The Role of Contemporary

Echocardiography in the Management of

Heart Failure

Gillian A Whalley, BAppSc, MHSc, DMU

A thesis submitted in partial fulfilment of the requirements for the degree of Doctor of Philosophy, Faculty of Medicine and Health Sciences, The University of Auckland, 2006

The University of Auckland

Thesis Consent Form

This thesis may be consulted for the purpose of research or private study provided that due acknowledgement is made where appropriate and that the author's permission is obtained before any material from the thesis is published.

I agree that the University of Auckland Library may make a copy of this thesis for supply to the collection of another prescribed library on request from that Library; and

I agree that this thesis may be photocopied for supply to any person in accordance with the provisions of Section 56 of the Copyright Act 1994

Signed:

Date: 21 January 2006

Abstract

Heart failure (HF) is an increasing and leading cause of cardiovascular morbidity, hospitalisation and death. Echocardiography is often used in HF patients because it provides important aetiological, diagnostic and prognostic information to assist physician management at moderate cost. This thesis has explored contemporary echocardiographic techniques for assessment of both diastolic and systolic function to ascertain their effectiveness and optimal utility. Assessment of systolic function in HF patients is optimised by the use of harmonic imaging and not enhanced with the use of transpulmonary contrast agents, whilst diastolic filling is optimised by the use of preload manipulation. When optimised in this way, echocardiography can be used to stratify HF patients in terms of risk of death and/or hospitalisation after discharge from hospital. This was confirmed in a meta-analysis of more than 6000 patients (1000 deaths) with HF or after acute myocardial infarction (AMI), where the presence of restrictive filling pattern (the most severe form of diastolic dysfunction) was associated with a four-fold increase in mortality in both patient groups. In addition, restrictive filling pattern also predicted development of HF post AMI and hospitalisation in patients with HF. This meta-analysis also evaluated the intermediate stages of diastolic dysfunction and found a stepped relationship between each grade and prognosis. The last part of this thesis explored the role of contemporary echocardiography for management of symptomatic patients in the community and found that the diagnosis of HF in the community may be optimised by using brain natriuretic peptide (BNP) as a first test to “rule-out” heart failure and then echocardiography, which was superior to BNP in patients with intermediate BNP levels to diagnose HF. Furthermore, the systolic echocardiographic parameters were important for diagnosis, whilst the diastolic parameters predicted future hospitalisation. In summary, contemporary echocardiography in HF patients should include comprehensive assessment of systolic function (using tissue harmonics imaging) and diastolic filling (utilising preload manipulation). This approach will optimise both diagnosis and prognosis and in turn may aid physician management.

This thesis is dedicated to my father,
Alan Whalley,
who sadly passed aways before its completion.

Acknowledgements

A project such as this is never possible without the significant contribution of many individuals. Firstly, I would like to acknowledge my supervisor, Associate-professor Robert Doughty. I have been fortunate to work closely with Rob throughout this project and many others. Both Rob and my first supervisor, Professor Norman Sharpe have provided incredible collegial and academic support for more than a decade, whilst simultaneously allowing me to develop my own research interests and ideas.

I have been fortunate to work closely with some very exceptional individuals. Foremost among those has been Greg Gamble, who provided encouragement, support, statistical analyses and scientific advice. Next, I would like to thank Helen Walsh for her expert technical assistance, and Susan Wright, Cara Wasywich and Ann Pearl who provided medical collaboration on these studies. Several research nurses and technicians helped with patients recruitment and data collection: Renelle French, Jenny Koenders, Stephanie Muncaster, Jenne Pomfret and Graeme Orsbourne. I would also like to thank James Aoina who helped with the meta-analysis data collection and the individual authors who confirmed or provided additional data for the meta-analyses. Lastly, I would like to acknowledge the large number of patients and healthy volunteers who participated in these studies. Without their generous support, there would be little to write about.

I would also like to acknowledge the generous financial support that I have received from the National Heart Foundation of New Zealand in the form of a post-graduate scholarship and several travel grants that have enabled me to attend and present this data at international scientific meetings. I have also received generous product support from Philips Ultrasound (Australia) and Schering NZ Ltd.

And finally, I would like to acknowledge the truly wonderful support I have received from my entire family – my mum Catherine, my sister Janet, my husband Darryl and our two children Matthew and Ryan. Collectively they have orchestrated their own lives to support me - allowing me sufficient time to devote to this project.

With heartfelt appreciation to you all.

Table of Contents

List of Tables

List of Figures

Publications

Chapter 1

Whalley, GA, Wasywich, CJ, Walsh, HJ, Doughty, RN. The role of echocardiography in the contemporary management of congestive heart failure. Expert Rev Cardiovasc Ther 2005;3(1):51-70

Chapter 2

Whalley, GA, Gamble, GD, Walsh, HJ, Wright, SP, Agewall, S, Sharpe, N, Doughty, RN. Effect of tissue harmonic imaging and contrast between observer and test-retest reproducibility of left ventricular ejection fraction measurement in patients with heart failure. Euro J Heart Failure 2004;6:85-93

Whalley GA, Doughty RN, Gamble GD, Sharpe N. Improved endocardial visualization with harmonics and contrast agents improves interpretation of wall motion score index. Euro J Echocardiography 2005;6:134-143.

Whalley, GA, Walsh, HJ, Gamble GD, Doughty, RN. Comparison of different methods for detection of diastolic filling abnormalities. J Am Soc Echocardiogr 2005;18:710-717.

Chapter 3

Whalley GA, Doughty RN, Gamble GD, Wright SP, Walsh HJ, Muncaster SA, Sharpe N. Pseudonormal mitral filling pattern predicts hospital readmission in patients with congestive heart failure. J Am Coll Cardiol 2002;39:1787-1795

Chapter 4

Whalley GA, Gamble GD, Doughty RN. Restrictive diastolic filling predicts death post acute myocardial infarction: A meta-analysis of prospective studies. Heart *(in press)*

Whalley GA, Gamble GD, Doughty RN. The prognostic significance of restrictive diastolic filling associated with heart failure: A meta-analysis Int J Cardiol *(submitted)*

Chapter 5

Whalley GA, Wright SP, Pearl A, Gamble GD, Walsh HJ, Richards AM, Doughty RN. Prognostic role of echocardiography and brain natriuretic peptide in symptomatic breathless patients in the community. J Am Coll Cardiol *(submitted)*

Abbreviations

A	late diastolic mitral valve inflow velocity
A Dur	mitral A wave duration
Aa	late diastolic tissue Doppler velocity of the mitral annulus
ACE	angiotensin converting enzyme
AF	atrial fibrillation
AMI	acute myocardial infarction
ANOVA	analysis of variance
ANP	atrial natriuretic peptide
AR	abnormal relaxation
AUC	area under the curve
AVPD	atrioventricular plane displacement
BNP	brain natriuretic peptide
CABG	coronary artery bypass graft
CHARM	Candesarten in Heart failure: Assessment of Reduction in Mortality and morbidity
CI	confidence interval
COMPANION	Comparison of medical therapy, pacing and defibrillation in heart failure
CV	coefficient of variation
D	pulmonary venous diastolic velocity
DT	deceleration time of early mitral inflow
E	early diastolic mitral valve inflow velocity
Ea	early diastolic tissue Doppler velocity of the mitral annulus
ECG	electrocardiogram
E:A ratio	early to late filling ratio
E:Ea ratio	ratio of mitral early filling velocity to early mitral annular velocity
E:Vp	ratio of mitral early filling velocity to mitral flow propagation velocity
EF	ejection fraction
FS	fractional shortening
GP	general practitioner
GTN	nitroglycerin
HF	heart failure
IHD	ischemic heart disease
IVRT	isovolumic relaxation time
JVP	jugular venous pressure
LA	left atrium/atrial
LOA	limits of agreement
LV	left ventricle/ventricular
LVEDP	left ventricular end-diastolic pressure
LVEDV	left ventricular end-diastolic volume

LVESV	left ventricular end-systolic volume
LVH	left ventricular hypertrophy
LVIDd	left ventricular end-diastolic internal dimension
LVO	left ventricular opacification
MI	myocardial infarction
MV	mitral valve
NT-proBNP	N terminal pro brain natriuretic peptide
NPC	natriuretic peptides in the community study
non-RFP	non-restrictive filling pattern
NYHA	New York Heart Association
PCWP	pulmonary capillary wedge pressure
PN	pseudonormal
pmol/l	picomoles per litre
PTT	pulmonary transit time
PV	pulmonary veins
PV AR	pulmonary veins atrial reversal
PW	pulsed wave
RFP	restrictive filling pattern
ROC	receiver operating characteristic
S	pulmonary venous systolic velocity
Sa	systolic tissue Doppler velocity of the mitral annulus
Tau	time constant of relaxation
TDI	tissue Doppler imaging
THI	tissue harmonic imaging
VO_2	oxygen uptake
Vp	mitral flow propagation velocity
WMSI	wall motion score index
2D	two-dimensional
3D	three-dimensional

Chapter 1 - The Role of Echocardiography in the Contemporary Management of Chronic Heart Failure

Introduction

Heart failure (HF) is a leading cause of cardiovascular morbidity and mortality and contributes significantly to the worldwide burden of cardiovascular disease[1]. Heart failure is predominantly a disease of the elderly[2] and arises in the setting of several risk factors and/or cardiovascular conditions, including coronary heart disease, valvular heart disease, hypertension, diabetes, myocarditis and cardiomyopathies. Patients with left ventricular (LV) dysfunction and HF have very poor prognosis[2,3] and those who do survive have multiple hospitalisations with very high costs associated with management.[4] Both HF incidence and the rate of heart failure related hospital admissions continue to rise. In the USA, between 1990 and 2000, the percentage of all hospitalisations increased from 2.6% to 3.4% per annum for a primary diagnosis of HF and 7.8% to 11.4% per annum for a secondary diagnosis of HF.[5] For many years, HF has been regarded by clinicians as left ventricular pump failure - Eugene Braunwald[6] once described HF as:

"The clinical manifestations of heart failure arise as a consequence of inadequate cardiac output and/or damming up of blood behind one or both ventricles"

Eugene Braunwald [6]

Increasingly HF is recognised as a complex clinical syndrome characterised by abnormalities of cardiac structure and function with associated neurohormonal activation. Four decades ago, the most common causes of HF were hypertension and primary valve disease. Since then, the incidence of HF has dramatically increased due to the increasing role of coronary artery disease. Management of patients with coronary artery disease has improved patient survival but paradoxically may be contributing to the increase in patients eventually developing HF. In addition, hypertension and diabetes already contribute significantly to the major burden of HF and echocardiography may have a larger role to play in the future as the world faces an epidemic of type 2 diabetes. As a result, HF is an increasingly common condition and echocardiography has a pivotal role to play with regard to understanding aetiology, indications for treatment, evaluating prognosis and to guide management.

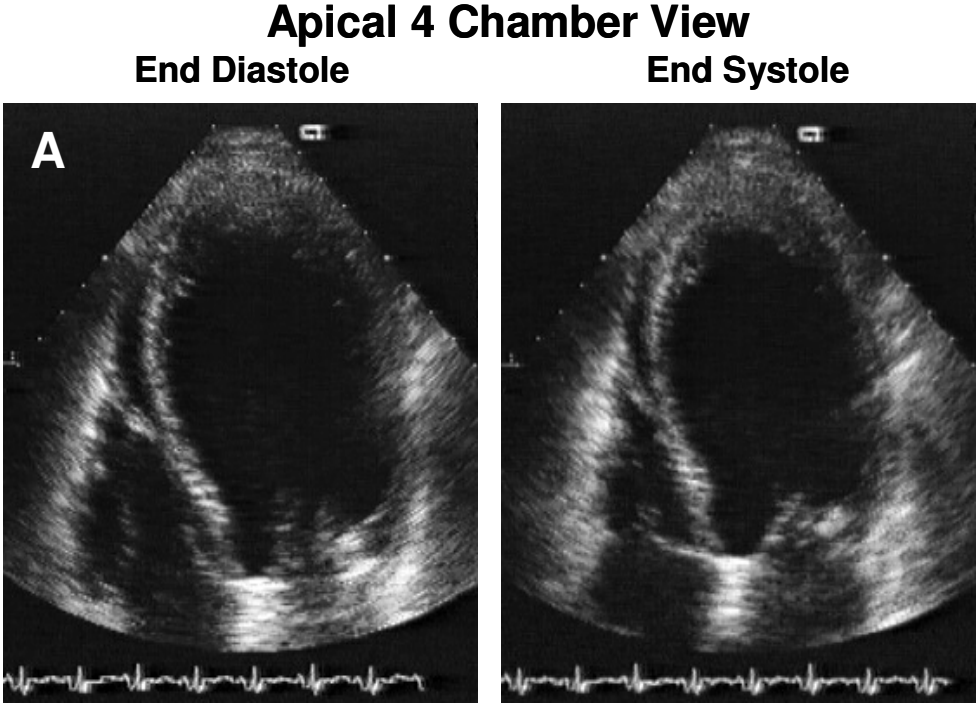
Echocardiography was introduced into clinical practice in the 1970's and rapidly grew in popularity once its outstanding ability to diagnose valve disease and to assess LV function was established.

Utilisation of echocardiography has continued to grow and ultrasound has advanced, particularly with the introduction of harmonics, tissue Doppler and digital imaging, allowing rapid assessment of cardiac structure and function. Echocardiography is the most widely used advanced imaging technique in cardiovascular medicine because it allows rapid, noninvasive assessment of cardiac function and structure in a wide variety of hospital and community settings at moderate cost.

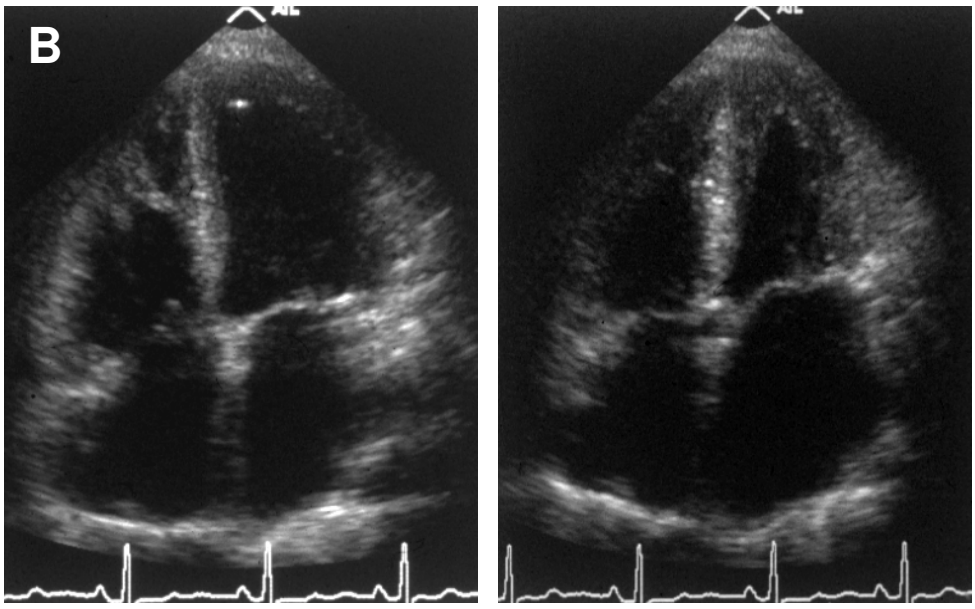
As our knowledge of the underlying causes and pathology of HF has extended beyond the assessment of pump function, so too have echocardiographic methods. Using the theory of pressure changes and gradients within the heart, it is possible to use Doppler ultrasound to assess both left atrial (LA) and LV pressures and their changes relative to one another in order to determine the effectiveness of diastolic filling of the LV. Diastolic filling, as assessed by Doppler echocardiography, is a useful surrogate for diastolic function of the LV and is used to identify, diagnose and quantify diastolic filling abnormalities.

Diastolic function may contribute significantly to the forward output of the ventricle. Frank Starling first described the importance of myocardial stretch upon subsequent contraction of the muscle. Whether HF is primarily due to systolic or diastolic LV dysfunction, the clinical syndrome and symptoms may be similar and difficult to differentiate in individual patients. Whilst it is rare for systolic dysfunction to exist in solitude (diastolic filling abnormalities are almost always present when contractile function is reduced) it is possible for diastolic dysfunction to exist in isolation. From an echocardiographic perspective, the differences are clearly apparent. In the setting of systolic impairment, the LV is likely to be dilated, spherical in shape and show impaired myocardial thickening, i.e. fibre shortening and depressed pump function (Figure 1A). In patients with primarily diastolic abnormalities, the LV may be small, with hypertrophied walls and the LA is usually dilated (Figure 1B). The ejection fraction (EF) may appear normal but the stroke volume that is generated from a small ventricular chamber is inadequate and thus forward output of the LV is significantly reduced (Figure 1B).

Figure 1 - Apical four chamber view in diastole and systole in systolic and diastolic heart failure



End-diastolic Volume = 225 ml, End-systolic Volume = 155 ml
Stroke volume = 70 ml, Ejection fraction = 31 %



End-diastolic Volume = 49 ml, End-systolic Volume = 22 ml
Stroke volume = 27 ml, Ejection fraction = 55 %

The role of echocardiography in heart failure diagnosis

Although the diagnosis of HF is based upon clinical findings, echocardiography is widely used and indeed advocated in patients with HF to determine aetiology, to document the degree of ventricular dysfunction and determine reversible or treatable causes of HF.[7.8] Recently published guidelines for HF diagnosis from both the American College of Cardiology/American Heart Association[8] and the European Society of Cardiology[9] include an objective measure of ventricular dysfunction. Thus, clinicians are increasingly relying upon echocardiography to confirm a clinical suspicion of HF and as a result, there is a call for open access echocardiography to be available to primary care physicians to aid their diagnosis of HF without consultation with a cardiologist.[10] However there remains debate regarding the level of expertise required by primary care physicians to both perform and interpret echocardiography. Whether echocardiography is requested by a primary care physician or a cardiologist, the goal remains similar - to establish the underlying anatomy and pathology and to assess both systolic and diastolic function.

Anatomy

In the case of HF patients, echocardiography is a very sensitive and specific way to identify correctable pathology, such as valve disease, coronary artery disease or pericardial constriction. Once the underlying pathology is established, echocardiography is useful for determining the severity of the cardiac disease, such as degree of dilatation, hypertrophy and haemodynamic compromise. This will often include emphasis upon the LV, in particular on size and function, but should not exclusively focus on the LV. Other contributing factors such as right ventricular involvement, pulmonary hypertension and the degree of valvular disease should not be overlooked.

Ventricular size and hypertrophy

Left ventricular dilatation can be assessed by M-mode or two-dimensional (2D) echo methods. The easiest and most commonly used method measures the chamber diameter from the parasternal M-mode or 2D view.[11] Dilatation, if present, will almost certainly be detected by this method but may in fact be significantly underestimated in patients with HF due to the spherical shape of the LV or indeed overestimated if the M-mode beam is not orthogonal to the LV long axis. In addition, many of the M-mode and simple 2D methods use algorithms to calculate LV volumes that make significant (and sometimes incorrect) assumptions about the LV geometry. Left ventricular size is

more accurately determined using a 2D biplane volumetric approach (typically the modified Simpson's or summation of discs method) from the apical four and two chamber views.[11] It is important that both M-mode linear dimensions and LV end-systolic and end-diastolic volumes be indexed to body size.

Let ventricular hypertrophy (LVH) is commonly seen in patients with HF resulting from hypertension[1] and can be assessed by simple linear measurements of the LV walls. LV mass can be calculated from the M-mode measurements[12] but is subject to the same limitations as mentioned for dimensions above. In the presence of LVH, LV wall thickness is usually increased, although in the setting of ventricular dilatation wall thickness might be within normal limits but calculated ventricular mass will usually be increased. Where HF is due to either hypertension or diabetes, wall thickness is commonly increased. In many cases, there will be clear dilatation of the LV chamber whilst in others, the chamber itself may not be dilated, or may even be smaller than anticipated. Where coronary heart disease is the cause of HF there may or may not be regional wall motion abnormalities, including the presence of infarction (wall thinning), dyskinesis and/or aneurysm.

The left atrium

The left atrial response to LV dysfunction is complex and differs depending upon the stage of ventricular involvement. Initially, LA contraction compensates for the compromised early filling, but as LV relaxation slows and end-diastolic pressure increases, this is diminished. LA pressure rises in response to increased LV end-diastolic pressure and at the same time increased LV stiffness shortens the passive filling time (corresponding to short deceleration time of the mitral inflow) and patients develop restrictive filling and LA dysfunction.[13]

LA diameter is often measured by M-mode echocardiography. However, M-mode may be inaccurate and significantly underestimate LA size.[14] Significant errors may occur due to beam angulation or where LA dilatation occurs along its long and axis. LA volume (or area) can be estimated using a modified Simpson's method (summation of discs) from the apical two and four

chamber views.[15] Left atrial volume is related to both systolic and diastolic LV function, is correlated with LV filling pressure [16] and independently associated with congestive HF.[17] Thus, it is recommended that LA area or volume be measured from the 2-D apical views in patients in whom ventricular dysfunction in suspected[18] and indexed to account for body size.

Left atrial function, or LA stroke volume, may also contribute significantly to forward output and is related to filling pressures[16] and LA dysfunction may occur in the presence of preserved LV EF and may be a contributing factor to the development of diastolic HF.[13]

Assessment of LV systolic function

The assessment of LV systolic function is an important goal of echocardiography in patients with HF[8,9] and there are a number of validated quantitative echocardiographic approaches for comprehensive assessment of systolic function.[19] Despite this, there remains wide variation in both the technique routinely used to assess systolic function and the way in which it is reported. There are a variety of approaches, from expert qualitative data (normal, mild, moderate or severe impairment) to complex quantitation.

The simplest quantification uses chamber diameter change over the cardiac cycle, or fractional shortening (FS), as a measure of global systolic function. This is usually done by placing an M-mode cursor through the LV cavity and provides a good estimate of systolic function. However, this M-mode method is biased towards the basal segments and is unreliable when regional wall motion abnormalities are present. The simplest method of global assessment, and the most commonly used in clinical practice, is subjective assessment of systolic function. Typically, LV function is viewed in several views and a thoughtful judgment is made about overall systolic function - the so-called “eye-ball” EF. Because this requires individual assessment of segmental function it is unquestionably subjective and dependent upon the interpreter’s experience. Despite this, eye-ball EF has been shown to quite accurate in experienced hands[20,21] but the results may be inconsistent in smaller laboratories.[22]

Assessment of regional wall motion abnormalities becomes particularly important in cases where coronary heart disease is the underlying cause of HF. Quantification of assessment of regional wall motion as recommended by the American Society of Echocardiography[11,23] correlates closely with EF by radionuclide assessment[24.25] and echocardiography.[26] It requires allocating a numeric score based on the assessment of function (normal, hypokinetic, akinetic, dyskinetic, aneurysmal), for all segments of the ventricle and averaging the results.[11,23] Many echocardiographers already do this in their mind but do not quantify or document the results. Despite being a simple incremental step from eyeballing ventricular function, this method is rarely used in clinical practice.

