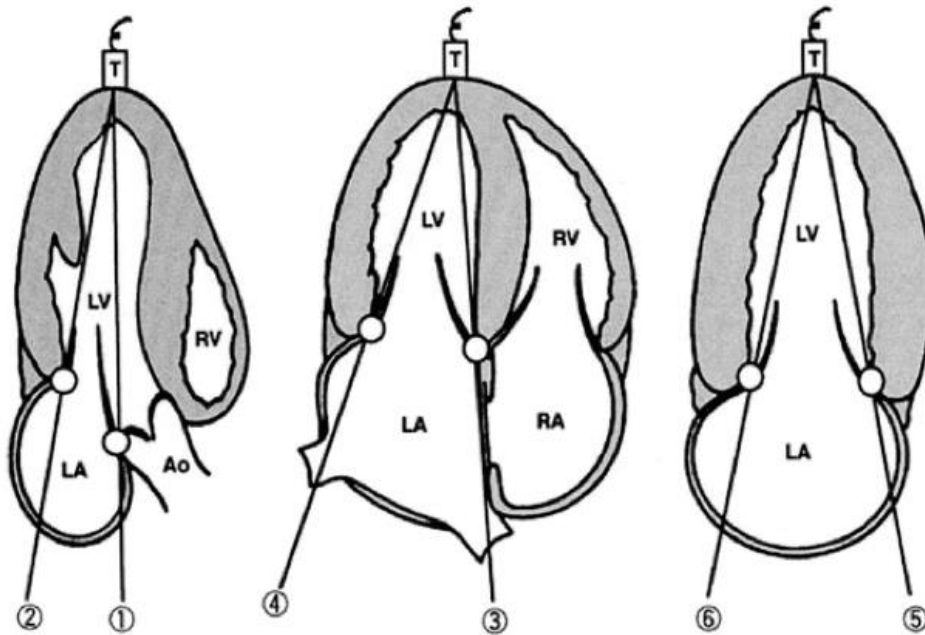


Diagram 2. 2 sampling sites for TDI at Mitral Ring. (Fukuda *et al*, 1998)

The Doppler cursor is positioned at two ring sites, (3) posteroseptal and (4) lateral, walls of the left ventricle.

The Ejection Fraction

A modified form of Simpson's rule is used in the apical views and averaged to measure the ejection fraction (EF). Similar techniques have been described elsewhere (Senior *et al*. (1994); Naik *et al*. (1995); Otterstad *et al*. (1997)). Real time two-dimensional imaging of the heart is then recorded for on-line as well as off-line analysis. The image was reviewed and frozen at ventricular end diastole. This point is defined as the point at which the mitral valve leaflets are at maximum opening in the maximally dilated ventricular cavity and occurs near the end of the T-wave of the ECG tracing. The cursor was then placed on the mitral ring at the base of the left ventricular and the inner contours of the left ventricular will be traced manually using the trace function of the ultrasound scanner. The cursor is positioned at the

apical end of the ventricular cavity, aligned perpendicular to the mitral plane and drawn to obtain the long axis length. This allows the internal software to section the cavity into discs of equal height thereby estimating the volume of the left ventricular cavity by summing the disc volumes. These are then entered the ejection fraction analysis programme of the ultrasound scanner. Then the left ventricle at end systole of the same heart beat is selected. This coincides with the QRS complex of the ECG and corresponds to the minimum size of the ventricular cavity prior to mitral valve opening. Then the endocardial surface is traced, the cavity divided into discs and the volume will be computed as previously stated. Then using the end diastolic and the end systolic ventricular volumes, the ejection fraction is calculated according to the equation.

Equation 1

$$EF = \frac{LV \text{ (end diastolic volume (ml))} - LV \text{ (end systolic volume (ml))}}{LV \text{ (end diastolic volume (ml))}} \times 100\%$$

The values of ejection fraction are then recorded on a Microsoft Excel spreadsheet for each patient.

Heart Rate

Heart rate is recorded using the ECG tracing by measuring the time interval in milliseconds (ms) between consecutive R-waves on the ECG, and dividing this value into 60,000ms to obtain the number of cardiac cycles per minute.

Interrogation of the Mitral Ring

In the apical four chamber view (AP4ch) the pulsed Doppler sample volume is placed on the mitral ring and on either side of the valve. This way, 2D views are used to guide the Doppler cursor to a total of two sites around the mitral ring, corresponding to the septal, and lateral walls of the left ventricular as shown in **Diagram 2**. Accurate positioning of the cursor on the ring is aided by colour TDI of the mitral area. Colour TDI can help distinguish the mitral ring from the valve leaflets and from the ventricular wall, and then the pulsed wave TDI mode was selected and the Doppler velocity pattern which is characteristic of the mitral ring motion was visualised in real time. The imaging controls are then adjusted to optimise the

signal clarity. The image was then frozen and the peak velocity of ring descent (S_m) measured, and similarly the E' and the A' are also measured. This is repeated at each of the two ring sites in every subject. This procedure has previously been described in the literature (Gulati *et al.* (1996); Fukuda *et al.* (1998)).








Data Processing

The averaged values of S' , E' , A' and E/E' are measured in each of the two ring sites, and calculated. Ejection Fraction is obtained using Simpson's method. The data are tabulated and entered onto an Excel worksheet. Patients were then divided into subject age ranges for 40 to 49 years, 50 to 59 years, 60 to 69 years and 70 to 79 years. Data are exported from Excel into SPSS (version 24) for statistical analysis.

Appendix 7.

Sample size calculator.

Determine Sample Size

Confidence Level:	95%	
Population Size:	260000	
Proportion:	0.2	
<input checked="" type="radio"/> Confidence Interval:	0.05	
Upper	0.25000	
Lower	0.15000	
<input type="radio"/> Standard Error	0.02551	
<input type="radio"/> Relative Standard Error	12.76	
<input type="radio"/> Sample Size:	246	

<http://www.nss.gov.au/nss/home.nsf/pages/Sample+size+calculator>.

Date accessed 05/12/2015.

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MPhil Research Project

Year of submission 2016

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