The gold standard of echocardiographic assessment of systolic LV function is currently 2D biplane volume assessment. Typically, this requires manual tracing of the blood-endocardial interface in diastole and systole in both the apical four and two chamber views. There are several adaptations of this method, based on different formulae but the Simpson's summation of discs is the most accurate in a wide range of clinical scenarios and is thus the recommended method.[11] This method is time-consuming, and requires significant operator expertise, but does provide a reasonable assessment of global systolic function and possibly more importantly, provides measurements such as LV volumes and EF that many clinicians are familiar with. Ultrasound manufacturers have attempted to make this method easier and less operator-dependent by introducing automated edge detection, but current ultrasound imaging is not always of sufficient quality to allow this technique to be employed reliably and it is not easily applied to large groups of patients.

All of the 2-D methods described thus far require clear endocardial definition, which is sometimes difficult to obtain. In a recent meta-analysis comparing 2D echocardiography methods with radionuclide assessment of LV EF, there was poor agreement between the methods (limits of agreement ± 7-25 %).[25] Specifically, the agreement for the Simpson's biplane volume approach was worse in patients with poor acoustic windows, low EF, atrial fibrillation (AF) and regional wall motion abnormalities.[25]

Both tissue harmonic imaging (THI)[28-36] and LV opacification (LVO) using transpulmonary contrast agents[37-44] improve endocardial visualisation and improve the diagnostic capability of echo,[42.45] both by increasing the number of segments seen and also enhancing the overall quality of the endocardial visualisation.

Both methods are now widely advocated for use in patients with sub-optimal images because they increase the number of patients in whom quantitative echocardiography may be performed. Harmonics imaging improves the quality and increases the number of segments visualised[28] and contrast echocardiography increases the accuracy and reproducibility of measurements.[46,47] Neither method has been tested in HF subjects in whom it has been suggested that LVO may not be as efficacious for endocardial visualisation in patients with low cardiac output.[48] However, this was observed using a first-generation contrast agent and newer agents may be efficacious in HF patients, but this remains unproven.

Echocardiographers are often focused on the 2D and now 3D views of the heart. But simpler M-mode techniques may still have something to contribute to overall assessment of LV function. The atrioventricular plane displacement(AVPD) or longitudinal motion of the LV myocardium contributes significantly to systolic function of the LV and was first described by Feigenbaum in 1967.[49] This can be measured by M-mode or 2-D echocardiography and is correlated with conventional measures of systolic function such as EF.[50] The systolic component of AVPD may not simply be reflective of longitudinal systolic function - in a small cohort of HF patients, AVPD was independently related to both FS and mitral deceleration time[51] and as such may be related to both systolic and diastolic function. Pulsed wave tissue Doppler (TDI) echocardiography is a modern replacement for this technique. The systolic annular velocity (Sa) may provide similar information as the M-mode AVPD and in a small study by Bruch et al, the systolic annular velocity (Sa) was lower in patients with diastolic HF compared to controls and lower still in systolic HF.[52]

Several quantitation techniques are also available for assessing regional wall motion: colour kinesis quantifies using acoustic quantification to determine the blood-myocardial boundary and thus determine myocardial motion;[53] centre line wall motion measures the motion of the myocardium along individual radial lines that dissect the LV through a hypothetical central point in the LV chamber and generates an average myocardial thickening on a regional basis;[19] anatomical M-mode allows true orthogonal planes to be used to assess motion of both the endocardial and epicardial walls[54] and TDI records the low velocity motion of the myocardium on a region by region basis.[55] The assessment of load independent wall stress and the calculation of mid wall shortening may become important measurements in the future, but are not widely available at present.[19] Measurement of the rate of pressure rise during isovolumic systolic contraction (dP/dT)[56] and the time constant of relaxation (Tau)[57] can also be reliably performed in the presence of mitral regurgitation. However these more advanced techniques require further development and acceptance within the echocardiographic community, before they can be routinely applied in all HF patients.

The role of stress echocardiography

The role of both exercise and dobutamine echo for identifying viable myocardium is clearly established.[58] Recently, dobutamine echocardiography has been applied to patients with coronary artery disease with severely depressed LV function. Although studied in a non-randomised manner, patients in whom viability was identified and revascularisation performed had significantly improved two year survival.[59,60] In patients with dilated cardiomyopathy, dobutamine echocardiography is useful in the differential diagnosis between idiopathic and ischaemic cardiomyopathy[61] but its prognostic role remains controversial.[62-66] Stress echo will continue to play an important role in patients with suspected coronary heart disease, however its routine application in all HF patients remains unproven.

Assessment of diastolic function

Echocardiography does not allow direct assessment of diastolic function, but filling pressure may be estimated by measuring the pressure gradients, blood flow and annular motion during the

diastolic phase of the cardiac cycle.[67] Based upon the ratio of early to late mitral valve diastolic filling and deceleration time, five progressive filling categories have been described: normal, abnormal relaxation, pseudonormal, reversible restrictive filling and non-reversible restrictive filling.[68-71]

Pulsed wave Doppler assessment of the mitral valve is now routinely used in clinical practice to non-invasively assess LV diastolic filling, although this is complicated in the presence of AF or a paced rhythm. The addition of pulmonary venous Doppler flow measurements helps to differentiate between true normal and pseudonormal filling and is useful for estimating LA pressure in patients with systolic dysfunction and advanced diastolic filling abnormalities[16,70,72-74] as well as in ischaemic patients with normal EF and only mild filling abnormalities.[75] Preload reduction, achieved with the Valsalva manoeuvre or sublingual glyceryl trinitrate, can also differentiate pseudonormal from true normal flow[70,76,77] as well as reversible from non-reversible restrictive filling.[78] Importantly, the Doppler changes observed with the Valsalva are correlated with changes in LV end-diastolic pressure (LVEDP).[79] Propagation velocity of the mitral inflow colour Doppler has also been used to assess advanced phases of diastolic filling.[80-82]

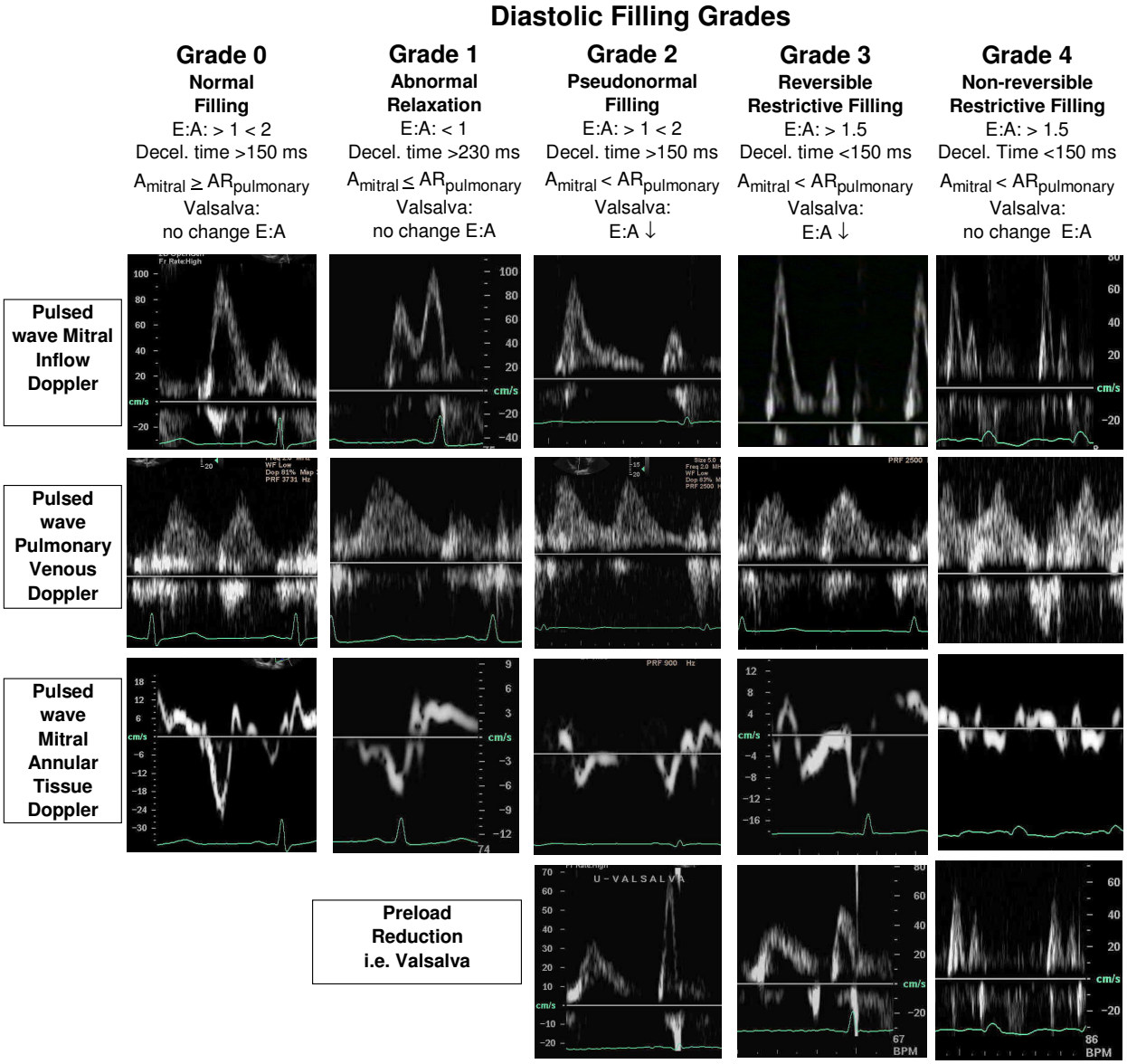
One of the most recent and clinically useful developments is tissue Doppler echocardiography,[83,84] which uses pulsed wave Doppler to assess the velocity of myocardial motion rather than blood flow. The mitral annular velocities mirror the mitral inflow pattern, but are less influenced by preload (i.e. do not pseudonormalise) and as a result the addition of tissue Doppler provides another means of confidently differentiating pseudonormal filling from normal filling. In addition, the ratio of mitral inflow velocity (E) to annular early velocity (Ea) provides the best non-invasive correlate of left atrial pressure regardless of EF,[84] in different filling patterns[83] and in patients with supraventricular tachycardia with normal and reduced EF.[85] The E/Ea ratio correlates well with and predicts both PCWP[83] and LVEDP.[84]

Although these methods of assessing diastolic function are reliable and extensively researched, they are not always well applied and often echocardiographic reports may be confused in their

nomenclature. One suggested approach describes the filling phases as grades from 0 to 4 (0 = normal, 1 = abnormal relaxation, 2 = pseudonormal, 3 = reversible restriction, 4 = non-reversible restriction).[70] This is attractive given that many other clinical scores are based on a similar system. Coupled with an objective measure of left atrial pressure elevation, such as the E/Ea ratio, this grading would provide a clinically useful assessment of diastolic function. The reporting of diastolic function needs to be consistent and based upon easily understood terminology.

For diagnostic and clinical purposes, a complete non-invasive haemodynamic study of diastolic filling should include pulsed wave Doppler assessment of the mitral valve, pulmonary veins and the LV outflow tract for assessing isovolumic relaxation time.[86] However, in HF patients the simple assessment of the diastolic filling pattern and its reversibility, together with an estimate of LA pressure (pulmonary venous Doppler and/or mitral annular TDI) may be helpful for both clinical management and prognosis (Figure 2).

Figure 2 - Diastolic filling grades based upon mitral, pulmonary venous and mitral annular pulsed wave Doppler



Relationship of diastolic echocardiography parameters measures with left atrial and ventricular pressure

It is important to distinguish between diastolic function and diastolic filling. Doppler echocardiography does not measure diastolic function *per se*, but rather provides an estimate of filling pressure. Many of the Doppler indices of diastolic filling have been correlated with filling pressures and as such are surrogates for filling pressure.[16,74-76,79-81,83-85,87-97](Table 1) The E:A ratio is related to filling pressure[16,88,89] and mitral E wave deceleration time is negatively correlated with LV stiffness[98] and filling pressures[88,90-93,95,96] and associated with higher neurohormonal activity.[99] Yamamoto and colleagues studied 83 patients undergoing coronary catheterisation and found that although deceleration time was negatively correlated ($r = -0.85$) with LVEDP in patients with EF < 50%, there was no relationship in patients with EF > 50%.[74] In another study, of patients with atrial fibriallation [AF], the relationship between LV filling pressures was stronger with deceleration time in patients with systolic impairment, but it was still demonstrated in those with EF > 45 %.[91] In that study, isovolumic relaxation time was also closely correlated with LV filling pressures. However the difference between mitral A wave and pulmonary venous atrial reversal duration was correlated with LVEDP regardless of EF.[74] These relationships are valid in AF where pulmonary capillary wedge pressure is negatively correlated with mitral deceleration time[92,95], IVRT[95] and pulmonary deceleration time.[92] This relationship has been validated in patients with normal EF and only mild systolic impairment.[75]

Table 1 - Non-invasive echocardiography surrogates of LV filling pressure

Study	Aetiology	N	Time Delay (echo v cath)	Invasive Pressure	EF %	Echo Parameters	r
Choong [76]	IHD: 9 pts Altered loading conditions	11	Simultaneous	Δ PCWP	-	Δ E velocity	0.58
Kuecherer [89]	Trans-oesophageal surgery	47	Simultaneous	LAP PCWP	>50	$SysFraction_{pulm\ vein}$ E:A ratio	-0.88 0.68
Appleton [16]	IHD: 96 %	70	< 1 hr	LVEDP	55	E:A PV_{Adur} - M_{Adur} $LA\ Volume_{min}$ LA EF	0.72 0.77 0.66 -0.70
				PCWP		E:A PV_{Adur} - M_{Adur} $LA\ Volume_{min}$ LA EF	0.72 0.56 0.70 -0.66
				LV pre-A		E:A PV_{Adur} - M_{Adur} $LA\ Volume_{min}$ LA EF	0.82 0.60 0.74 -0.67
Nishimura [88]	97 (42 EF < 40 %)	97	Simultaneous	Mean LAP	-	$Decel.\ Time_{mitral}$ E:A	-0.73 0.49
Yamamoto [74]	IHD: 100%	82	+/- 3 hours	LVEDP	≤50	$Decel.\ Time_{mitral}$ PV_{Adur} - M_{Adur}	-0.85 0.80
					>50	$Decel.\ Time_{mitral}$ PV_{Adur} - M_{Adur}	ns 0.69
Hofman [87]	Trans-oesophageal Surgery	32	Simultaneous	LAP	58	$S:D_{pulm\ veins}$ $S\ VTI_{pulm\ veins}$	-0.83 -0.65
Pozzoli [90]	DCM: 100 %	231	Simultaneous	PCWP	25	Decel. Time $SysFraction_{pulm\ vein}$	-0.67 -0.76
Nagueh [91]	AF	30	Simultaneous	PCWP (27) LVEDP (3)	48	IVRT Peak Acc E	-0.76 0.84
					<45	$Decel.\ Time_{mitral}$	0.78
					>45	$Decel.\ Time_{mitral}$	0.22
Chirrillo [92]	AF	35	Simultaneous(25) +/- 28 min (13)	PCWP	41	$Decel.\ Time_{pulm\ veins}$ $Decel.\ Time_{mitral}$	-0.91 0.50
Temporelli [93]	HF: IHD 71%	35	Simultaneous	PCWP	22	$Decel.\ Time_{mitral}$	-0.95
Brunner-La Rocca [79]	IHD: 88 %	78	< 30 min	LVEDP pre-A 8.1 mmHg LVEDP post-A 14.6 mmHg	60 %	PV_{Adur} - M_{Adur} %↓ E:A (Valsalva) PV_{Adur} - M_{Adur} %↓ E:A (Valsalva)	0.43 0.57 0.62 0.72
Traversi [95]	AF, HF IHD 50 %	51	Simultaneous	PCWP	25	$Decel.\ Time_{mitral}$ $SysFraction_{pulm\ vein}$ IVRT	-0.60 -0.67 -0.70
Poerner [75]	IHD: E:A < 0.9	82	+/- 4 hours	LVEDP LV preA	68	PV_{Adur} - M_{Adur} PV_{Adur} - M_{Adur}	0.70 0.62
Nagueh [83]	Mixed	60	Simultaneous	PCWP	-	E/Ea (lateral)	0.87
Nagueh [85]	Sinus Tachy DCM: 33% IHD: 33%	100	Simultaneous	PCWP	<45 ≥45	E/Ea (lateral) E/Ea (lateral)	0.86 0.72
Ommen [84]	IHD: 73 % HF: 27%	96	Simultaneous	Mean LVDP	46	E/Ea (lateral) E/Ea (septal)	0.51 0.64
		36			>50	E/Ea (lateral) E/Ea (septal)	0.40 0.47
		60			<50	E/Ea (lateral) E/Ea (septal)	0.49 0.60
Yamamoto [96]	HF EF < 40%	45	Within 24 hours	PCWP LVEDP	35	Ea (posterior) Ea (posterior)	-0.94 -0.70
Dokainish [97]	ICU	50	Simultaneous	PCWP	41	E/Ea (average)	0.69
Garcia [94]	Surgery altered loading conidtions	14	Simultaneous	LA (tau)	57	Vp	-0.78
Firstenberg [81]	Normal Altered loading conditions	7	Simultaneous	PCWP	-	E/Vp	0.81
Schwammenthal [80]	IHD: 85 %	14	Within 24 hours	LVEDP	50	E/Vp	0.73

Abbreviations: Δ = change, $Decel.\ Time_{mitral}$ = mitral deceleration time, $Decel.\ Time_{pulm\ veins}$ = diastolic pulmonary venous deceleration time, E = early mitral filling velocity, Ea = early tissue Doppler velocity of mitral annulus, HOCM = hypertrophic cardiomyopathy, LVEDP = left ventricular end-diastolic pressure, M_{Adur} = mitral valve A wave duration, PCWP = pulmonary capillary wedge pressure, Peak Acc E = peak acceleration rate of the mitral E velocity, PV_{Adur} = pulmonary vein atrial reversal duration, $S\ VTI_{pulm\ veins}$ = velocity time integral of systolic pulmonary vein velocity, $S:D_{pulm\ veins}$ = ratio of systolic to diastolic pulmonary venous flow, $SysFraction_{pulm\ vein}$ = ratio of systolic pulmonary filling to total filling, Vp = mitral flow propagation velocity.

In some early studies, the systolic fraction of the pulmonary veins was a significant correlate of LA pressure in sinus rhythm[87,89,90] and AF.[95] The difference between the mitral and pulmonary venous A duration is observed in higher grades of diastolic filling abnormalities and correlates with LV end-diastolic pressure.[16,75,79,96,100] These relationships have also been tested under manipulated loading conditions.[76]

Propagation velocity (Vp) of the mitral inflow colour Doppler is a relatively preload-independent measure of ventricular relaxation that is correlated with Tau, the time constant of relaxation.[94] The ratio of E velocity to propagation velocity (E/Vp) may also be useful for predicting both pulmonary congestion and LVEDP[80,81] and appears to be the best correlate of pulmonary capillary wedge pressure (PCWP) in normal subjects.[81]

The most promising measurement for assessment of filling pressures is pulsed wave tissue Doppler echocardiography. This is easy to apply and is both sensitive and specific for detecting elevated or normal LVEDP regardless of EF.[83,84,96] These relationships have also been evaluated in sinus tachycardia, where the ratio of mitral E to annular E velocity (E/Ea) was the best correlate of PCWP irrespective of EF.[85] In the intensive care setting, E/Ea was a better predictor of PCWP than brain natriuretic peptide (BNP) levels.[97] Several studies have generated formulae that include various echocardiographic measurements to estimate filling pressure,[90,92] but these are not well understood and the calculations complex. As a result they are rarely applied in everyday clinical situations.

Doppler echocardiography provides an imprecise assessment of LV filling pressure and is dependent upon many other factors such as preload, afterload and heart rate. In most cases, however a comprehensive approach utilising several different measurements will provide a clinically useful estimate of filling pressure.

Systolic versus diastolic heart failure

It is widely believed that coronary artery disease is the underlying aetiology of HF in about two-thirds of patients.[101] However, this premise is based upon baseline data collected during large pharmacotherapy trials that selected patients on the basis of impaired LV systolic function and are therefore subject to selection bias. In contrast, many studies suggest that around 40 percent of patients with clinical HF have no discernable systolic dysfunction by echocardiography or ventriculography.[102] This group of patients with so-called “diastolic HF” are often described as having HF with preserved systolic function. This is probably a misnomer and a more appropriate description might be “HF with preserved LV EF” as subtle systolic dysfunction may be present but the assessment method lacks the sensitivity for detection. Methods such as strain-rate imaging, stress echocardiography and tissue Doppler imaging may prove to be particularly useful in this area, where crude measurements of EF fail.[17]

The ACC/AHA guidelines for diagnosing diastolic HF, or rather HF with preserved systolic function, do not currently advocate a role for diagnostic echocardiography beyond assessment of systolic function.[8] The European guidelines[9] recognise that echocardiography can assess diastolic function and refer to another European Society of Cardiology document for diagnostic criteria.[104] These criteria are cumbersome and not easily applied in clinical practice. Given the growing body of literature in support of diastolic filling and pressure assessment using Doppler echocardiography, this probably needs review. It is now possible to grade diastolic filling in the same way as systolic dysfunction and the grades of diastolic function have been shown to be related to outcome, independent of systolic function (see below).

The role of echocardiography for diagnosis of HF in primary care

Many primary care physicians rely upon clinical findings, sometimes with a chest x-ray or a trial of diuretic therapy to diagnose HF[105,106] and compared to hospital-based practice they utilise echocardiography less frequently to make their HF diagnosis of HF.[106] In a cross-sectional study performed in the United States, where 63% of HF patients in the community received an echocardiogram within three weeks of their symptomatic event, the patients who received an echo were less likely to be admitted to hospital, twice as likely to receive angiotensin converting enzyme

(ACE) inhibitors and had better five-year survival (adjusted for gender, age and NYHA class).[107] The group who were not referred to echo were older, had milder symptoms and were more likely to be female.

Many general practitioners feel access to echocardiography would improve their HF patient management,[105] despite there being no definitive data to support improved outcome with open-access echocardiography. In a recent review of five open access echo services in the United Kingdom it was found that 80% of the patients were referred with suspected HF, and approximately 20% of those patients had demonstrable systolic impairment.[108] However, open access echocardiography has not been rigorously trialled and the current supportive evidence is mostly anecdotal. Further, whilst it is easy to diagnose structural abnormalities or systolic impairment, it is more challenging to diagnose diastolic HF if one is to use the complex European Society of Cardiology Working Group guidelines.[104] In addition to providing confirmation of diagnosis, primary care physicians anticipate open access echocardiography will contribute to their treatment decisions, and while there are clear treatment guidelines for structural abnormalities and systolic dysfunction, the data are limited in diastolic HF.

Prognostic Value of Echocardiography in Heart Failure

Despite optimal medical therapy, mortality associated with congestive HF (HF) remains high.[2,3] One-year mortality rates after the first hospitalisation for HF are approximately 30-40%.[109] This prognosis is worse than many cancers.[110] Several clinical, functional and echocardiography parameters predict survival, including New York Heart Association (NYHA) classification[111], peak oxygen uptake[112,113] end-systolic volume,[114] EF,[112,115,116] creatinine clearance[117] and echo-Doppler indices of diastolic function.[78,96,118-147] Echocardiography may allow clinicians to determine which patents will fare worst, to identify those patients who may benefit the most from newer or more intensive treatments, or simply allow patients to better plan for their remaining years.

Heart size and systolic function

Simple m-mode measurements may be useful for determining prognosis.[116,139] In the Val-HeFT trial, patients with the largest LV internal diastolic dimension (LVIDd) ($\geq$ 7.5 cm) were twice as likely to die early as those with the smallest, but still dilated ventricles (< 6.3 cm).[116] The same was true for m-mode derived EF and those patients with the worst EF and largest LVIDd responded better to treatment. However, the difference between the first (EF $\geq$ 32 %) and fourth quartile (EF < 22%) was only 10 absolute points in EF. In such a large cohort of patients (N=5010) small differences in EF yielded important prognostic information, but current echocardiographic techniques are not accurate enough to detect such small differences in individual patients. In fact, in multivariate analyses, EF is often not an independent prognostic indicator.[148]

Patients with severely depressed systolic function do have poor prognosis and for every 10 % decline of EF below 45%, 4 year mortality increases approximately 10%. No effect is observed above 45 %.[115] In a small cohort of Framingham subjects who had HF at the time of study enrolment, patients with a normal EF (>50%) had better survival rates than those with EF < 50% but were still significantly worse than population controls.[149] Although survival may be better in patients with preserved EF, readmission rates are similar to those observed in patients with reduced EF[150] and once a patient is admitted to hospital for exacerbation of HF symptoms, there may be little difference in either death or readmission rates.[151] Subjective assessment of LV systolic function (i.e. normal/mild versus moderate/severe impairment) by a single experienced, cardiologist has been shown to predict death in an unselected group of patients.[21]

Atrioventricular plane displacement also predicts mortality in HF patients[152] and in patients with coronary artery disease with no or mild LV impairment where EF is not predictive.[153] Systolic annular velocity measured by TDI is a similar measurement to AVPD and also predicts death in a mixed cohort of patients, not specifically HF.[143] Thus, echocardiographic assessment of systolic function may aid prognostication in patients with HF, but may not provide a complete prognostic picture.

Diastolic measurements

There are now more than twenty-five studies evaluating the use of diastolic echocardiography measurements for predicting events in patients with heart failure. This collectively represents more than 5000 patients and over 1000 events (death or transplantation) (Table 2),[78,96,118-145] and more than twenty studies in patients after acute myocardial infarction (AMI).[146,147,154-174] The differentiation of restrictive filling patterns (high E:A ratio, short deceleration time) from non-restrictive patterns or short deceleration time in isolation provides important independent prognostic information in HF patients [78,96,118,120-126,128-131,133-137,139-142,144] and after myocardial infarction. [155-165,167-174] Short deceleration time is also a useful prognostic indicator in patients with AF.[129] When restrictive filling is further categorised into reversible (responsive to pharmacological preload reduction) and non-reversible (unresponsive) the latter is associated with worse outcome.[78,127,130,175] Further, patients who respond to preload manipulation also respond better to beta-blocker therapy.[175] Peak oxygen uptake (VO_{2max}) is also reduced in HF patients with restrictive filling[176] and the combination of both restrictive filling and reduced peak VO_{2max} provides additional prognostic information to either on their own.[139,141] Shortened isovolumic relaxation time is also associated with increased mortality.[138]

Although the relationship between restrictive filling and outcome has been studied extensively, further classification of patients with non-restrictive filling patterns is also important, but has not been studied extensively. Colour M-mode propagation velocity[156] and pulmonary venous Doppler[137] have been used to identify patients with elevated filling pressure and thus presumed pseudonormal filling and in both cases was related to prognosis. Identification of pseudonormal filling using preload reduction for prognosis in HF patients has not been investigated and may provide an easily applied clinical tool to identify patients at intermediate risk.

Other pulsed Doppler measurements such as the Tei or myocardial performance index also predict long-term outcome in both HF[177] and post myocardial infraction.[167] Data are emerging showing that tissue Doppler measurements are useful for predicting cardiac events. In HF patients, with impaired systolic function, the systolic annular velocity (Sa) predicts all cause mortality.[96] In a study of patients undergoing echocardiography, but not specifically with HF, Ea predicted death

over a mean of 23 months.[143] In another study, E/Ea > 15 added important prognostic information to clinical data and EF, by predicting death in patients post myocardial infarction in patients with reduced EF (<40%) and normal EF (>40%).[146] Even in asymptomatic subjects, advanced diastolic filling patterns have been shown to predict death.[178]

Table 2 - Echocardiographic assessment of diastolic function and prognosis

Study	Year	Study design Follow-Up	Aetiology	EF	N	Number of Events	Echo Endpoint	Event Free %
Pinamonti [120]	1993	Prospective 2 years	DCM: 100 %	25 %	79	4 deaths 10 Tx	Decel. Time ≤ 115 ms Decel. Time > 115 ms	79 100
Werner [122]	1994	Prospective 2.5 years	DCM:100 % EF < 50 %	33 %	57	15 deaths 4 Tx	Decel. Time ≤ 140 ms Decel. Time > 140 ms	97 77
Guannuzzi [125]	1996	Prospective 4 years	HF EF < 35 %	26 %	508	100 deaths	Decel. Time > 125 ms Decel. Time ≤ 125 ms	55 87
Rich [123]	1999	Prospective 1 year	HF Prior MI: 25%	16 > 45 % 23 < 45 %	39	8 deaths	Decel. Time > 160 ms Decel. Time < 160 ms	88 64
Hurrell [129]	1998	Retrospective 5 year	IHD: 60%	SR: 29 % AF: 39 %	367	120 deaths	Decel. Time ≤ 130 ms: AF Sinus rhythm	39 42
Bettencourt [134]	2000	Prospective 1.5 years	HF IHD: 53 %	34 %	139	39 deaths	Decel. Time ≤ 130 ms Decel. Time > 130 ms	80 43
Yong [140]	2001	Prospective Post-CABG 1 year	IHD: 100 %	28 %	40	5 deaths 3 Tx	Decel. Time ≤ 150 ms Decel. Time > 150 ms	63 95
Morales [141]	2002	Prospective 1 year	HF IHD: 35%	25 %	60	8 deaths 2 Tx 15 HF	Decel. Time > 165 Decel. Time 130-165 Decel. Time < 130	83 80 44
Temporelli [158]	2004	Prospective 4 years	IHD Post-MI	47 %	571	47 deaths	Decel. Time >130 ms Decel. Time ≤130 ms	93 80
Tabet [136]	2000	Prospective 1.5 years	HF IHD: 18 %	< 45 %	100	17 deaths 16 Tx	Decel. Time >145 ms Decel. Time ≤145 ms Non-Restrictive Restrictive	65 37 82 54
Xie [121]	1994	Prospective 1 year	HF IHD: 55 %	26 %	100	26 deaths	Non-Restrictive Restrictive	95 81
Nijland [155]	1997	Prospective 3 years	IHD: 100% Post MI	40-50%	95	10 deaths	Non-Restrictive Restrictive	100 22
Pozzoli [78]	1997	Prospective 1.5 years	HF EF < 35 %	23 %	173	41 deaths 9 Tx	Non-Restrictive Reversible Restrictive Non-Reversible Restrictive	94 81 49
Temporelli [130]	1998	Prospective 4 years	HF IHD: 76 %	22 %	144	37 deaths	Reversible Restrictive Non-Reversible Restrictive	89 63
Faris [142]	2002	Retrospective 5 years	DCM: 100%	FS 18%	337	74 deaths	Non-Restrictive Restrictive	80 61
Pinamonti [127]	1997	Prospective 4 years	DCM: 100%	25 %	110	28 deaths 13 Tx	Non-Restrictive Reversible Restrictive Non-Reversible Restrictive	97 96 13
Pozzoli [154]	1995	Prospective 1 year	Post MI	30 %	101	53 mixed	E:A Ratio: < 1 >1, NYHA I or II >1, NYHA III or IV	90 64 36
Dini [137]	2000	Prospective 15 months	IHD: 70 % EF< 45 %	31 %	145	29 deaths	Filling pattern: 1 2 3	91 67 66
Møller [156]	2000	Prospective 1 year	Post MI	54 %	121	33 deaths	Filling pattern: 0 1 2 3	100 87 52 35
Liu [144]	2003	Prospective Post CABG 2.5 years	IHD: 100%	53 %	102	19 mixed	Filling pattern: 0 1 2 3	92 83 75 58
Wang [143]	2003	Prospective 2 years	IHD: 16% HF: 18.5 % Normal: 32%	not reported	518	46 deaths	Sa: > 5 cm/s 3 - 5 cm/s < 3 cm/s Ea: > 5 cm/s 3 - 5 cm/s < 3 cm/s	98 91 72 99 91 75
Hillis [146]	2004	Prospective 2 years	IHD: 100 % Post MI	48 %	250	29 deaths	EF > 40: E/Ea < 15 E/Ea > 15 EF > 40: E/Ea < 15 E/Ea > 15	97 66 89 53
Florea [138]	2000	Prospective 3 years	HF IHD: 63 %	55 %	185	54 deaths	IVRT > 30 ms IVRT ≤ 30 ms	78 52
Møller [157]	2003	Prospective 2 years	IHD, post MI	46 %	314	46 deaths	LA volume < 32 ml/m^2 LA volume > 32 ml/m^2	95 70
Sabharwal [145]	2004	Prospective 5 years	HF IHD: 100 %	26 %	109	44 deaths	LA volume < 60 ml LA volume > 60 ml	85 55
Hansen [139]	2001	Prospective 3 years	HF IHD: 28 %	22 %	311	65 deaths	VO_{2max} ≤ 14 ml/min/kg: RFP Non-restrictive VO_{2max} >14 ml/min/kg: RFP Restrictive	52 80 80 94

Abbreviations: CABG = coronary artery bypass grafting, DCM = dilated cardiomyopathy, Decel. time = deceleration time of passive mitral filling velocity (E), Ea = early mitral annular tissue Doppler velocity, EF = ejection fraction, HF = heart failure, IHD = ischaemic heart disease, IVRT = isovolumic relaxation time, LA = left atrium, MI = myocardial infarction, NYHA = New York Heart Association class, RFP = restrictive filling pattern, Sa = systolic mitral annular tissue Doppler velocity, Tx = cardiac transplantation, VO_{2max} = peak maximum oxygen uptake.

Beyond left ventricular function

When assessing patients with HF and LV dysfunction, the evaluation of right ventricular function may add further prognostic information[179-182] and thus should be considered. Both mitral and tricuspid regurgitation are commonly found in the presence of HF[1] and LV systolic dysfunction. Long-term survival in HF is predicted by worsening atrioventricular valve regurgitation.[183] Mitral regurgitation has been shown to be prognostically important in both ischaemic[184] and non-ischaemic HF.[185]

LA volume is a powerful predictor of mortality after myocardial infarction, providing additional information to clinical variables, systolic and diastolic function[157] and has recently been shown to predict mortality in ischemic HF patients with depressed systolic function.[145] In this study, many of the diastolic echo parameters predicted mortality, but in multivariate analyses, LA volume was the only independent predictor of death.

The Role of Echocardiography in Heart Failure Management

Echocardiography is often used by clinicians to guide their clinical management of HF patients and for both patient and physician reassurance. Typically, clinicians refer HF patients for echocardiography to assess LV function and often request quantification of systolic function. This approach may be too narrowly focussed and thus may not provide optimal management.

Ejection fraction is not the diagnosis

Many of the contemporary medical therapies have only been tested and shown to be beneficial in clinical trials in patients with EF < 35 - 40%, including ACE-inhibitors,[186-191] beta-blockers[192] and spironolactone.[193] Because many treatments have only been extensively proven in patients with low EF, echocardiography is often used to determine the indication for many HF therapies. Whilst the efficacy of many treatments in patients with higher EF remains uncertain, EF appears to have replaced HF as the treatment goal. Many clinicians have become focused on the need to quantify EF before initiating treatment. However, current ehcocardiographic techniques may not be precise enough to accurately determine the EF. Further, using arbitrary cut-off values of EF for

deremining the systolic dysfunction do not reflect the inherent variability of such measurements - neither the within patient, nor between days, nor observer measurement variability.

Echocardiography guidance for device implantation

Echocardiography is used to guide physicians' use of devices such as implantable defibrillators or biventricular pacemakers. Implantable defibrillators have been shown to reduce mortality in patients with HF due to coronary heart disease and severe systolic dysfunction (EF <30-40%).[198-200] However, these devices have only been trialled and shown to be beneficial in patients with EF below 30-40% and are thus only recommended in those subjects with advanced systolic impairment.[198,199]

Cardiac resynchronisation using biventricular pacemakers is indicated in HF patients with severely depressed LV systolic function and left bundle branch block (wide QRS complex) and significantly improves LV function, reduces LV volumes and the degree of mitral regurgitation.[201,202] The recently published COMPANION study in patients with advanced HF and severe LV impairment, showed a beneficial effect upon death and hospitalisation for biventricular pacing, with and without the addition of an implantable defibrillator, over optimal medical management.[200] Echocardiography has been used to demonstrate the improvement in LV systolic function with biventricular pacing and also its reversal with cessation of pacing.[201] Simultaneous right and left ventricular chamber pacing overcomes the dyssynchrony of the ventricles. Tissue Doppler techniques may be useful to document dyssynchrony prior to pacemaker implantation by measuring the timing of events in the right and left ventricles and also to demonstrate the correction of timing abnormalities with biventricular pacing.[201,202-204] Further, echocardiography measures, including tissue Doppler[204] and the duration of mitral regurgitation and dP/dT of the upstroke of the mitral regurgitation[205] can be used to predict those patients who will benefit most from biventricular pacing.

Summary

Echocardiography can play an important role in the management of patients with HF for diagnosis, prognosis and to assist medical management. Ejection fraction, a measure of systolic ventricular function is the most commonly used echocardiographic measurement but is often not measured precisely, if at all. Assessment of diastolic function has become a very important role of echocardiography in patients with HF, especially given the large numbers of patients in whom systolic function appears within normal limits. Unfortunately, current guidelines and methods make interpretation of diastolic measurements difficult.

For both diastolic and systolic measurements, current echocardiographic techniques are highly accurate when differentiating severe dysfunction from normal or very mildly impaired function. But, it is the intermediate phases of dysfunction where current echocardiographic methods may lack precision and require refinement.

Echocardiography has much to offer the HF physician beyond simple diagnosis and identification of pathology. But in order for echocardiography to be used optimally, the assessment of cardiac function needs to be precise and reproducible. These methods should also display excellent diagnostic sensitivity, add independent prognostic value and be widely available in a wide variety of patients and clinical settings.

Objectives

This thesis will investigate the role of contemporary echocardiography in patients with HF both for establishing diagnosis and aetiology, but also for providing prognostic information and to assist management. Specifically, optimisation of both systolic and diastolic measurements using contemporary methodology will be investigated, with specific reference to reproducibility and diagnostic accuracy. Secondly, the role of echocardiography for prognostic purposes will be evaluated in a group of patients with established HF. Thirdly, a meta-analysis of the diastolic filling pattern for predicting mortality and development of HF in patients with established HF and patients suffering acute myocardial infarction will be undertaken. Lastly, the role of echocardiography for

diagnosis of HF and prognosis of symptomatic patients in the community will be evaluated and compared to brain natriuretic peptide.

Key Points:

- Heart failure, which is increasing in prevalence, is associated with significant mortality and morbidity and is a leading cause of cardiovascular morbidity, hospitalisation and death
- Echocardiography can provide essential information for physician management of heart failure patients by providing important aetiological and diagnostic information
- Echocardiography may also assist with prognosis in patients with heart failure
- Echocardiography in patients with HF should be comprehensive and extend beyond the assessment of LV systolic function
- Assessment of diastolic filling should be considered in all patients with high clinical suspicion of HF and those patients with established systolic impairment
- Current echocardiographic techniques lack the precision required for repeat assessment of systolic function in individual patients

Chapter 2 - Quantification of Left Ventricular Function in Heart Failure - Effects of Measurement Variability

In order to maximise the diagnostic and prognostic benefits of echocardiographic LV volumes and ejection fraction (EF), the measurements must be accurate, reproducible and free of bias to accurately detect clinically relevant changes. Reproducibility is often considered in three parts: intra-observer variability, inter-observer variability and test-retest variability. Each of these are sequentially dependent and as a result test-retest variability poses the largest challenge in clinical medicine. Measurement reproducibility is the sole determinant of the smallest change that repeat examinations can detect and it depends upon several factors including the patient, sonographer, ultrasound equipment, image acquisition, storage techniques, image analysis and interpretation.

Many laboratories recognise the need to establish measurement consistency within individual sonographers or readers (intra-observer reproducibility) and between different readers (inter-observer reproducibility), it is perhaps even more important to determine the reproducibility of measurements obtained on two completely different days (test-retest reproducibility). Whilst it is common for studies to report either intra-observer or inter-observer variability for EF measurements[28,47] it is rare to report test-retest variability. Test-retest reproducibility best mimics the true clinical setting – it is often months, perhaps even years between follow-up visits and measurement reliability becomes a crucial issue. In HF patients clinical status may change frequently, thus it is imperative that the test-retest reproducibility of echocardiographic measurements be sufficient to detect small but clinically important changes. Because the causes and sources of measurement variability are different for systolic and diastolic measurements different techniques need to be employed to minimise measurement variability in each case.

During the last decade, ultrasound imaging has undergone a rapid transformation: the introduction of broadband transducer technology, digital beam formers, enhanced digital processing and storage of images, harmonic imaging and myocardial Doppler techniques. Thus, it may be inappropriate to compare the accuracy of echocardiography a few years ago with the imaging in modern laboratories.

Many new techniques are evaluated and tested in healthy controls prior to routine introduction into clinical practice, but such techniques are often not tested in the patient groups in whom the test is

intended for and thus most likely to be beneficial and used. Therefore, the primary aim of this research was to evaluate new methods of assessing both systolic and diastolic function in a cohort of patients with HF and a comparison group of healthy controls.

Part A - Systolic Function

Background

Two-dimensional (2D) echo has been used successfully as an endpoint in many HF trials to detect small changes in EF in groups of patients[190,206,207] and is often used as a threshold for the initiation of pharmacotherapy.[208,209] In addition, systolic parameters such as LV end-systolic volume (LVESV),[114] EF,[111,112,210] and change in EF[111,211,212] are important prognostic indicators in HF. As is the echo-derived wall motion score index (WMSI)[24,213,214] which is also closely correlated with EF.[24,215]

While echocardiography has been used in groups of patients, it remains relatively insensitive for detecting changes in EF in individual patients. 2D echo measurements of EF are variable, lack precision and have inferior reproducibility when compared to magnetic resonance imaging (MRI).[216] At best it is possible to differentiate a difference of 10% in EF, but more commonly only gross differences are discernable. As a result, quantitative 2D echo techniques are often regarded as time-consuming and unreliable, principally because of the manual identification and tracing of the endocardial-blood boundary involved, which is both observer-dependent and affected by image quality. Image quality is determined by machine performance, patient factors, and sonographer experience.

Current echo techniques for measuring EF and WMSI are hampered by poor endocardial definition in patients with HF, who often have dilated ventricles with displaced apices, making visualisation of all wall segments even more difficult. Thus, if echocardiography is to be routinely applied to patients to assess systolic function, it needs to be highly accurate and reproducible in order to detect small changes.

Modern digital ultrasound machines have improved image resolution and better depth penetration, resulting in superior gray scale B-mode images, even in patients with very large hearts. In addition, both tissue harmonic imaging (THI)[28-35] and LV opacification (LVO) using new transpulmonary contrast agents [36-47] improve endocardial visualisation and improve the diagnostic capability of echo [42,45,217,225] by increasing the number of segments seen and also enhancing the overall quality of the endocardial visualisation and are now widely advocated for use in patients with sub-optimal images. These methods may also increase the number of patients in whom quantitative echocardiography may be performed.

Improved intra-observer and inter-observer variability with THI [28] and contrast LVO [47] has been reported, but no studies have specifically targeted patients with HF. Furthermore, no studies have evaluated the test-retest reproducibility of these methods, which is potentially the most important parameter when considering the usefulness of a test for follow-up or monitoring of patients over time.

Most of the studies that investigated the role of LVO for endocardial definition were performed in patients with ischaemic heart disease. The enhanced endocardial visualisation observed in other patient groups may not necessarily be the same in patients with HF, who often have enlarged hearts and abnormal geometry, both of which may contribute to non-uniform endocardial visualisation, since regional differences in visualisation with fundamental imaging, as well as with harmonic imaging and contrast LVO[29,34] has been demonstrated in other patient groups. Further, it has been suggested that LVO may not be as efficacious in patients with low cardiac output.[48]

The ACC/AHA guidelines for management of HF advocate repeat measurement of EF where a change in clinical status has occurred that might have an effect on cardiac function.[8] This is based upon expert opinion rather than objective evidence. This viewpoint probably arises from the clinical trial data showing a beneficial effect upon LV remodelling and EF with many contemporary HF treatments such as ACE-inhibitors[206,218,219] and beta-blockers.[26,207,220-223]

In the acute coronary syndrome setting, the benefit of repeat echocardiography has been established. In a very large study (N = 756), those patients in whom LV volume increased or EF decreased within three months of their acute event were more likely to experience recurrent myocardial infarction or develop HF, but only when measurements were made by the centralised core laboratory - when the individual sites' measurements were considered, no prognostic benefits were observed.[224] Thus, it would appear that in the usual clinical setting determination of systolic function by repeat echocardiography in all patients would not be clinically useful.

If endocardial visualisation with LVO and harmonics imaging is improved in HF patients and this leads to improved assessment of systolic function, in particular more precise, unbiased and reproducible EF measurements and better assessment of regional wall motion, this would potentially have important and widespread implications for the management of HF patients.

Aims

To evaluate the role of both harmonic imaging and contrast for improving endocardial visualisation and assessment of systolic function. Specifically, to determine whether the improvement in endocardial visualisation is uniformly distributed throughout the LV cavity and whether the determination of WMSI is affected by echo technique and to subsequently determine whether the improved endocardial visualisation impacted upon the intra-observer, inter-observer, and test-retest variability and reproducibility associated with volume and EF measurements.

Methods

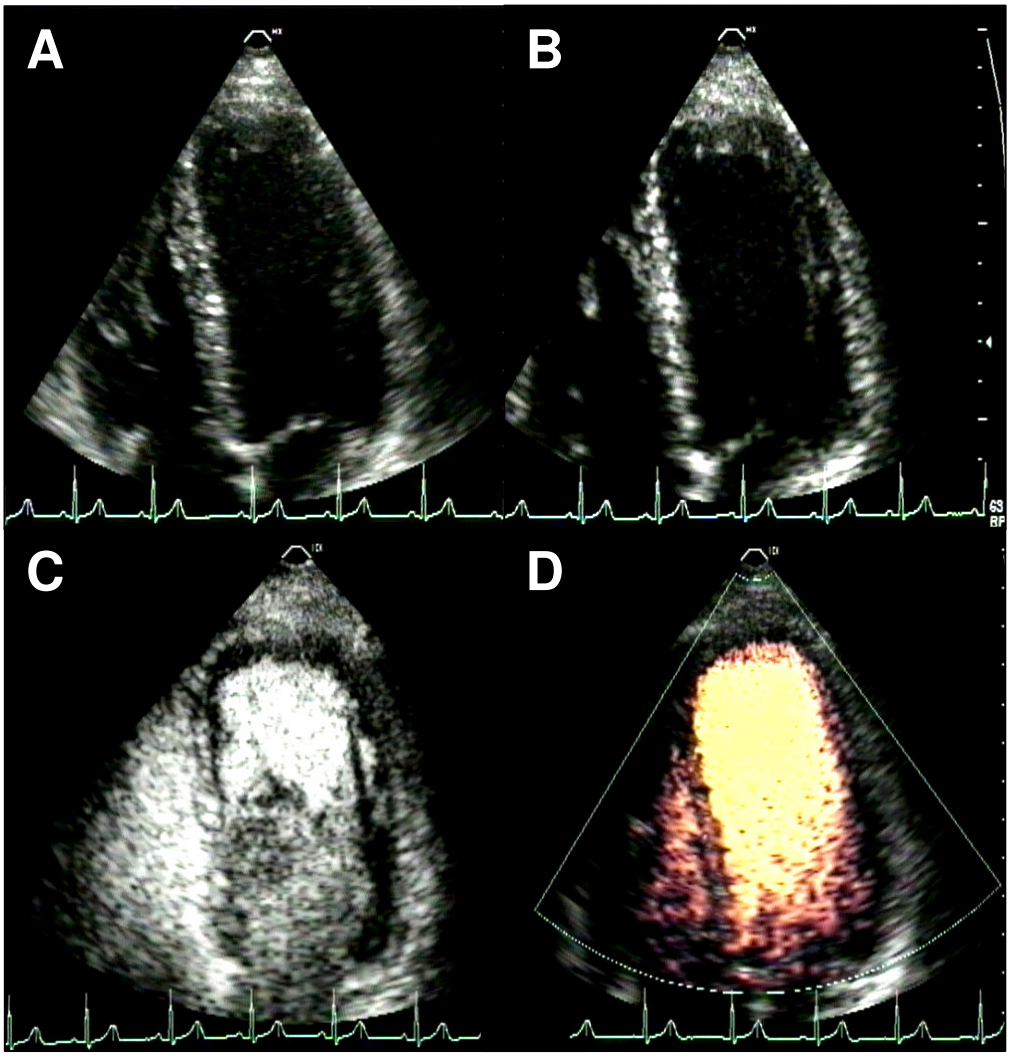
Subjects

Thirty-one subjects with chronic HF and 30 healthy volunteers, who were not selected on the basis of echo quality, were studied. HF patients were clinically stable with NYHA class II symptoms at the time of the study, all had at least one prior hospital admission for exacerbation of HF symptoms. The healthy volunteers were free of clinical cardiovascular disease at the time of the examination and completed a health questionnaire, physical examination and an electrocardiograph (ECG) performed, prior to commencing the study. All subjects provided written informed consent and the study was approved by the Auckland Ethics Committee. All subjects underwent the same echo protocol on two different days (at least 1 day apart, median 7 days, range 2 -10 days).

Study Imaging Protocol

All subjects were examined lying on their left side and images were obtained by an experienced research ultrasonographer according to a standard protocol using the same ultrasound machine (ATL HDI-3000 or HDI-5000, ATL Ultrasound, Bothell, WA). Standard diagnostic echo views were obtained in five thoracic windows and recorded onto super-VHS videotape and digitally acquired. All analyses were performed off-line (Nova Microsonics/Kodak Eastman, Mahwah, NJ). Apical four and two chamber views were optimised: depth was set to maximise the LV chamber on the screen, eliminating most of the left atrial chamber from view, and the focus placed in the mid cavity level. Two ECG triggers were set: at end-diastole (on the R wave) and at end-systole (the smallest LV cavity volume). Six to ten beats for each view were obtained under each condition and in the same order for each subject: 1) fundamental imaging; 2) harmonic imaging (factory tissue harmonics settings); 3) harmonic imaging with Levovist®; 4) dual triggered Power Doppler with Levovist®.(Figure 3)

Figure 3 - Apical four chamber view at end-diastole by four methods



A = Real-time fundamental grey scale imaging, B = Real-time harmonic grey scale imaging, C = Real-time harmonic imaging with contrast injection, D = Dual-triggered power Doppler imaging with contrast injection.

Contrast protocol

The ultrasound machine was set to the factory settings for Levovist®. Grey scale images were obtained using contrast specific harmonics machine settings (mechanical index 1.2, frame rate medium) and recorded in real-time. These settings were considered standard at the time of this study and were recommended by both the ultrasound machine manufacturer and the comntrast manufacturer. Intravenous access was obtained via a cannula in the subjects' right arm. A three-way tap was put in place and the line flushed with saline. Levovist® (Schering NZ Ltd) is an air based contrast agent composed of galactose (99.9%) and palmitic acid (0.01%). Contrast was prepared according to the manufacturer's instructions (4g, in solution 400 mg/ml) and given as a bolus followed by a 0.9% saline flush. Six to ten cardiac cycles of the four and two chamber views were recorded onto videotape and then immediately repeated using with power Doppler (mechanical index 1.3, PRF 2000, wall filter high) and dual ECG triggering on every cardiac cycle.

Contrast performance – degree of opacification

LV cavity opacification was graded for both the apical four and two chamber view at end-diastole and end-systole according to the following criteria: 0 = no contrast seen in the cavity; 1 = partial opacification of the cavity; 2 = full opacification, but not uniformly dense throughout cavity; 3 = full chamber opacification with uniformly dense opacification. The time taken from initial appearance of contrast in the right ventricle (RV) until first appearance in the LV was recorded as a measure of pulmonary transit time (PTT).

Endocardial visualisation

The twelve segments seen in the apical four and two chamber views were graded for visualisation: 0 = not visible, 1 = barely visible, 2 = well visualised. The grading was performed by reviewing the videotapes, in random order by one observer (GW) without knowledge of the results of the other methods or any clinical details.

Left ventricular volume measurements

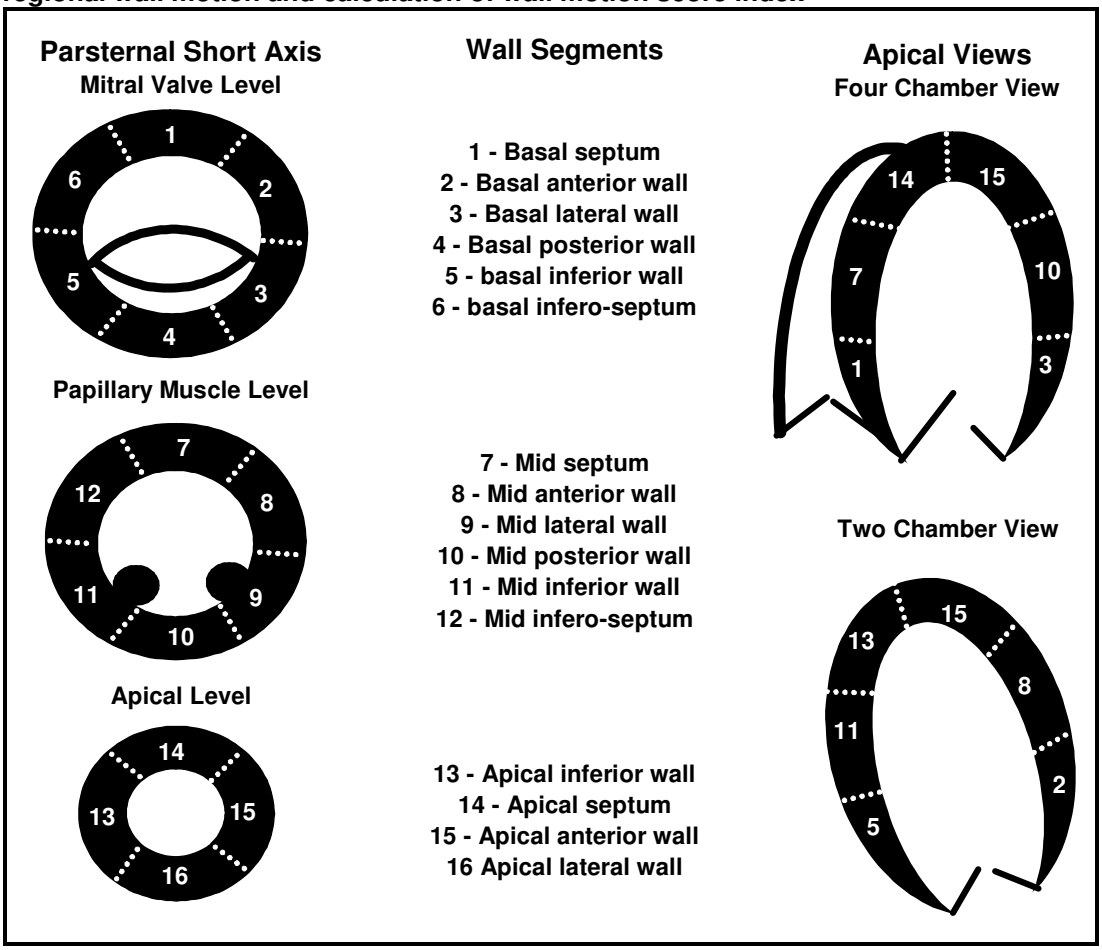
LV volumes were calculated according the modified Simpson's biplane method using the apical four and two chamber views. The endocardial borders were manually traced at end-diastole (the

largest LV area just prior to the QRS wave) and end-systole (the smallest LV area close to the end of the T wave) for three different cardiac cycles. The papillary muscles were included in the blood volume.[11] One observer (GW) measured all volumes on both visits and repeated measurements on visit one only. A second observer (RD) measured all volumes on visit one only. All measurements were made in random order, without any knowledge of previous measurements or clinical details. LV volumes were measured when a minimum of ten segments were visualised.

Left ventricular wall motion scoring

Only segments visible in the apical four and two chamber views were scored (Figure 4). One observer scored each of the twelve segments in random order according to ASE guidelines (1=normal, 2=hypokinetic, 3 =akinetic, 4=dyskinetic, 5=aneurysmal).[11] Wall motion was scored under three different imaging modalities: fundamental, second harmonic imaging and contrast + harmonic imaging. It was not possible to blind the observer to the imaging modality or LV function, although the observer was unaware of the identity, clinical details and other echo measurements of all subjects.

Figure 4 - American Society of Echocardiography twelve segment model for analysis of regional wall motion and calculation of wall motion score index



Note: Only the apical segments (right) were used for this analysis

Statistics

Least squares regression was used to look at effects across all three groups and Student's T-test was used to determine significance of pair wise comparisons. Significance was maintained at p=0.05 throughout the analysis. Two way analysis of variance (ANOVA), with Tukey's post hoc analysis was used to compare the proportions of segments visualised (not visualised, barely visualised, well-visualised) by each method and the differences between HF patients and control subjects. Segments were grouped according to anatomical position (anterior, inferior, posterior, septal, basal, mid and apical walls) and further two-way ANOVA performed. Wilcoxon non-parametric analysis of variance was used to compare the relationship between EF and WMSI by each echo method.

Bias was assessed by comparing the mean values obtained by each method for each echo parameter and comparing the measurement difference in relation to the mean measurement,

according to the Bland-Altman method. Reproducibility was assessed by the mean difference and confidence interval (limits of agreement) for each method and coefficient of variation, calculated as the standard deviation of the difference divided by √2 expressed as a percentage of the mean for that measurement. Least squares regression was used to look at effects across all four groups and Student's t-test was used to determine significance of pair wise comparisons. Significance was maintained at p=0.05 throughout the analysis. All analysis was carried out for the whole group and separately (HF and control subjects).

Results

Subjects

The HF patients were clinically stable (87% in NYHA class I or II), with mixed etiology of HF (39% hypertension, 19%, revascularisation, 23% diabetes). There were more men than women (24:7) and 25% were in atrial fibrillation. Patients were receiving standard HF treatment including ACE-inhibitors (94%) and diuretics (97%)(Table 3). Few patients in this cohort were receiving beta-blockers because the study was performed prior to the publication and dissemination of the large beta-blocker HF trials.

Table 3 - Baseline clinical characteristics and medications in patients with heart failure

Clinical Details	
Diabetes	7 (23 %)
Hypertension	12 (39 %)
Prior revascularization	6 (19 %)
Permanent pacemaker	1 (3 %)
Atrial fibrillation	8 (26 %)
NYHA class I/II/III/IV	8/19/4/0
Heart rate (bpm)	71.0 ± 9.3
Systolic BP (mmHg)	127.1 ± 18.2
Diastolic BP (mmHg)	73.9 ± 11.4
Creatinine (mmol/l)	0.14 ± 0.05
Medications	
ACE-inhibitors	29 (94 %)
Warfarin	8 (26 %)
Beta-blockers	1 (3 %)
Calcium antagonists	11 (36 %)
Diuretics	30 (97 %)
Digoxin	6 (19 %)
Amiodarone	7 (23 %)

Values shown are mean ± standard deviation or numbers of patients (%)
Abbreviations: BP = blood pressure, JVP = jugular venous pressure, NYHA = New York Heart Association functional class, ACE = angiotensin converting enzyme.

The HF patients were older, but there were no differences between the groups in gender distribution, current smoking rates, height, weight or body surface area. The HF patients had larger LV end-diastolic volume (LVEDV) and LV end-systolic volume (LVESV), larger left atrial area, lower EF and higher WMSI (Table 4).

Table 4 - Baseline demographics and echocardiography measurements in HF patients and healthy controls

	Heart failure Patients	Healthy Controls	t-test
Number of subjects	31	30	
Age (years)	76.7 ± 7.0	37.6 ± 13.8	p < 0.01
% male	77	59	p = 0.12
% current smokers	13	10	p = 0.76
Height (cm)	165.4 ± 7.4	170.5 ± 6.6	p = 0.05
Weight (kg)	74.2 ± 14.2	73.0 ± 9.8	p = 0.44
BSA (m^2)	1.81 ± 0.18	1.85 ± 0.13	p = 0.74
LV end-diastolic volume (ml)	164.7 ± 93.9	95.9 ± 15.7	p < 0.0001
LV end-systolic volume (ml)	100.3 ± 78.1	33.0 ± 8.8	p < 0.0001
2D stroke volume (ml)	64.4 ± 20.7	63.0 ± 9.9	ns
2D ejection fraction (%)	45.4 ± 14.4	66.0 ± 5.8	p < 0.0001
Wall motion score index	1.85 ± 0.63	1.05 ± 0.14	p < 0.0001
Left atrial diameter (cm)	4.29 ± 0.68	3.84 ± 6.45	p < 0.001
LV end-diastolic dimension (cm)	6.65 ± 1.03	5.58 ± 0.56	p < 0.001
LV end-systolic dimension (cm)	5.15 ±1.25	3.79 ± 0.63	p < 0.001

Values are mean ± standard deviation, Student's t-test (unpaired, two way) to test difference between the group means.

Left ventricular opacification

Contrast performance was different between the two groups: opacification was consistently lower quality in the HF patients and pulmonary transit time (PTT) was prolonged in the HF patients (Table 5). PTT was positively correlated with LVEDV (r=0.29, p=0.03), LVESV (r=0.32, p=0.01) and negatively correlated with EF (r-0.32, p=0.02) and opacification grade (4-chamber systole: r=-0.38, p=0.003, 4-chamber diastole: r=-0.23, p=0.8, 2-chamber systole: r=-0.24, p=0.07, 2-chamber diastole: r=-0.32, p=0.01). PTT was not related to NYHA functional class (p=0.91) or heart rate (r = -0.25, p=0.17) but there was a trend towards correlation with the level of jugular venous pressure (JVP) (r=0.33, p=0.07).

Table 5 - Contrast performance in heart failure patients and healthy controls

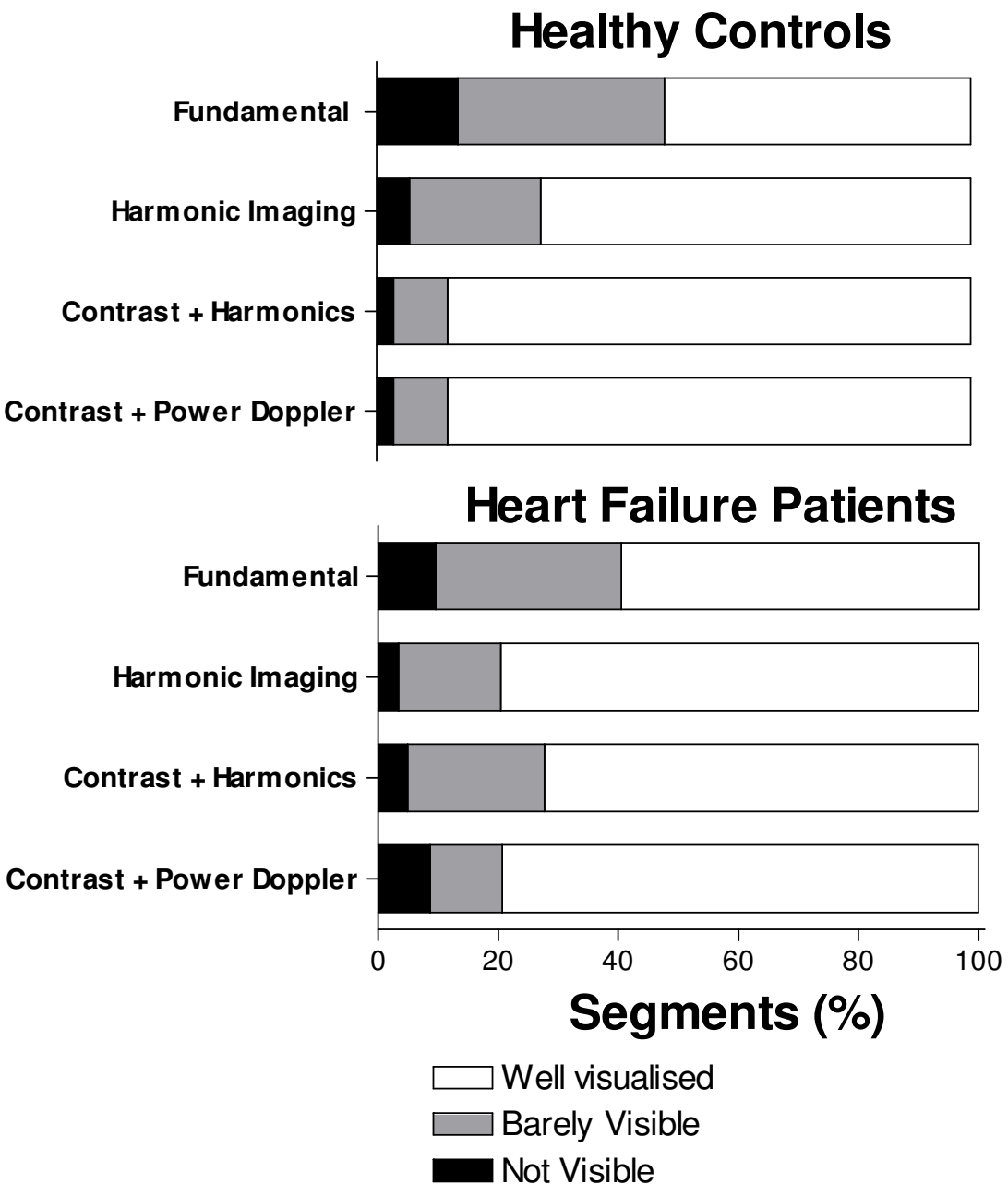
Contrast Performance	Heart Failure Patients	Control Subjects	
Opacification Grade (0-3)			t-test
4-chamber diastole	1.5 ± 0.76	1.9 ± 1.08	p = 0.13
4-chamber systole	2.4 ± 0.67	2.8 ± 0.51	p = 0.02
2-chamber diastole	1.4 ± 0.83	1.8 ± 1.04	p = 0.06
2-chamber systole	2.4 ± 0.67	2.6 ± 0.56	p = 0.25
Pulmonary transit time (s)	7.6 ± 2.2	5.9 ± 0.97	p = 0.0006

Values shown are mean ± standard deviation or numbers of patients. P value is Student's t-test (two-tailed). Contrast performance was measured on a scale of 0-4: 0 = no contrast visible in the LV cavity; 1 = partial opacification of the LV cavity; 2 = full, but not uniformly dense opacification; 3 = full and uniformly dense cavity opacification.

Endocardial Visualisation

Endocardial visualisation with fundamental imaging was good at baseline and there was a consistent improvement in the number segments either visualised or well visualised with THI in both groups (Figure 5). In the controls, there was an additional benefit of LVO, but no further benefit using LVO triggered power Doppler imaging. However, in the HF patients, no further improvement in endocardial visualisation was seen with LVO, either used alone with THI or in conjunction with triggered power Doppler imaging.

Figure 5 - Endocardial visualisation by four echocardiographic methods in heart failure patients and healthy controls



Using two-way ANOVA, there was a significant difference in wall visualisation between the three methods (p=0.0021) and between HF patients and control subjects (p=0.03) but no interaction between the methods and subject category (p=0.76) (Table 6). In the healthy control group, wall definition was subjectively improved with both THI and contrast LVO imaging. The number of segments not visualised dropped from 49 (13.6%) with fundamental imaging to 20 (5.6%) with THI and further reduced to 10 (2.8%) with contrast LVO (overall, Tukey's post hoc p=0.01). In the HF patients, endocardial visualisation improved with THI, but no further improvement was seen with contrast LVO. In the HF patients, 36 (9.7%) segments were not visualised with fundamental imaging, this was reduced to 13 (3.5%) segments with THI, but when contrast LVO was used, the number of non-visualised segments increased to 18 (4.8%) (p=0.06).

Table 6 - Endocardial visualisation in HF patients (n=31) and healthy controls (n=30)

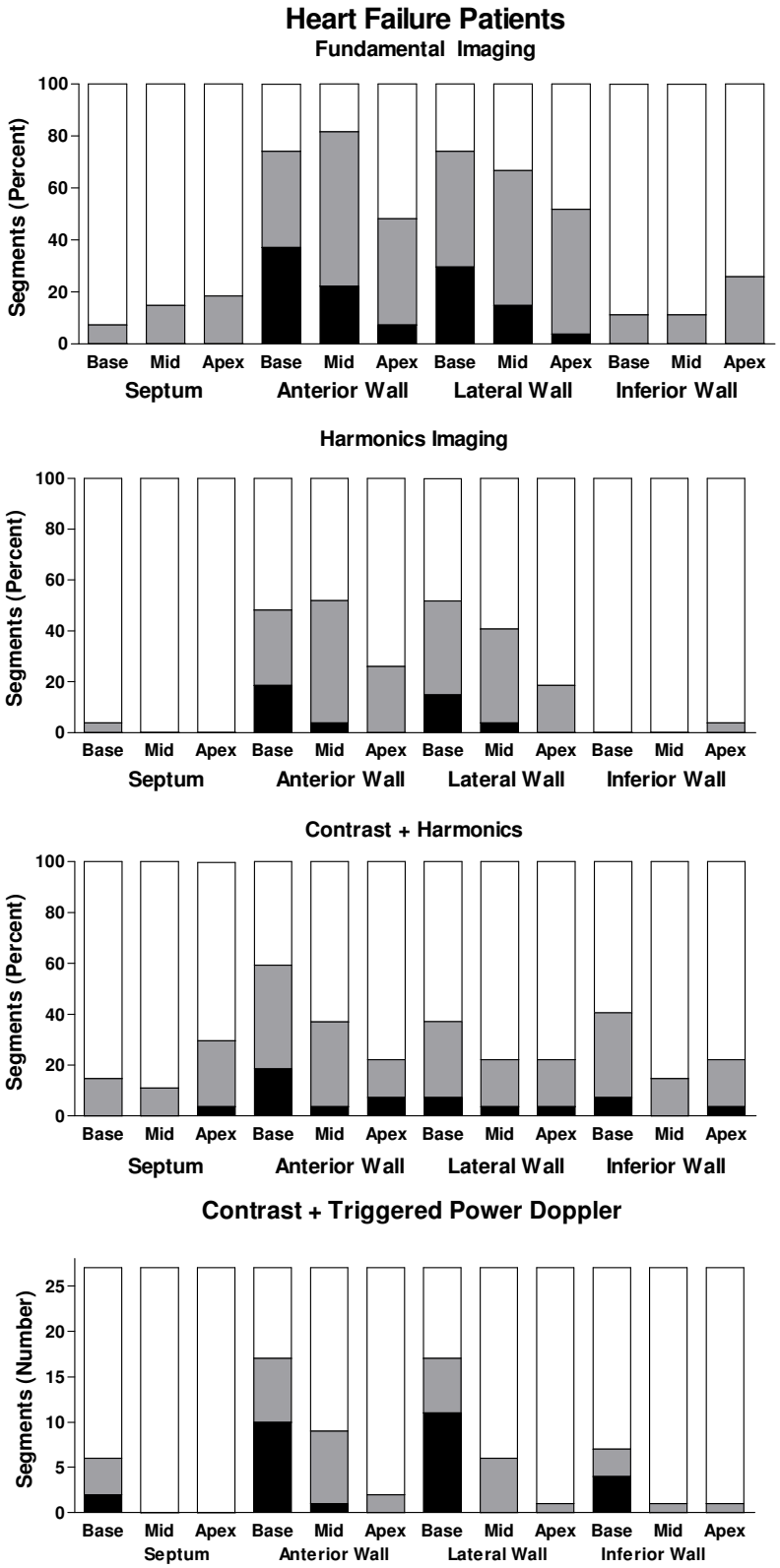
	Number of segments (%)		
Method	**Not Visible**	**Barely Visible**	**Well-Visualised**
Control subjects (30 subjects, 360 wall segments)			
Fundamental	49 (13.6 %)	125 (34.7 %)	186 (51.7 %)
Harmonic Imaging	20 (5.6 %)	80 (22.2 %)	260 (72.2 %)
Contrast + Harmonics	10 (2.8 %)	33 (9.2 %)	317 (88 %)
Contrast + Power Doppler	30 (8.3 %)	17 (4.7 %)	313 (86.9 %)
Column effect:	p = 0.001*	P < 0.0001**	p < 0.0001***
Heart Failure Patients (31 subjects, 372 wall segments)			
Fundamental	36 (9.7 %)	115 (30.9 %)	221 (59.4 %)
Harmonic Imaging	13 (3.5 %)	63 (16.9 %)	296 (79.6 %)
Contrast + Harmonics	18 (4.8 %)	85 (22.9 %)	269 (72.3 %)
Contrast + Power Doppler	32 (8.6 %)	45 (12.1 %)	295 (79.3 %)
Column effect:	p = 0.0013 †	P < 0.0001 ††	p < 0.0001 †††

Overall effect HF v controls, p = 0.018
* fundamental different to harmonic and contrast; harmonic different to contrast; no difference contrast v power; ** fundamental different to harmonic and contrast; harmonic different to contrast; no difference contrast v power; *** fundamental different to harmonic and contrast; harmonic different to contrast; no difference contrast v power; † fundamental different to harmonic and contrast; no difference fundamental v power, no difference harmonic v contrast; †† fundamental different to all others; harmonic different to contrast; no difference harmonic v power; contrast different to power; ††† fundamental different to all others; harmonic different to contrast; no difference harmonic v power; contrast different to power.

Regional differences in endocardial visualization

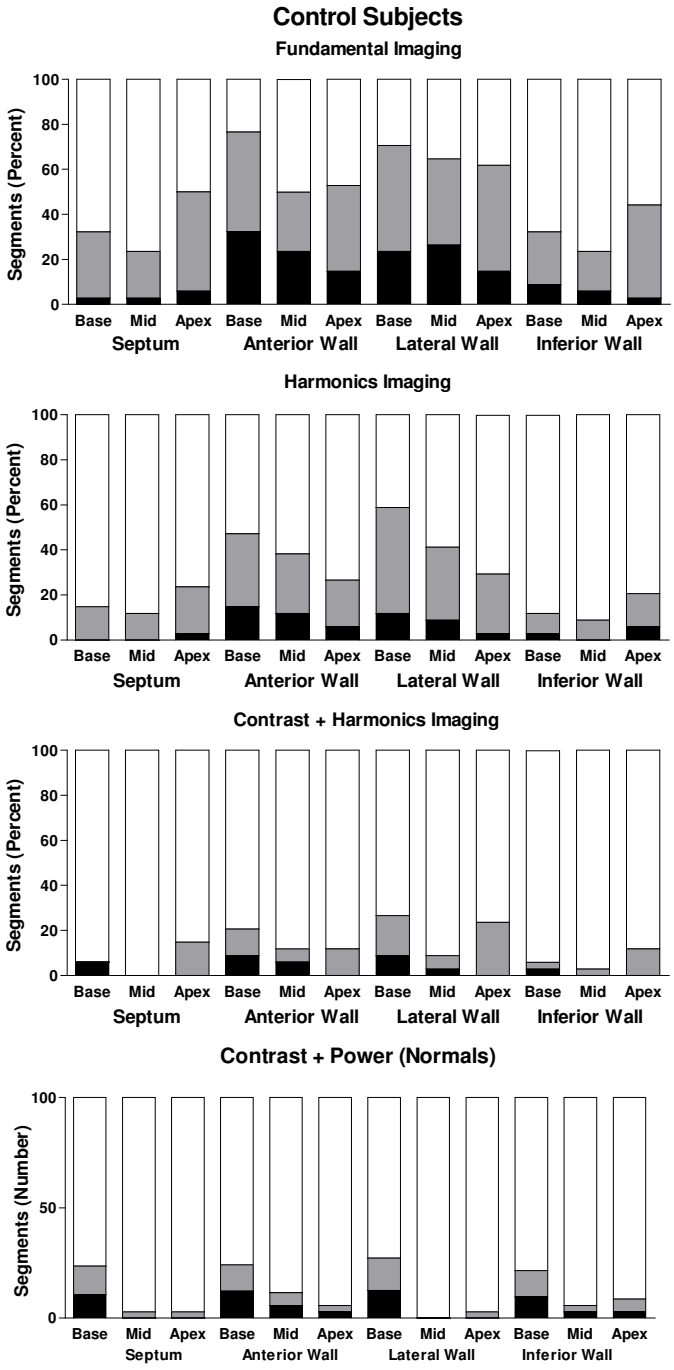
There were regional differences in endocardial visualisation in both groups with fundamental imaging and the other echo methods (Figure 6, Figure 7). The anterior and lateral walls were the least well visualised with fundamental imaging but improved with THI and contrast LVO (anterior: $p=0.0026$, lateral: $p=0.0003$). There was no effect upon endocardial visualisation associated with the different echo methods in either the inferior or septal walls (inferior: $p=0.30$, septal: $p=0.20$). There was also a depth-related decline in endocardial definition, with progressive deterioration from the apex to the base of the heart. Endocardial definition was improved by the different echo methods in all three regions: base ($p=0.0007$), mid ($p<0.0001$) and apex ($p=0.04$). Comparing the HF patients with the control subjects, endocardial definition was improved in the anterior ($p=0.04$) and lateral walls ($p=0.03$), but not in the inferior ($p=0.40$) and septal walls ($p=0.50$). HF patients had worse basal visualisation by any method ($p=0.001$) but similar mid ($p=0.50$) and apical ($p=0.80$) visualisation as the control subjects.

Figure 6 - Regional endocardial visualisation by four echo methods in heart failure patients



Legend: black bar = not visible, grey bar = barely visible, white bar = well visualised

Figure 7 - Regional endocardial visualisation by four echo methods in control subjects



Legend: black bar = not visible, grey bar = barely visible, white bar = well visualised

Left ventricular volume measurements

In both groups, LV volume and EF measurements were similar using either THI or fundamental imaging. However, in the control subjects real-time LVO with THI resulted in larger LVEDV but similar LVESV and higher EF. LVO with triggered Power Doppler imaging resulted in smaller (similar to the non-contrast) LVEDV but larger LVESV and hence, lower EF. In the HF patients, both the LVEDV and LVESV were smallest with LVO and triggered Power Doppler, and although the EF was closer to the non-contrast values, it was still significantly different to that measured with THI (Table 7).

Table 7 - Left ventricular volume measurements (Simpson's biplane method) obtained with four different imaging modalities in patients with heart failure and control subjects

	Fundamental Imaging	Harmonic Imaging	Contrast + Harmonics	Contrast + Power Doppler
Heart Failure Patients:				
End-diastolic volume (ml)	164.3 ± 89.0	161.9 ± 92.7	177.3 ± 101.0 †	151.2 ± 72.2 #
End-systolic volume (ml)	103.5 ± 79.6	99.8 ± 79.4	104.8 ± 85.3	96.0 ± 66.3
Stroke Volume (ml)	60.7 ± 17.9	62.1 ± 19.4	72.5 ± 25.9 †	55.2 ± 17.4 *
Ejection fraction (%)	43.3 ± 14.4	44.9 ± 14.1	47.7 ± 15.8 †	41.9 ± 15.7 *
Control subjects:				
End-diastolic volume (ml)	93.4 ± 15.5	95.1 ± 16.2	99.7 ± 16.3 ††	93.7 ± 14.6
End-systolic volume (ml)	32.3 ± 7.5	32.8 ± 7.8	30.5 ± 6.4	36.0 ± 7.7 *
Stroke Volume (ml)	61.0 ± 10.5	63.3 ± 10.5	69.2 ± 11.8 †	57.7 ± 9.6 *
Ejection fraction (%)	65.4 ± 4.9	66.8 ± 4.5	69.7 ± 3.9 †	61.7 ± 5.0 **

Values are mean ± standard deviation. Student's t-test two-tailed paired p>0.05 non significant.
† p < 0.01, contrast compared to all other methods; †† p < 0.05, contrast compared to all other methods; ‡ p = 0.01, contrast compared to fundamental, p = 0.02, contrast compared to power; * p < 0.01, power compared to contrast and harmonics; ** p < 0.001, power compared to fundamental and harmonics; # p = 0.01, power compared to fundamental

Wall motion score index

Despite significant changes in subjective visualisation, WMSI was similar by the three real-time echocardiographic methods (fundamental, harmonic and contrast), in both groups of subjects (Table 8). WMSI was slightly higher than 1 in the healthy controls, reflecting the fact that some of the control subjects may have had mild hypokinesia. This may reflect the unscreened "real-world" control population and also the fact that the wall motion analysis was performed by an observer who was blind to the clinical status of all patients during analysis and interpretation.

Table 8 - Wall motion score index by the three real time echo methods in heart failure patients and healthy controls

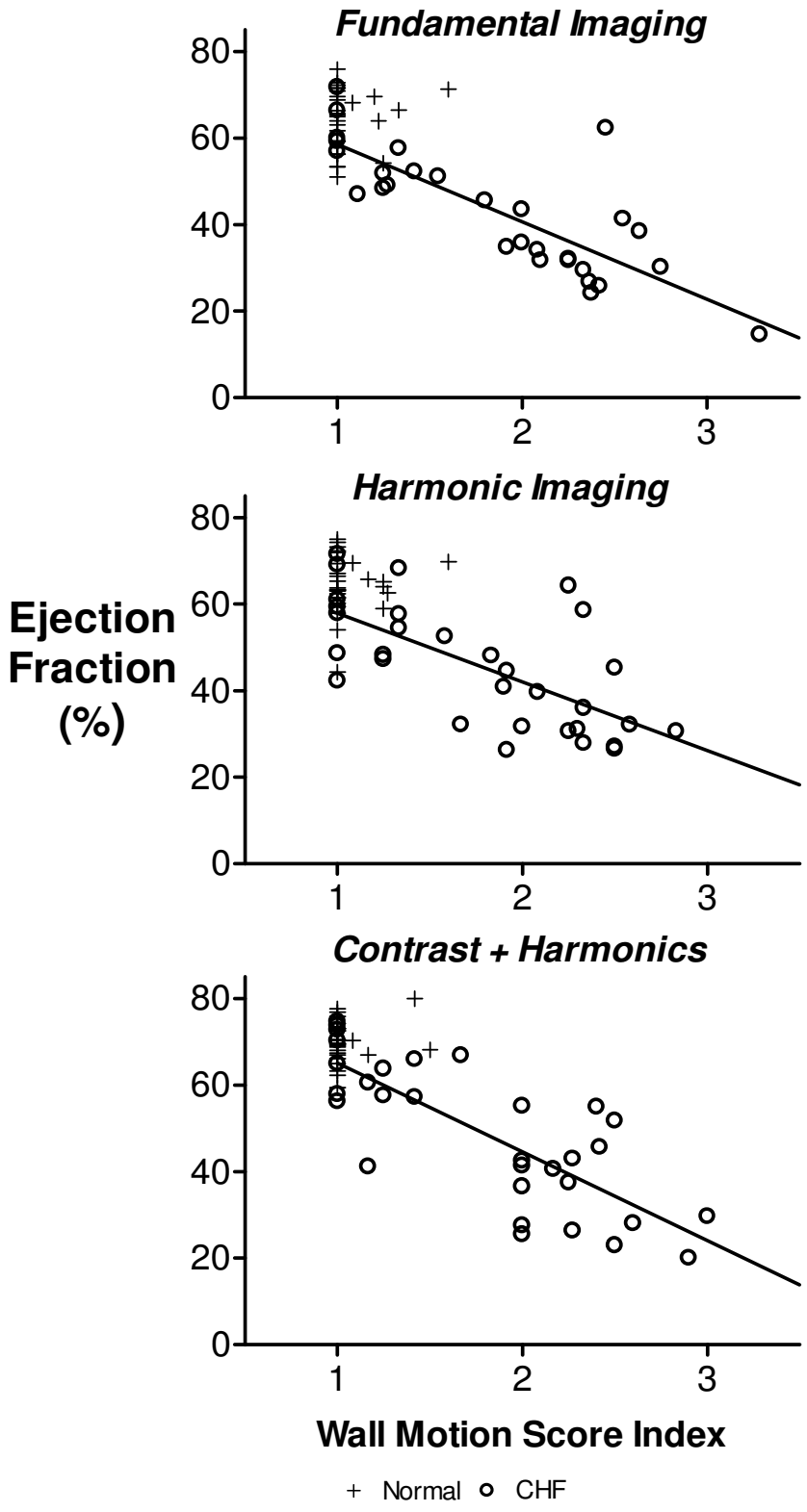
	Heart Failure Patients n = 31	Healthy Controls n = 30	Diff HF v C
WMSI (fundamental)	1.85 ± 0.63	1.05 ± 0.14	P < 0.0001
WMSI (harmonic)	1.77 ± 0.59	1.06 ± 0.14	p < 0.0001
WMSI (contrast)	1.78 ± 0.59	1.04 ± 0.12	P < 0.0001

ANOVA column effect, not significant between the echo methods
Abbreviations: Diff = difference, C = healthy control subjects, HF = heart failure patients, WMSI = wall motion score index

Relationship between wall motion score index and ejection fraction

In the HF patients, WMSI was significantly correlated with EF and this was unaffected by imaging modality (p = 0.294, Wilcoxon analysis of variance). Wall motion score index was not correlated with EF in the healthy controls due to clustering of values around 1, which is consistent with normal systolic function (Figure 8).

Figure 8 - Correlation of wall motion score index with ejection fraction by different echo methods



Intra-observer, inter-observer and test-retest variability and reproducibility

Comparing the four methods, the limits of agreement and coefficients of variation (CV) for EF were not significantly different (Table 9).

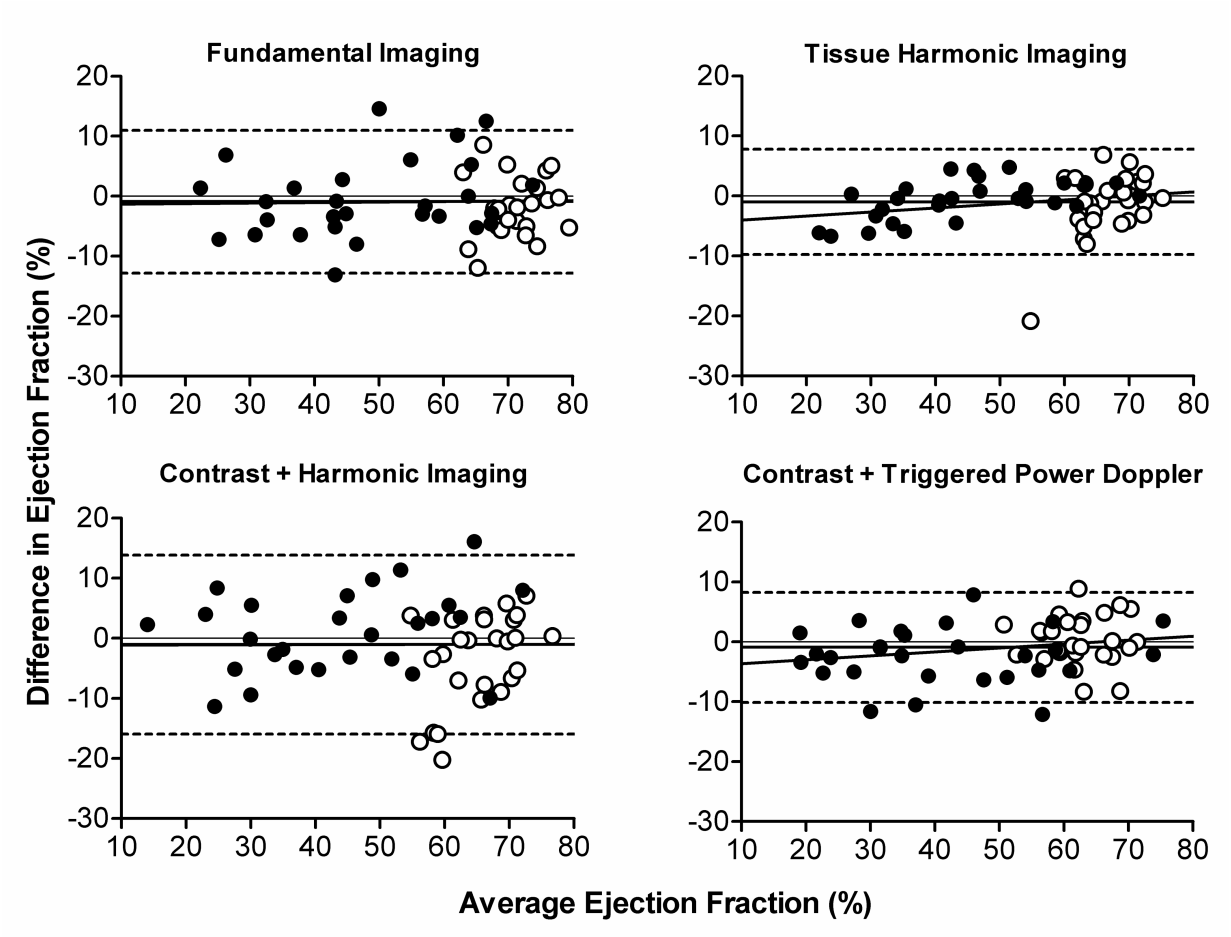
Table 9 - Intra-observer, inter-observer and between days reproducibility for ejection fraction, by four different echo methods

		Fundamental Imaging	Harmonic Imaging	Contrast + Harmonics	Contrast + Power Doppler
Intra-observer	Δ ejection fraction, %	-1.5 ± 5.2	-1.25 ± 4.5	-1.4 ± 5.9	-0.96 ± 4.7
	LOA	-11.9, 8.9	-10.2, 7.7	-13.1, 10.3	-10.3, 8.4
	CV (%)	6.8	5.7	7.1	6.5
	CV – heart failure (%)	9.7	8.2	9.8	9.1
	CV – controls (%)	4.7	3.8	4.8	4.3
Inter-observer	Δ ejection fraction, %	0.89 ± 5.6	1.42 ± 4.9	- 0.04 ± 6.2	-1.8 ± 4.9
	LOA	-10.3, 12.1	-10.2, 7.7	-13.1, 10.3	-10.3, 8.4
	CV (%)	7.4	6.2	7.6	6.7
	CV – heart failure (%)	10.3	8.9	8.4	9.5
	CV – controls (%)	5.2	4.1	5.7	4.2
Test-retest	Δ ejection fraction, %	-1.1 ± 7.8	-1.3 ± 8.0	1.51 ± 7.6	-0.23 ± 8.3
	LOA	-16.7, 14.5	-17.4, 14.8	-13.7, 16.8	-16.8, 16.3
	CV (%)	10.2	10.3	9.3	11.4
	CV – heart failure (%)	13.9	13.9	12.8	16.5
	CV – controls (%)	6.9	7.3	6.3	7.2

Abbreviations: Δ ejection fraction = change in ejection fraction (absolute percent), LOA = limits of agreement, CV = coefficient of variation

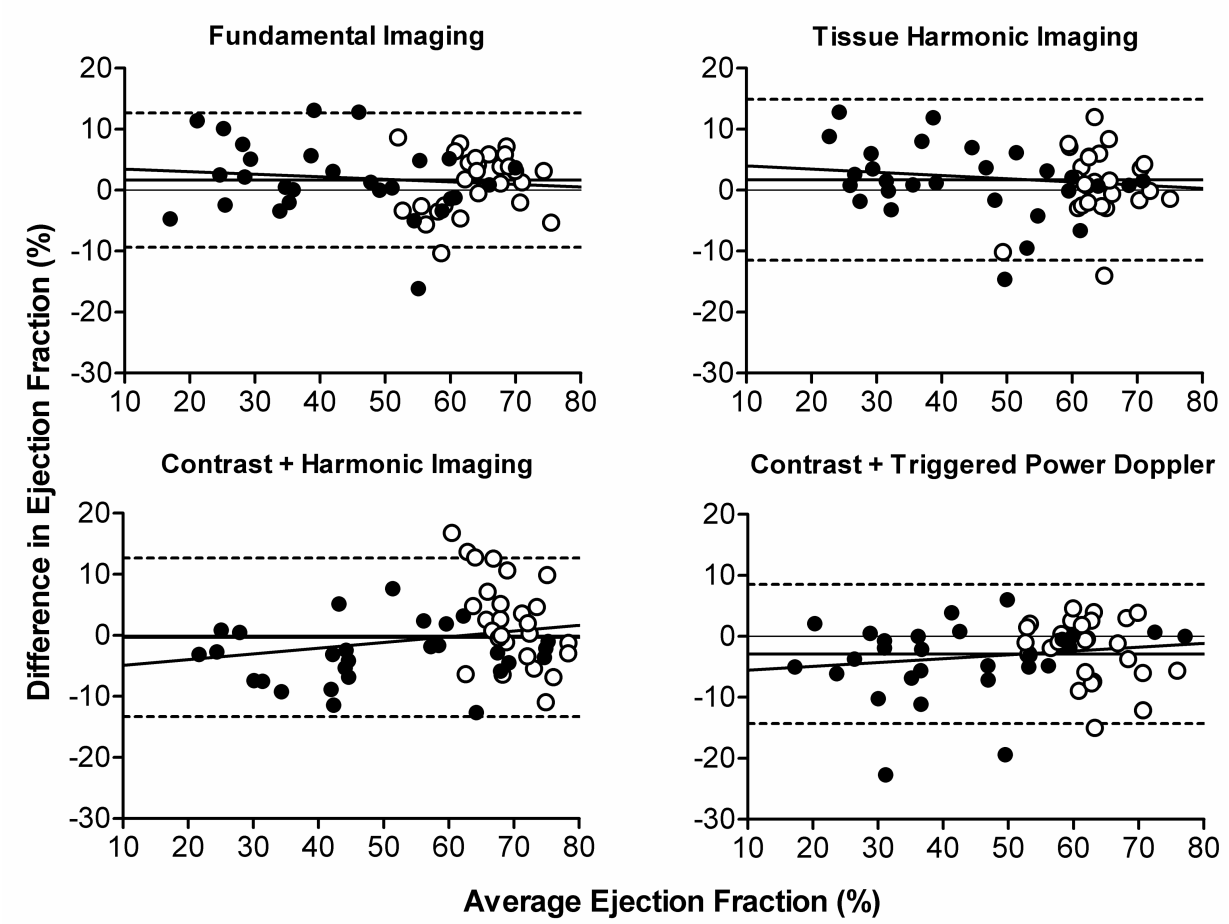
Bland and Altman plots confirmed that the variation was similar and no bias was associated with repeat measurements of EF by any method for intra-observer variability (Figure 9), inter-observer variability (Figure 10) and test-retest variability (Figure 11). The limits of agreement were wider for the HF patients compared to controls. No modality offered any significant improvement in the spread of data and THI consistently exhibited the lowest spread and smallest CV.

Figure 9 - Inter-observer variability associated with ejection fraction measurements by four different echo modalities



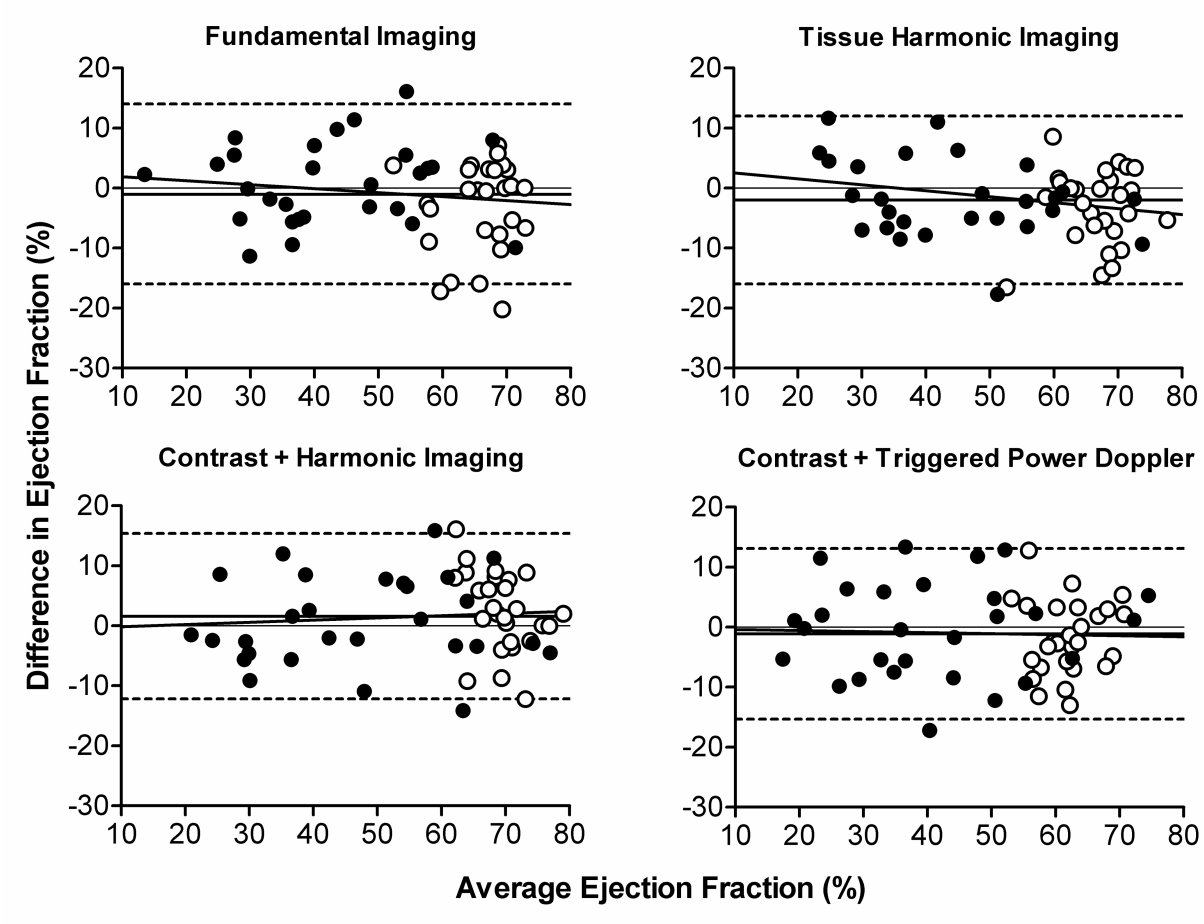
Legend: open circles = healthy control subjects, closed circles = heart failure patients

Figure 10 - Intra-observer variability associated with ejection fraction measurements by four different echo modalities



Legend: open circles = healthy control subjects, closed circles = heart failure patients

Figure 11 - Test-retest variability associated with ejection fraction measurements by four different echo modalities



Legend: open circles = healthy control subjects, closed circles = heart failure patients

Discussion

This research investigated the role of THI and contrast LVO for improving endocardial wall visualisation and measurement of systolic function in patients with HF and a comparison group of healthy controls. The main aim was to investigate the variability and test-retest reproducibility of LV volume and EF measurements using and comparing fundamental imaging, THI and LVO. This study specifically targeted patients with clinical HF, a group of patients in whom accurate measurements may potentially have the most clinical impact. Four main findings arise from this study. Firstly, in this study population endocardial definition is enhanced with THI compared to fundamental imaging, but not substantially further improved with the use of contrast. Secondly, the contrast performance was different in HF patients compared to control subjects and there are important regional differences in endocardial visualisation. Thirdly, these methods are not interchangeable nor do they reliably detect LV dysfunction because LVO produced different LV volumes and EF measurements when compared to non-contrast imaging and failed to detect important systolic dysfunction in some patients. Lastly, the intra- and inter-observer and test-retest variability was considerably lower with non-contrast imaging than previously reported and the addition of contrast had little further effect upon any measure of reproducibility.

Enhancement of endocardial borders

Improvement of endocardial visualization was observed in all patients with THI and supports the findings of many other studies that THI improves endocardial wall definition when compared to fundamental imaging.[28-36] Several studies have demonstrated improved endocardial visualisation with LVO [36-47] compared to fundamental imaging and this study supports those findings. However, our findings comparing LVO to THI were inconsistent between the two groups of subjects studied. There was a further incremental improvement in endocardial definition with LVO in the control subjects, but not in the HF patients. In fact, endocardial definition was slightly inferior with LVO compared to THI in patients with HF.

Regional differences in endocardial visualisation

There were important differences between the different regions of the heart, in particular the anterior and lateral walls were least well visualised in all subjects. In the HF patients, the basal segments were poorly imaged at baseline and failed to improve with the use of contrast LVO. The

reason for the lack of improvement in the basal segments may arise for several reasons. Firstly, the HF patients were selected on the basis of a clinical diagnosis of HF, and as a result, many had significantly dilated hearts. This dilatation meant that the basal segments were located far from the transducer face and the walls were close to the edge of the ultrasound sector. There are physical differences in the ultrasound beam at the base of the heart compared with the apex. In particular, the beam width is wider and the slice thickness increased at depth. Both of these factors may contribute to poor resolution, which may not have been improved with either THI or contrast LVO. This may explain why the basal segments were, in general, the least well imaged of all twelve segments. The proximity of some walls with the edge of the ultrasound sector also poses resolution problems. The effect of side-lobe artifacts might be significantly worse in these walls and may explain why the visualisation of the anterior and lateral walls was inferior to either the septum or inferior wall. The combination of these depth-related and sector edge artifacts resulted in poor imaging of the basal anterior and inferior walls. However, even with harmonic imaging and contrast LVO some segments in these areas remained non-visualised.

Harmonic imaging has previously been shown to be particularly useful for improving visualisation of the lateral and anterior walls[29] through reduction of side-lobe artifacts[34] and also in the basal segments of the heart.[226] Whereas contrast has shown little benefit for visualising the basal segments of the heart.[227] Although these benefits were observed in the current study for healthy controls, the lack of consistency in HF may have resulted because the HF patients have larger hearts with different geometrical shape resulting in more pronounced beam width and side-lobe artifacts.

Previous studies have compared both THI and LVO to fundamental imaging in the same patients with variable results.[29,36,227-230] Two of those studies did not demonstrate any improvement of LVO over THI.[227,228] Of those studies demonstrating a benefit of LVO, many were performed in the intensive care unit.[36,217,229-231] Portable echocardiography performed in sub-optimal lighting conditions and ventilated patients, poses an entirely different situation than that normally experienced in the echo laboratory and there is considerable evidence that in such situations, contrast contributes significantly to patient management.[217,229-231] Thus, it does appear that in

different circumstances, THI may provide maximum benefit, whilst in other situations LVO is necessary and that suboptimal endocardial visualisation does not always necessitate the use of contrast.

Comparison of modalities for determination of LV volumes and ejection fraction

This study showed that measurements made by the different methods are not the same and thus not interchangeable. Importantly, in both groups the range of measurement of EF was large: 7.8% in the controls and 6.5% in patients with HF. This may mask or magnify real changes that may be present. It also may result in misclassification if the EF measurements alone are used.

Several studies have demonstrated that echo LV volumes are smaller than those obtained by angiography,[232,233] radionuclide ventriculography[36] or biplane MRI techniques.[234] However, since the difference in LVEDV and LVESV is of similar magnitude, the EF obtained by echo is similar to the other methods.[36,233] The addition of contrast results in larger LV volumes[36,233] and better agreement with radionuclide EF measurements[235] and hence has been considered more accurate. LVO with triggered power Doppler has been shown to produce larger LV volumes than other echo measurements, which are in better agreement with angiographic volumes.[233] Although LVEDV with LVO was significantly larger in the current study, this was not the case for the triggered power Doppler images. This may represent a true finding, or the power Doppler volumes may be underestimated for one or more reasons. Firstly, the power Doppler images were collected using the same injection of contrast as the LVO images. The time delay was minimal and there did not appear to be a significant reduction in LVO with Power Doppler, but this cannot be reliably excluded. The second reason relates to loss of signal at the base of the heart due to attenuation by a large ventricular blood volume. Thirdly, some of the HF patients had abnormal rhythms, including AF and ventricular ectopics, which may have affected the ECG triggering, although this did not appear to be a problem in these patients at the time of imaging. Power Doppler itself has some technical limitations, including low frame rate, and although we attempted to overcome these by using triggered imaging which is not dependent upon frame rate, this may have introduced other translational errors. In general, however the lack of improved visualisation with non-Power contrast imaging is the most important point of this study and thus the influence of the technical failings of Power Doppler methodology assume less importance.

Wall motion score index

This study demonstrated excellent correlation between WMSI and EF in HF patients by all methods, but without significant benefit of either THI or contrast LVO. This correlation was of a similar magnitude to that observed in another study comparing WMSI obtained with fundamental and harmonic imaging to EF measured by nuclear methods.[236] Importantly, no significant differences were seen between the mean WMSI obtained by the different methods, which means that these may be interchangeable, which is not the case for EF measurements. This probably reflects the way that WMSI is calculated - if a segment is not visualised, it is not included in the calculation of WMSI and thus has no effect on the overall value. Thus, when one or two segments are not visualised the overall effect upon WMSI may be minimal. In isolated cases, such as a small localised infarction or aneurysm, this might lead to underestimation of global dysfunction. However, the improvement of endocardial visualisation with harmonics will minimise such errors, as well as increase diagnostic confidence.

Whilst WMSI is an important global measure of LV function and provides important prognostic information it does not provide any specific diagnostic information or provide aetiologic explanations for the compromised LV function. However, the resolution of a single wall segment, and hence understanding of its basal functional status, may change clinical management. Thus, any method which has the potential to convert even one non-visualised wall segment to a visible one has significant clinical potential.

The lack of correlation between WMSI and EF in the healthy controls reflects the insensitivity of the method as a useful discriminator of function within the normal range. This is primarily because the method has only one category for normal function, whereas it has four categories for abnormal function.

Intra-observer, inter-observer and test-retest variability of EF measurements

The current study did not find significant improvements in the variability of EF measurement with LVO to warrant widespread advocation of its use. However, compared to other studies, the baseline variability was significantly lower in our study population with fundamental imaging

compared to studies performed using older ultrasound equipment.[237-239] For example, in one study the confidence interval was approximately twice that of the current study.[238]

Expert versus non-expert readers

LVO improves “non-expert” reading and measurement of echocardiograms[47] and has been advocated on this basis. The current study demonstrates, that it is possible to achieve highly reproducible measurements of EF by non-contrast echocardiographic methods, and that in this case, the widespread use of contrast is not warranted. Although LVO minimises the bias associated with non-expert measurements, it is questionable whether a time-consuming technique, which adds considerable cost to an echocardiogram should be chosen to make up for sub-optimal conditions. The increased cost of using contrast in all patients in whom LV function is being assessed must be weighed up against the cost of ultrasound equipment upgrades and continuing education and training for staff.

Performance of contrast in patients with heart failure

Chamber opacification was inferior in patients with HF and this may be explained by multiple factors. Firstly, the bubbles are exposed to ultrasound for a longer period, which leads to excessive bubble destruction and loss of signal. Secondly, the larger blood volume may attenuate the signal considerably and result in loss of signal in the basal segments. Thirdly, the concentration of contrast may be weaker due to increased blood volume. Lastly, the higher pulmonary artery pressure may slow the transfer rate through the lungs and hence dilute the concentration of contrast in the LV cavity. In the current study, the PTT was related to larger LV volumes, reduced EF, advanced diastolic filling pattern and higher jugular venous pressure (JVP). Hence, it is likely that those patients with worse HF, may benefit the least from using contrast for LVO.

As previously discussed, the measurement of EF in patients with HF and thus the inferior performance of contrast for LVO in this setting has important implications for its widespread use. Data regarding the use of contrast in patients with depressed systolic function are limited. In a previous study, using an earlier agent (Albunex) 64% of patients with systolic dysfunction had no chamber opacification at all.[48] The current study is in general agreement, although LVO was more successful with the current agent (Levovist®) which is consistent with animal data.[240] Several studies have directly compared different contrast agents in different patient populations and found that newer agents, such as Optison, provide better opacification than older agents such as Albunex[42,43] and thus further work with different agents in HF patients may be required.

When this study was perforemed, Levovist was the only agent available and approved for intravenous administration for the purpose of LV opacification. In addition, the physics of ultrasound display with contrast agents was rapidly evolving. Although the recommended approach at the time was to utilise high mechanical index imaging, current methods use different agents and machine settings.

Limitations

Although all measurements were made in random order, without knowledge of clinical details or prior measurements, it was not possible to blind the observers to the imaging modality. The study lacks an external validation with a gold standard technique for LV volume assessment. However, many other studies have compared both THI and LVO with such techniques. The focus of the current study was to assess the effects of endocardial border enhancement upon reproducibility. The individual imaging modalities have consistently been proven to provide different measurements, but for long-term follow-up, the actual measurements may assume less importance in favor of the ability to detect smaller changes. What is clearly important is that once an imaging modality has been chosen or used at baseline, the same modality should be used for follow-up studies.

This study was limited to the twelve segments seen in the apical four and two chamber views collectively. To include all 16 segments, would have necessitated including short axis images of the LV. Because of attenuation through the LV cavity during contrast LVO, imaging and interpretation of the posterior wall would have been very poor. Thus, in order to make a fair comparison, we chose to only use the apical views.

This study was not restricted to patients with sub-optimal echocardiograms. Most other studies have done so, and whilst this may identify the patients with the potential for the most improvement, the objective of the current study was to determine the general applicability of the method in patients with HF.

All of the imaging in the current study was performed using state-of-the-art echocardiography equipment and by a sonographer with considerable quantitative echocardiography experience in an

academic research setting. It is conceivable that with older equipment and less operator or reader expertise, different results may have been obtained.

Part B - Diastolic Function

Background

The echo-Doppler indices of diastolic filling are also important predictors of outcome. [78,96,118-145] There is a graded prognostic outlook associated with the phases of diastolic filling: restrictive filling pattern is associated with very poor long-term outcome compared to non-restrictive filling pattern[78,96,118-145,155] and reversible restrictive filling (responsive to preload reduction) is associated with higher survival rates than non-reversible restrictive filling (unresponsive to preload reduction).[127,130,142,247]

Pulsed wave (PW) Doppler assessment of mitral valve (MV) inflow is routinely used in clinical practice to non-invasively identify the five progressive filling categories: normal, abnormal relaxation, pseudonormal, reversible restrictive filling and non-reversible restrictive filling based upon early (E) and late (A) peak filling velocities and E deceleration time.[68-71] On its own, MV Doppler does not permit differentiation between true normal and pseudonormal filling patterns. Preload reduction, can differentiate pseudonormal and true normal patterns,[76-78] and also differentiate reversible from non-reversible restrictive filling.[78]

Pulmonary venous (PV) Doppler flow, when used in conjunction with MV inflow may differentiate between true normal and pseudonormal filling and is also useful for estimating left atrial (LA) pressure.[16,72-74] However, transthoracic PV Doppler recordings are frequently suboptimal [242] and thus the role of PV Doppler for evaluation of pseudonormal filling has recently been questioned.[243] This situation is further confounded in patients with HF who often have enlarged hearts. In such patients, the pulmonary veins are located a significant distance from the transducer and the PW Doppler at this depth is less accurate. Transpulmonary contrast agents have been shown to be very useful for improving sub-optimal PV Doppler signals[244] and improve the haemodynamic information obtained in HF patients.[245]

Current HF management guidelines do not include repeat assessment of diastolic function in response to treatment. This reflects the limited availability of data regarding the efficacy of therapies for treatment of patients with preserved systolic function, so the effectiveness of

treatment in these patients remains uncertain. Of interest, several small studies have demonstrated that it is possible to alter the diastolic filling pattern of patients. For example, Capomolla et al demonstrated that patients in whom diastolic filling was affected by preload manipulation (i.e. reversible restrictive or pseudonormal) were more tolerant of beta-blocker therapy (Carvedilol) and had better outcome.[175] Similarly, Pallazzouli et al report long-term reversal of the restrictive filling is more common in HF patients randomised to Carvedilol compared to placebo.[246] Given that these filling patterns have been shown to be independently and incrementally prognostic,[78,127,130] it might be reasonable to perform repeat echocardiography to determine if the filling pattern has changed over time, or with treatment. However, this has only been demonstrated in highly selected small groups of patients with impaired systolic function, so caution needs to be applied when extrapolating to patients with HF and normal EF. In this setting, echocardiographic assessment of diastolic filling is essentially a surrogate for measurement of LA pressure, as such the methods need to be both sensitive and reproducible in order to be clinical useful.

Aims

To compare the effectiveness of pulmonary venous Doppler with preload manipulated mitral Doppler for assessment of diastolic filling pattern and to determine the test-retest reproducibility of these methods. A secondary aim was to compare three different preload reduction methods.

Methods

Subjects

Patients were recruited as outlined in Part A, but this analysis was restricted to a sub-group of the main study: 20 HF patients and 25 healthy controls. Eleven of the original HF population were excluded from this analysis because of atrial fibrillation.

Mitral valve inflow Doppler

Mitral valve PW Doppler recordings were obtained from the apical four chamber view with a 5 mm PW Doppler sample volume placed distal (5-10mm) to the mitral annulus between the MV leaflets.[248] The Doppler interrogation beam was carefully aligned with the direction of MV flow. All Doppler recordings were optimised to maximise the signal on the screen, eliminate excess gain,

minimise wall filters, and were recorded at a sweep speed of 100 mm/s. Only end-expiratory signals were analysed.

Contrast enhancement of pulmonary venous Doppler recordings

Contrast was administered as described in Part A. Doppler recordings were made as previously described. PV Doppler was performed by placing a 5 mm PW Doppler sample volume in the right upper PV in the apical four-chamber view.

Non-standardised Valsalva

All subjects were instructed in the performance of a Valsalva manoeuvre (forced expiration against a closed glottis) and each practiced the manoeuvre at least once. MV inflow Doppler was then recorded during the Valsalva manoeuvre. Preload reduction was considered adequate if the mitral E velocity dropped by 20%. The Valsalva was repeated up to three times in order to obtain adequate signals. Figure 12 shows the MV inflow response to the Valsalva manoeuvre in two HF patients obtained during the study.

Diastolic echocardiographic measurements

Triplicate measurements of all variables were made offline (Nova Microsonics/Kodak Eastman, Mahwah, NJ) by one observer who was blinded to the subjects' clinical details. Measurements were made according to standard methods and include: i) Mitral valve (Figure 13A): MV early peak filling velocity (E), MV late peak filling velocity (A), MV E wave deceleration time (DT), MV A wave duration, isovolumic relaxation time (IVRT), ii) Pulmonary veins (Figure 13B): PV peak systolic velocity, PV peak diastolic velocity, PV atrial reversal velocity, PV atrial reversal duration. The following variables were calculated: E:A ratio, PV atrial reversal/MV atrial reversal.

Figure 12 - Effect of preload reduction on mitral inflow

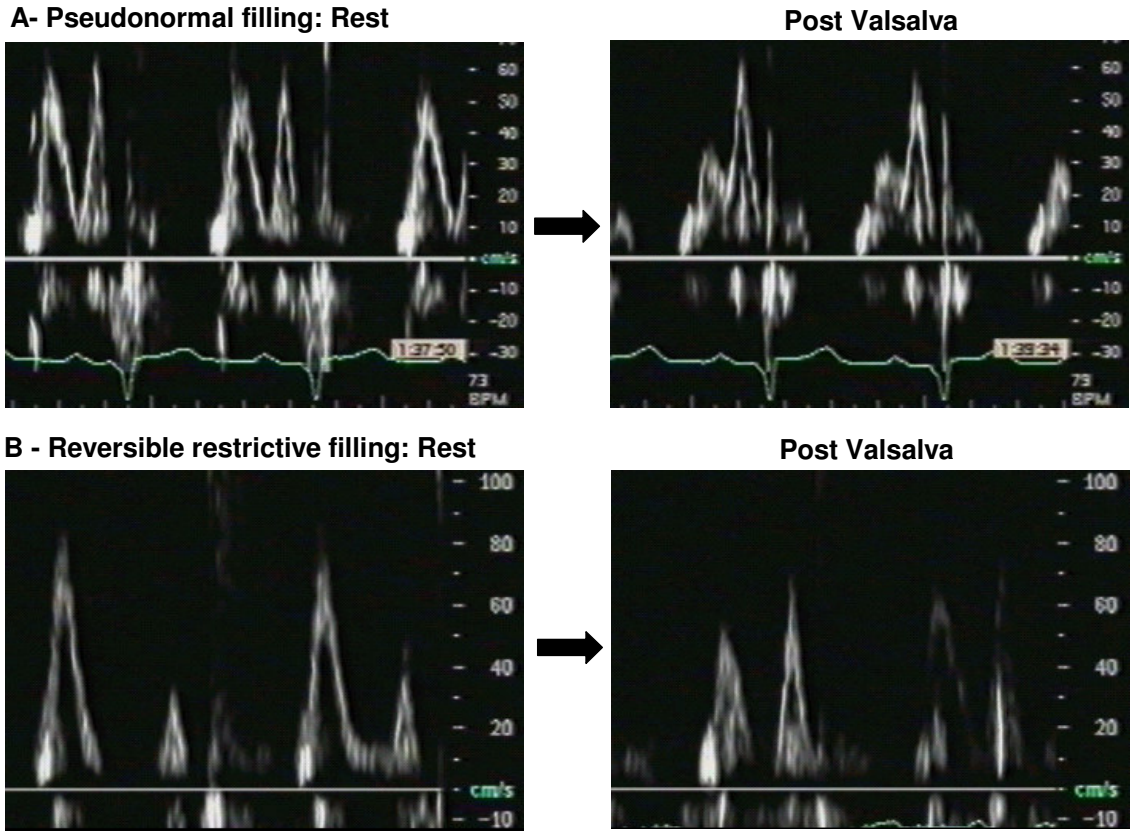
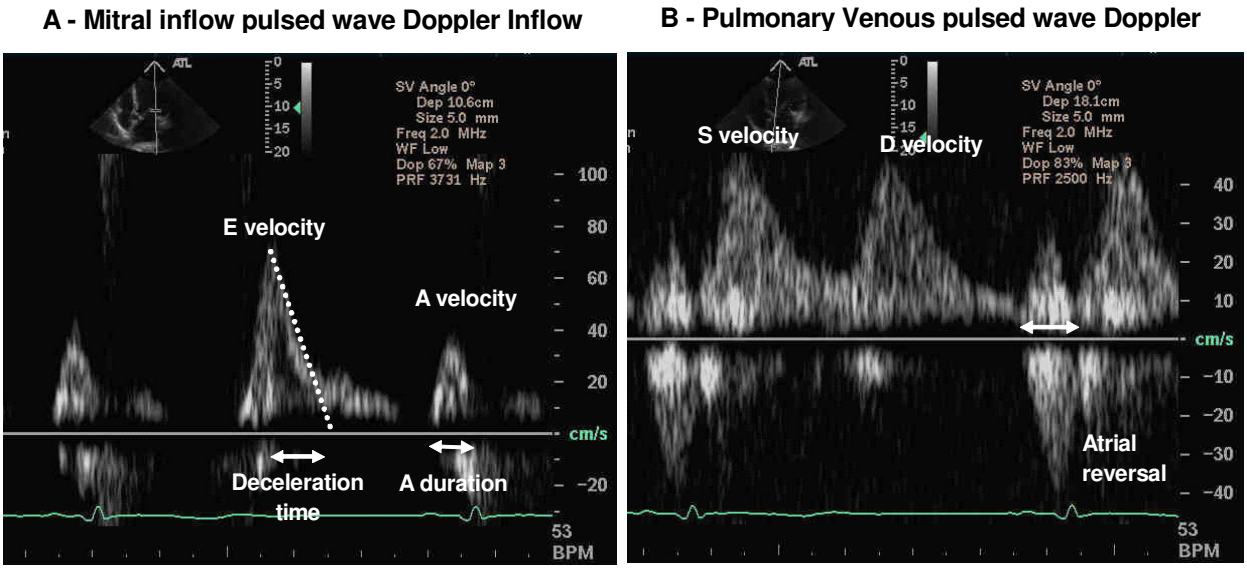


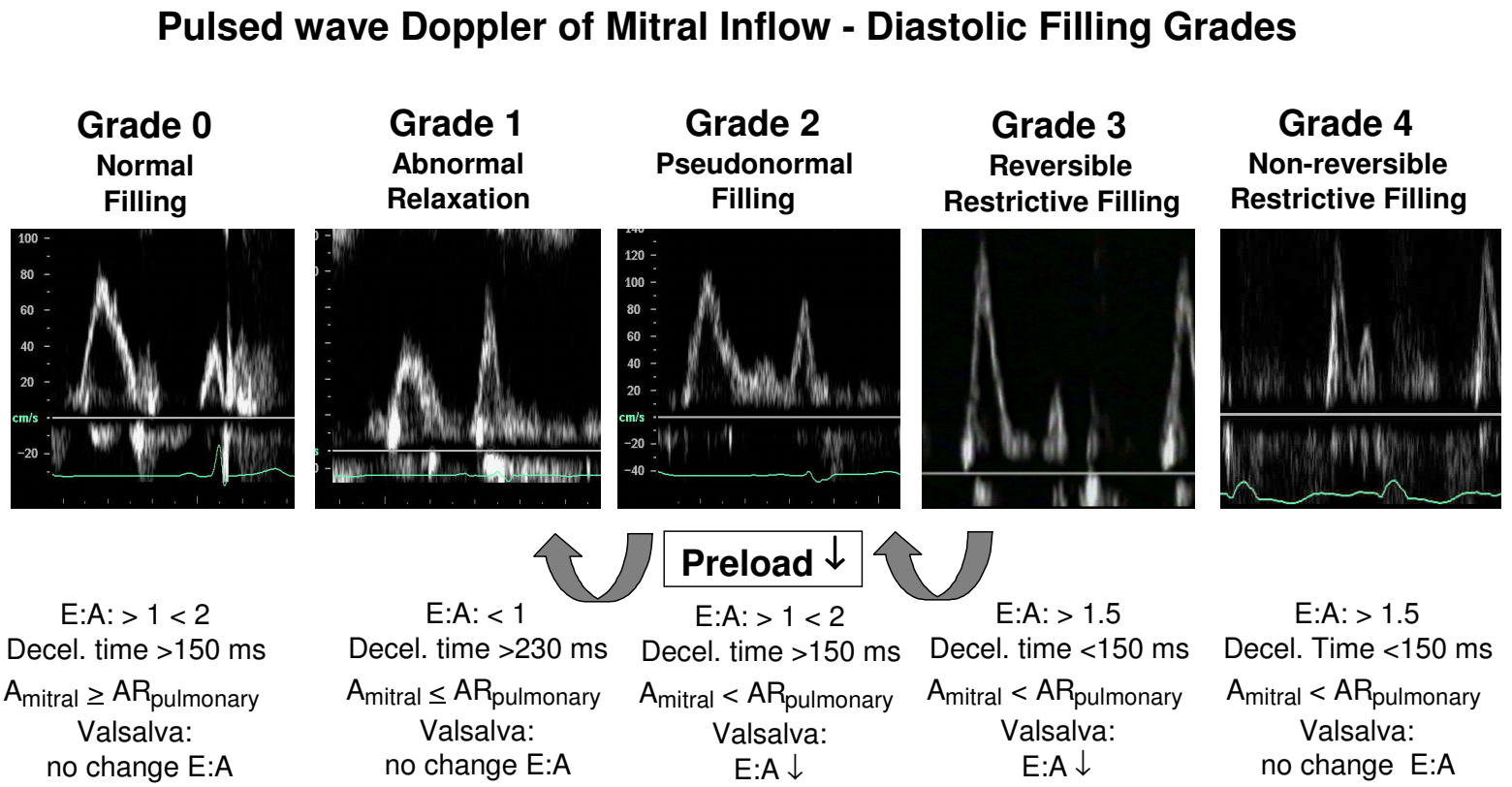
Figure 13 - Diastolic Doppler measurements - mitral inflow and pulmonary veins



Differentiation between diastolic filling patterns

After the baseline measurements were made, each subject was classified into one of the following categories of filling patterns[69]: normal filling: E:A ratio 1.0-2.0 and DT 0.15 – 0.23 s; abnormal relaxation: E:A ratio < 1.0 and DT > 0.23 s; Pseudonormal filling: E:A ratio 1.0-2.0, but E:A ratio < 1.0 and DT > 0.23 s with Valsalva and/or PV atrial reversal duration/ MV A wave duration ratio >1.2; RFP: E:A ratio > 2.0 and DT < 0.15 s; reversible restrictive filling: E:A ratio > 1.5 and DT < 0.150 ms and responsive to preload manipulation; non-reversible restrictive filling: E:A ratio > 1.5 and DT < 0.150 ms and unresponsive to preload manipulation (Figure 14).

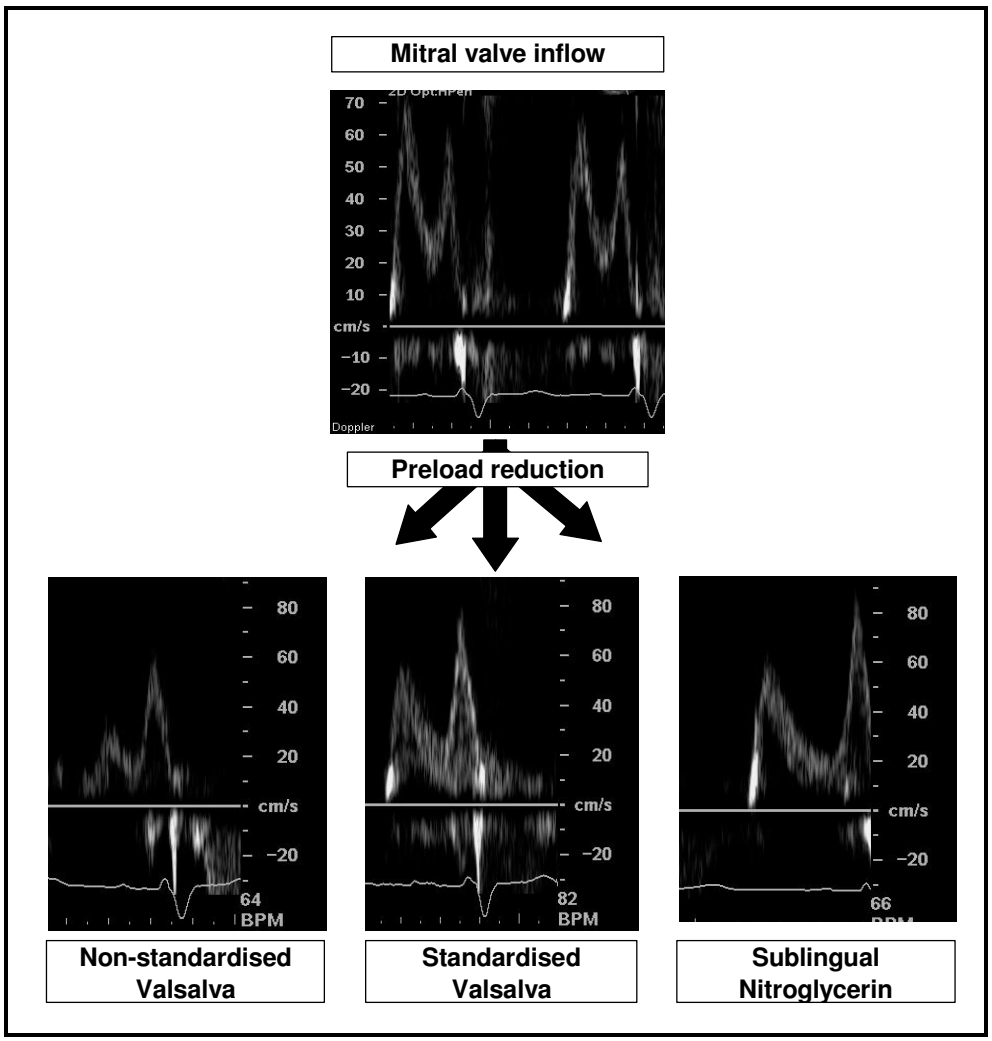
Figure 14 - Diastolic filling grades by pulsed wave mitral inflow Doppler



Evaluation of preload reduction methods

The non-standardised Valsalva was then compared to both the standardised method[249,250] and pharmacological preload reduction method in a sub-group of subjects (Figure 15). Nineteen subjects (HF = 10, Normal = 9) were asked to repeat the Valsalva by blowing into a hollow tube which was attached to a mercury sphygmomanometer. They were instructed to blow sufficiently hard to keep the mercury at a level of 40 mmHg. All MV Doppler recordings were made once a steady state had been achieved. After a rest period, each subject was subsequently given a single dose (400ug) of nitroglycerin (GTN) administered as a spray under the tongue. Continuous monitoring of the MV pulsed wave Doppler was then performed for up to five minutes.

Figure 15 - Mitral valve inflow Doppler - Effect of three different preload manipulations



Statistics

Comparisons between the HF patients and the healthy volunteers were tested with the Student's t-test and between preload reduction methods with ANOVA (significant main effects explained using Dunnetts test). All tests performed were 2 tailed and a p value of < 0.05 was considered significant. For sensitivity, specificity and predictive values calculations, the "gold standard" or correct test was considered to be the highest filling pattern obtainable (by any method) as the true pattern. For example, if one method revealed a normal filling pattern and another method revealed pseudonormal, then the correct one was deemed to be pseudonormal. With the exception of restrictive filling, in which case, if any preload method revealed reversible restrictive filling this was considered the true pattern.

Results

This analysis is based upon the 20 HF patients and 25 healthy controls in whom complete Doppler was available. As mentioned previously, 12 HF patients were excluded because of AF.

Diastolic echocardiography parameters

The HF patients had lower E velocity, higher A velocity, lower E:A ratio and longer deceleration time compared to the controls. Heart rate, IVRT and PV forward velocity measurements were similar between the groups and the retrograde PV atrial velocity was higher in the HF patients. There was a reduction in the E:A ratio in both groups in response to the Valsalva manoeuvre but no differences in heart rate was observed during Valsalva in either group (Table 10).

Table 10 - Doppler measurements of diastolic filling

	Heart Failure Patients (n = 20)		**Healthy Controls (n = 25)**	
	Baseline	**Valsalva**	**Baseline**	**Valsalva**
Heart rate	68.3 ± 11.4	68.8 ± 12.7	64.9 ± 7.3	62.5 ± 10.8
E Velocity (cm/s)	58.8 ± 17.7	31.6 ± 8.8§	68.1 ±14.8*	44.4 ± 13.9§
A Velocity (cm/s)	65.9 ± 25.7	54.5 ± 15.5	49.8 ± 15.7*	47.2 ± 12.8†
E:A ratio	0.89 ± 0.51	0.58 ± 0.75	1.37 ± 0.69*	0.94 ± 0.72§
Deceleration time (s)	0.215 ± 0.099	-	0.188 ± 0.039*	-
IVRT (s)	0.063 ± 0.021	-	0.061 ± 0.014	-
Mitral A duration (s)	0.167 ± 0.038	-	0.150 ± 0.020	-
PV systolic velocity (cm/s)	44.6 ± 8.9	-	51.4 ± 15.5	-
PV diastolic velocity (cm/s)	50.1 ± 21.1	-	53.5 ± 14.9	-
PV AR duration (s)	0.141 ± 0.030	-	0.122 ± 0.030	-
PV AR velocity (cm/s)	44.5 ± 6.1	-	23.5 ± 5.3*	-
PV AR duration-Mitral AR	0.026 ± 0.079	-	0.028 ± 0.051	-

* $p < 0.0001$ heart failure v controls; § $p < 0.001$ Valsalva v baseline; † $p = 0.05$ Valsalva v baseline;
values are mean ± standard deviation
Abbreviations: AR = atrial reversal, E:A ratio = early to late filling ratio, IVRT = isovolumic relaxation time, PV = pulmonary vein

Diastolic filling classification

Diastolic filling grade was different depending upon the method used. MV Doppler was the least accurate. Nine subjects were considered to have suboptimal or incomplete PV recording pre-contrast and thus all of the results presented are based upon PV recordings obtained with contrast. The addition of PV Doppler offered slight improvement by identifying subjects with pseudonormal filling. These subjects were also identified by preload reduction (Valsalva), as were an additional six subjects with pseudonormal filling that were undetected by PV Doppler. In addition, the Valsalva manoeuvre identified a further three subjects with reversible restrictive filling(Table 11).

Table 11 - Classification of diastolic filling grade

	Diastolic Filling Grade				
Visit One	**0**	**1**	**2**	**3**	**4**
Mitral inflow pulsed wave Doppler	22	17	-	-	6
+ pulmonary venous Doppler	20	17	2	-	6
+ contrast enhancement	21	17	1	-	6
+ preload reduction	14	17	8	3	3

Number of subjects: HF = 20, Control = 25
Diastolic filling classification: 0 = normal, 1 = abnormal relaxation, 2 = pseudonormal filling, 3 = reversible restrictive filling, 4 = non-reversible restrictive filling

Test-retest of diastolic filling grade classification

All four methods correctly identified the subjects with an abnormal filling pattern, but there was clinically important variability in the detection of all other filling patterns on different days (

Table 12). Only the preload method correctly identified all of the patients with normal or abnormal filling patterns on both days. Although there were small differences in the detection of pseudonormal and reversible restriction between days, non-reversible restriction was correctly identified with Valsalva on both days, but the other methods displayed poor agreement (Table 12). Comparing the combination of advanced filling grades (pseudonormal and restrictive grades) to the other grades (normal and abnormal relaxation) only the grade obtained with Valsalva concurred between days.

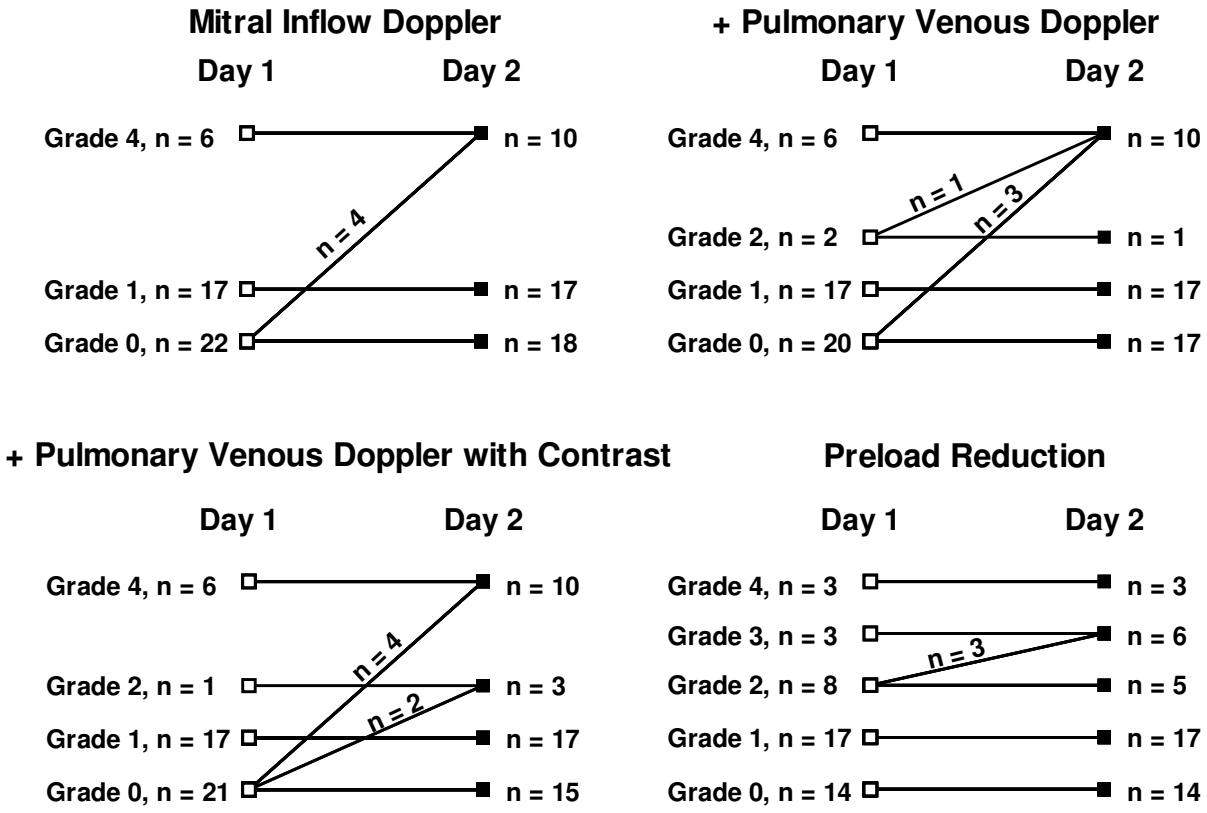
Table 12 – Classification of diastolic filling grade

	Diastolic Filling Grade				
Visit One	**0**	**1**	**2**	**3**	**4**
Mitral inflow pulsed wave Doppler	22	17	-	-	6
+ pulmonary venous Doppler	20	17	2	-	6
+ contrast enhancement	21	17	1	-	6
+ preload reduction	14	17	8	3	3
Visit Two					
Mitral inflow pulsed wave Doppler	18	17	-	-	10
+ pulmonary venous Doppler	17	17	1	-	10
+ contrast enhancement	15	17	3	-	10
+ preload reduction	14	17	5	6	3

Number of subjects: HF = 20, Control = 25.
Diastolic filling classification: 0 = normal, 1 = abnormal relaxation, 2 = pseudonormal filling, 3 = reversible restrictive filling, 4 = non-reversible restrictive filling

The movement between the grades is illustrated in Figure 16 and is most marked within all methods, with the exception of preload reduction. The latter only misclassified three subjects but on each occasion each subject was identified as having advanced diastolic filling abnormalities which would be associated with high filling pressure and may not be clinically misleading. Conversely, important misclassification occurred with all the other methods.

Figure 16 - Movement of subjects within diastolic categories on each visit



Sensitivity, specificity and predictive values

Comparing the sensitivity and specificity of these methods for detection of any grade of abnormal diastolic filling from normal filling, the addition of PV Doppler increased both the sensitivity and specificity, but neither the MV nor the PV method reached the diagnostic accuracy of preload manipulated MV valve Doppler (Table 13). The same was true when used to detect advanced filling patterns (pseudonormal and restrictive filling) compared to normal or abnormal relaxation patterns. The positive predictive value was similar and high for all methods, but the negative predictive value was poor for the non-preload methods (Table 13).

Table 13 - Sensitivity, specificity, positive and negative predictive values of the different methods: Detection of any abnormal diastolic filling grade

	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
Detection of any abnormal filling pattern				
MV Doppler	74.2% (CI:55.4,88.1)	93.3% (CI:68.1,99.8)	95.8% (CI:55.4,88.1)	63.6% (CI:40.7,82.8)
+ PV Doppler	80.7% (CI:62.5,92.6)	93.3% (CI:68.1,99.8)	96.2% (CI:80.4,99.9)	70.0% (CI:45.7,88.1)
+ contrast enhancement	77.4 (CI:58.9,90.4)	93.3% (CI:68.1,99.8)	96.0% (CI:79.7,99.9)	66.7% (CI:43.0,85.4)
+ preload reduction	100 %	100 %	100 %	100 %
Detection of pseudonormal or restrictive filling				
MV Doppler	42.9% (CI:17.7,71.1)	96.9% (CI:83.8,99.9)	85.7% (CI:42.1,99.6)	79.5% (CI:63.5,90.7)
+ PV Doppler	57.1% (CI:28.9,82.3)	96.9% (CI:83.8,99.9	88.9% (CI:51.8,99.7)	83.8% (CI:68.0,93.8)
+ contrast enhancement	50.0% (CI:23.0,76.9)	96.9% (CI:83.8,99.9)	87.5% (CI:47.4,99.7)	81.6% (CI:65.7,92.3)
+ preload reduction	100 %	100 %	100 %	100 %

Number of subjects: HF = 20, Control = 25.
Normal filling (grade 0) versus all other grades (2-4); gold standard for comparison is preload reduction.
Abbreviations: CI = 95% confidence interval, MV = mitral valve, PV = pulmonary venous.

Comparison of different preload reduction manoeuvres

In a subgroup of patients (n=19) all three preload reduction methods were tested. Compared to baseline, mitral valve E:A ratio was significantly reduced and the deceleration time prolonged with all three methods (non-standardised Valsalva, standardised Valsalva and GTN) but no differences were detected between the three methods (ANOVA) (Table 14). Minor differences in the final classification of diastolic filling occurred with the different methods (Table 15). Importantly, the non-standardised Valsalva appeared as accurate as the other two methods.

Table 14 - Effect of preload reduction method upon mitral inflow pulsed wave Doppler

	Baseline MV Doppler	Non-standardised Valsalva	Standardised Valsalva	Nitroglycerin (GTN)	ANOVA
E:A ratio	1.60 ± 0.60	0.85 ± 0.44*	0.85 ± 0.43*	0.93 ± 0.48*	ns
Deceleration time (s)	195.2 ± 58.3	0.241 ± 0.07†	0.247 ± 0.06†	0.215 ± 0.06†	ns
∆ E:A ratio	-	- 0.31 ± 0.42	- 0.31 ± 0.39	- 0.23 ± 0.23	ns
∆ Deceleration time (s)	-	0.048 ± 0.089	0.052 ± 0.082	0.021 ± 0.064	ns

* $p < 0.005$ all methods compared to baseline, † $p < 0.05$, all methods different to baseline
abbreviations: E:A ratio = early to late filling ratio

Table 15 - Classification of diastolic filling grade by five methods

	Diastolic Filling Grade				
Method	**0**	**1**	**2**	**3**	**4**
Mitral inflow pulsed wave Doppler	8	8	-	-	3
+ pulmonary venous Doppler (Contrast)	6	8	2	-	3
+ preload reduction (Valsalva)	5	8	3	3	0
+ preload reduction (standardised Valsalva)	6	8	2	3	0
+ preload reduction (nitroglycerin)	5	8	3	2	1

Number of subjects: HF = 10, Control = 9.
Diastolic filling classification: 0 = normal, 1 = abnormal relaxation, 2 = pseudonormal filling, 3 = reversible restrictive filling, 4 = non-reversible restrictive filling

Discussion

This study has compared optimal transthoracic recordings of PV Doppler and found that they do not reach the diagnostic accuracy of preload manipulation for classification of diastolic filling abnormalities. Further, it has demonstrated that a non-standardised Valsalva manoeuvre performs equally well to both standardised (measured) Valsalva and pharmacological preload reduction (with GTN). To our knowledge, this study is the first study to investigate the test-retest agreement of these methods for correctly identifying diastolic filling grades in HF patients. The results indicate that a simple Valsalva manoeuvre may reveal important advanced diastolic filling abnormalities and thus may be an essential part of the echo examination of patients with HF.

Assessment of diastolic filling is now considered to be a routine part of contemporary echocardiographic assessment.[251] Given the graded prognosis associated with the higher diastolic filling grades (pseudonormal, reversible restrictive and non-reversible restrictive) even in the setting of depressed systolic function,[78,118,125,128,130,137,144] it is paramount that these grades of advanced filling abnormalities are accurately identified.

Diastole is a complex series of events where the pressure gradient between the LV and LA is in constant flux due to changes in the myocardial properties induced by ventricular relaxation and in response to atrial systole. The fluctuations in the pressure gradient give rise to the passive and active phases of mitral filling that are easily assessed by Doppler echocardiography. The ratio of these two phases (E:A ratio) was the earliest, and remains the most common, measure of diastolic filling. Indeed, several patterns of diastolic filling are now well recognised on this basis.[69-72] MV Doppler used in isolation is insufficient to detect two advanced filling patterns (pseudonormal and reversible restrictive filling).

Pulmonary venous Doppler has been widely used to identify pseudonormal filling on the basis that there is some retrograde blood flow into the pulmonary veins during atrial contraction. If the LV pressure is high, blood will flow for a longer time into the passive pulmonary veins. The comparison of the time duration of the MV forward flow during atrial contraction (A wave) to the time duration of this retrograde PV flow (atrial reversal) is related to LVEDP – longer PV atrial reversal duration

indicates higher pressure. [16,74,75,79] With optimal visualisation of the PV blood flow, it is possible to detect pseudonormal filling in many patients and in two recent studies of patients undergoing diagnostic coronary angiography, PV Doppler was superior to preload reduction for identifying elevated LVEDP[75] but may not be obtained as reliably as MV inflow during Valsalva.[79] Further, in patients with HF, the pulmonary veins are further away from the transducer and thus the signal may be even more suboptimal. The current study used a transpulmonary contrast agent (Levovist) to enhance the PV signal, but despite this, the technique remained inferior to preload manipulation.

Preload manipulation is essential for correct identification of reversible and non-reversible restrictive filling. This is an important clinical distinction because the latter is associated with much higher mortality rates.[78,127,130] Reduction in venous return to the heart (preload) lowers the LA filling pressure allowing changes in mitral pulsed wave Doppler velocities to be identified. This can be achieved in two ways, by increasing intra-thoracic pressure with a Valsalva manoeuvre or by using a fast-acting vasodilator such as sublingual nitroglycerin. The latter is a potent vasodilator with rapid action and can be administered in a quantifiable dose. The Valsalva manoeuvre is dependent upon patient skill and effort and as a result, the degree of preload reduction is variable. Preload manipulation can identify both pseudonormal filling and also the reversible form of the restrictive filling phase. The change in E:A ratio with preload reduction correlates with invasive measurements of LVEDP obtained in response to a non-standardised Valsalva manoeuvre,[79,241] standardised Valsalva manoeuvre[250] and nitroglycerin administration.[241]

This study has shown that after minimal training, adequate preload reduction can be achieved in all subjects using a non-standardised Valsalva manoeuvre. The non-standardised Valsalva resulted in similar MV inflow changes as the standardised approach and sublingual nitroglycerin. The findings of this study suggest that it may not be necessary to obtain PV Doppler measurements when preload manipulation is achievable and that without preload manipulation misclassification of many patients may occur. Although all methods showed good positive predictive value, that is if you find an abnormal filling pattern it is likely to be true, the methods that did not use preload had poor negative predictive value. This is a known pitfall of using both MV and PV Doppler for detecting

abnormal filling patterns - if a normal filling pattern is observed it does not necessarily follow that diastolic filling (or filling pressure) is normal. Preload manipulation offers significant benefit over the other methods in this regard. For the purposes of this analysis, we have assumed that the highest filling pattern obtainable (by any method) is the true pattern. This may be incorrect, but reflects current clinical use of preload manipulation and classification of patients on this basis does identify groups of patients at progressively higher cardiovascular long-term risk.

This study did not evaluate the newer modality of tissue Doppler imaging (TDI). It has been previously shown that TDI is Complementary to MV and PV Doppler for differentiating pseudonormal filling[252-254] and to identify elevated LV filling pressures.[83,84] However, in the setting of severely depressed systolic function, TDI velocities are often very low making the technique particularly challenging in such patients. When adequate signals are obtained, pulsed wave TDI is useful for identifying pseudonormal filling, but it does not directly provide information about the reversibility of restrictive filling. Currently, TDI is useful for differentiating subjects with low LA pressure and those with very high LA pressures. There remains an intermediate group in whom TDI is ambiguous in relation to LA pressure estimation. TDI is Complementary to the methods described here, because it provides a surrogate measure of LA pressure.[83,84] Neither TDI nor preload reduction should be viewed as independent - preload reduction allows you to document the correct diastolic filling phase and TDI provides an estimation of LA pressure.

The day-to-day variation observed for MV Doppler and pulmonary venous Doppler probably possibly reflects fluctuations in fluid status and hence preload in HF patients despite apparent clinical stability. This variation can be so pronounced that an individual may shift between filling patterns almost daily as a result of changes in preload and LA pressure. The use of the Valsalva manoeuvre in this situation reduces the preload to a minimum level and hence if preformed well enough, is able to detect the underlying filling grade such that might be present if the patient had optimal fluid balance. This finding may be unique to HF patients.

Limitations

This is a small cross-sectional study and lacks a comparison with a gold standard such as invasive measurement of LA or LV pressure, which would have confirmed the presence of elevated filling pressures. However, many previous studies have compared these mitral Doppler measurements with invasive pressure measurement. These methods are thus quite established. This study did not evaluate the role of trans-oesophageal echocardiography measurements of PV return, which almost certainly would have resulted in better quality Doppler recordings. However, we do not believe that this is routine clinical practice and it was the intention of the study to investigate common clinical parameters. Lastly, the comparison with newer indices such as Tissue Doppler annular velocities would have been a useful way to confirm the presence of advanced filling patterns and elevated filling pressures. But at the time this study was conducted this technology was unavailable in our laboratory.

Conclusions

The accurate assessment of diastolic filling pattern in patients with HF can provide important prognostic information, even in the setting of depressed systolic function. This study has shown that preload reduction, such as might be achieved through the Valsalva manoeuvre is an essential part of the assessment of diastolic function in HF patients. Preload reduction is superior to PV Doppler assessment or pulsed wave tissue Doppler because in addition to identifying those patients with pseudonormal filling and hence mildly increased filling pressures, preload reduction is able to differentiate between reversible and non-reversible restrictive filling, which are respectively associated with high and very high filling pressures. Thorough assessment of diastolic filling grade, including a preload challenge, should form part of any echocardiographic examination of HF patients and will ultimately lead to better prognosis, which in turn may lead to optimising management of such patients

Summary

Harmonic imaging significantly improved endocardial wall visualisation in both the control subjects and HF patients and a small incremental improvement was seen with the use of contrast for LVO. However, contrast enhancement of endocardial borders was inferior in patients with HF and this appeared to be related to the delayed passage of contrast through the lungs, which in turn was

related to worse HF. On a segment by segment basis, harmonic imaging and contrast LVO improved endocardial visualisation, but is wall segment specific. In particular, segments which lie at the extremes of the ultrasound sector were not as well visualised with fundamental imaging and thus may have the most room for improvement with the use of contrast LVO. All of the methods performed differently in patients with HF compared to control subjects with normal sized and functioning hearts. Importantly, WMSI was not affected by these different methods.
This study has important and clinically relevant implications for the initial assessment and serial follow-up of systolic function in patients with HF. Harmonic imaging should be used routinely for regional wall motion analysis and measurement of EF in HF patients, but contrast LVO should be carefully considered in light of the specific location of non-visualised segments and heart size. Further, this study has demonstrated that the LV volumes and EF measured by fundamental, harmonic and contrast imaging are not comparable and thus not interchangeable for follow-up assessments.

The current study found no significant differences in test-retest reproducibility using contrast. To our knowledge, this is the first study to target patients with HF to evaluate the potential benefits of THI and LVO for echo measurement of EF. The variability observed in this study is the lowest yet published in the literature (similar to 3D echo and MRI). It probably reflects optimal echo imaging in an academic institution, but it may also indicate the quality benchmark we should expect from the latest ultrasound equipment. The results of the study suggest that, with excellent equipment and optimised non-contrast imaging the benefits of contrast may be minimal.

The accurate assessment of diastolic filling pattern in patients with HF can provide important prognostic information, even in the setting of depressed systolic function. This study has shown that preload reduction, such as might be achieved through the Valsalva manoeuvre is an essential part of the assessment of diastolic function in HF patients and is superior to PV Doppler assessment. Thorough assessment of diastolic filling grade, including a preload challenge, should form part of any echocardiographic examination of HF patients and will ultimately lead to better prognosis, which in turn may lead to optimising management of such patients.

Key Findings:

- Assessment of systolic function in patients with heart failure is optimised by the use of harmonic imaging and not enhanced with the addition of transpulmonary contrast agents
- Assessment of diastolic filling is optimised by the use of preload manipulation to correctly identify true diastolic filling patterns

Chapter 3 - Predicting Future Hospitalisations and Mortality in Heart Failure Patients after Hospital Discharge

Background

Despite optimal medical therapy, mortality associated with congestive heart failure (HF) remains high.[2,3] Several clinical and functional parameters predict survival, including New York Heart Association (NYHA) classification,[111] peak oxygen uptake,[112,113] end-systolic volume,[114] ejection fraction,[112,115,116] creatinine clearance[117] and echo-Doppler indices of diastolic filling.[78,96,118-147]

Pulsed wave Doppler assessment of the mitral valve is routinely used in clinical practice to non-invasively assess LV diastolic filling. On its own, mitral Doppler does not permit differentiation between true normal and pseudonormal filling patterns. Pulmonary venous Doppler flow, when used in conjunction with mitral inflow helps to differentiate between true normal and pseudonormal filling and is useful for estimating LA pressure.[16,72-74,89] However, transthoracic pulmonary venous Doppler recordings are frequently suboptimal[242] and other methods are required. Preload reduction, achieved with the Valsalva manoeuvre or sublingual nitroglycerin, can assist differentiation of pseudonormal and true normal patterns[70,76,77] and also differentiate reversible from non-reversible restrictive filling.

The differentiation of restrictive filling patterns from non-restrictive patterns provides important independent prognostic information.[78,96,118-146] Reversible restrictive filling (responsive to pharmacological preload reduction) is associated with better outcome than non-reversible restrictive filling (unresponsive).[78,127,130] However, little is known about the prognostic significance of other non-restrictive filling patterns in HF patients.

In patients with acute myocardial infarction (AMI) and normal systolic function, the presence of pseudonormal filling (identified using colour m-mode echocardiography) within 24 hours of the AMI predicted cardiac death and LV dilatation[156] and the effect falls in between that observed for patients with restrictive filling and abnormal relaxation patterns. Similarly, a short deceleration time is associated with adverse remodelling[164] and development of HF post AMI,

[155,159,161,164,169,170,266] although the presence of a restrictive filling pattern is the single best predictor of cardiac death.[155]

We hypothesized that the intermediate pseudonormal filling would provide additional prognostic information in HF beyond the simple classification of non-restrictive or restrictive filling patterns, which most studies have previously used. Thus, the aim of the current study was to investigate whether the distinction of different patient groups based upon filling pattern was associated with survival or readmission in a chronic heart failure population.

Methods

Subjects

Patients included were those enrolled in a randomised, controlled, trial of integrated heart failure management carried out at our institution between 1996 and 1999.[267] The intervention had a beneficial effect on multiple readmission rates, bed days and quality of life but not on mortality.[267] Patients were eligible if they had been admitted to the general medical wards at Auckland Hospital with a primary diagnosis of heart failure. Exclusion criteria were kept to a minimum to allow a wide range of patients to be enrolled, and included: i) a surgically remediable cause for heart failure, such as severe aortic stenosis, ii) consideration for heart transplantation, iii) inability to provide informed consent, iv) terminal cancer and v) participation in any other clinical trial. In addition, for the current analyses only patients with sinus rhythm at the time of the baseline echo examination were included. Heart failure was diagnosed on the basis of typical symptoms and signs, with review of the chest X-ray, ECG and echocardiogram. The Auckland Ethics Committee approved the study and written informed consent was obtained from each patient during the index admission just prior to hospital discharge. Details of the clinical history, physical examination, blood biochemistry, ECG and chest X-ray were recorded prior to discharge.

The intervention trial involved follow-up over 12 months. The primary end-points for the analysis in this report were all-cause mortality, all-cause first readmission and a combined end-point of both

mortality and first readmission at one year. Outcome data was collected from hospital records, general practice records and death certificates.

Echocardiographic methods

All patients were examined lying on their left side and images were obtained according to a standard protocol using one of two ultrasound machines (ATL HDI-3000, ATL Ultrasound, Bothell, WA or Acuson XP128, Acuson Corp, Mountainview, CA). Images were recorded onto videotape and digitally acquired for off-line analysis. Mitral valve Doppler recordings were obtained from the apical four chamber view with a 5 mm pulsed wave Doppler sample volume placed distal (5-10mm) to the mitral annulus between the mitral valve leaflets.[248] The Doppler interrogation beam was carefully aligned with the direction of mitral flow. Pulmonary venous Doppler was attempted in all subjects, by placing a 5 mm pulsed wave Doppler sample volume in the right upper pulmonary vein in the apical four-chamber view. Isovolumic relaxation time (IVRT) was recorded by placing the sample volume adjacent to the anterior mitral valve leaflet, in the left ventricular outflow tract in a five-chamber view. The signal was considered optimal when a clear aortic valve closure click was observed as well as the onset of early mitral flow. All Doppler recordings were optimised to maximise the signal on the screen, eliminate excess gain and minimise wall filters, and were recorded at a sweep speed of 100 mm/s and only end-expiratory signals analysed.

Patients were instructed in the performance of a Valsalva manoeuvre (forced expiration against a closed glottis) and each practiced the manoeuvre at least once. Mitral valve inflow Doppler was then recorded during the Valsalva manoeuvre. Preload reduction was considered adequate if the mitral velocities dropped by 20%. The Valsalva was repeated up to three times in order to obtain adequate signals. In addition, a full clinical echocardiographic examination was performed. M-mode recordings were made from the parasternal long axis view and were used to calculate LV size, wall thickness, mass and fractional shortening. Left ventricular volumes and ejection fraction (EF) were measured using Simpson's biplane method from the apical four and two chamber views. Left atrial area was measured in the apical four-chamber view at end-systole. All echocardiographic images were obtained by specially trained research sonographers, without knowledge of the patients' clinical details.

Echocardiographic measurements

Triplicate measurements of all variables were made offline (Nova Microsonics/Kodak Eastman, Mahwah, NJ) by one observer who was blinded to the patients' clinical details. Measurements were made according to standard methods and included: i) 2-dimensional and m-mode measurements: left ventricular end-diastolic dimension (LVEDD), left ventricular end-systolic dimension left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV), left atrial area, ii) Doppler measurements: mitral valve peak early filling velocity (E), peak late filling velocity (A), deceleration time (DT) of the mitral E wave, A wave duration (A dur), isovolumic relaxation time (IVRT), pulmonary venous peak systolic velocity (S), peak diastolic velocity (D), atrial reversal velocity (AR), atrial reversal duration (AR dur), The following variables were calculated: E:A ratio = E velocity/A velocity, AR dur – A dur, stroke volume (SV) = LVEDV – LVESV, ejection fraction (EF) = SV/LVEDV x 100%.

Differentiation between diastolic filling patterns

After the baseline measurements were made, each subject was classified into one of the following categories of filling patterns[121,125]:

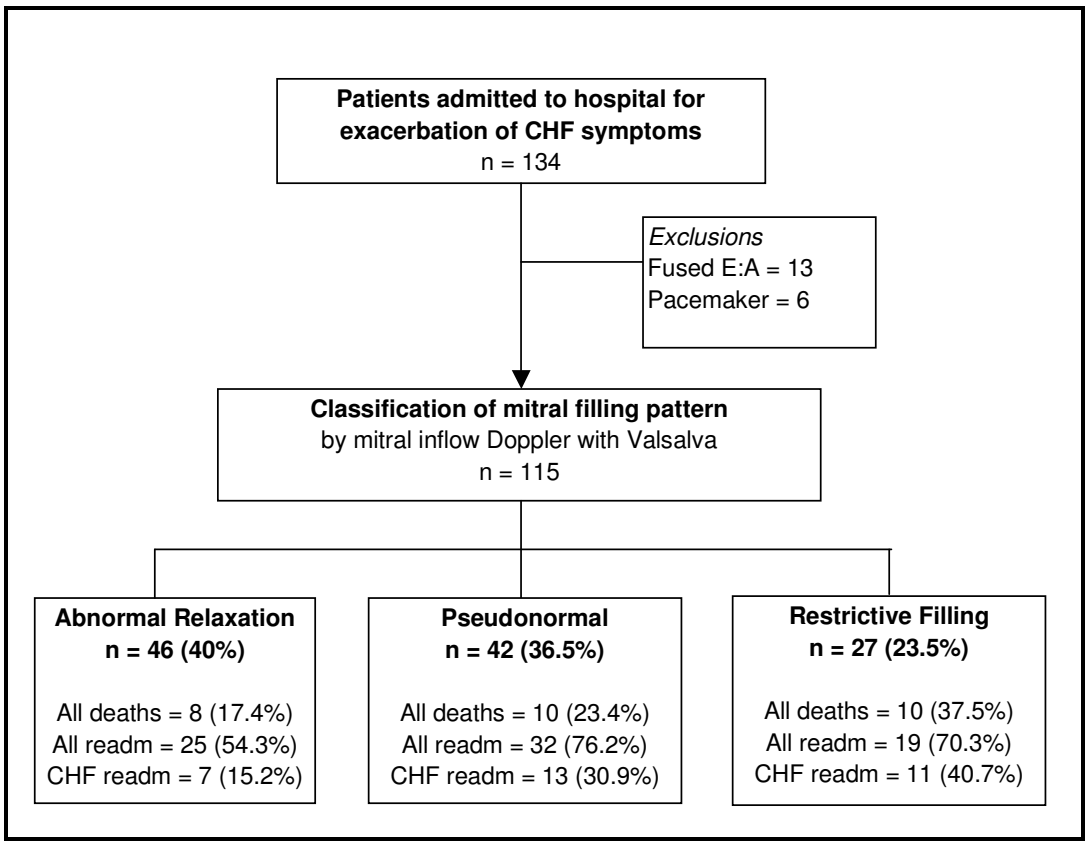
- normal filling: E:A ratio 1.0-2.0 and deceleration time 0.14 – 0.23 s
- abnormal relaxation: E:A ratio < 1.0 and deceleration time > 0.23 s
- pseudonormal filling: E:A ratio 1.0-2.0 and deceleration time 0.14 – 0.23 s, but E:A ratio < 1.0 and deceleration time > 0.23 s with Valsalva and/or pulmonary atrial duration: A wave duration ratio >1.2;
- restrictive filling: E:A ratio > 2.0 and deceleration time < 0.14 s

Patients exclusions and final mitral filling class

Patients were excluded if complete mitral Doppler measurements could not be obtained. In total, 19 (14.2 %) of the original study participants were excluded: 13 (9.7%) due to tachycardia and fused MV Doppler and 6 (4.4 %) who had a permanent pacemaker. This left 115 (85.8%) patients in

whom complete Doppler assessment was possible at baseline, patients were divided into three groups: abnormal relaxation (40%), pseudonormal (36.5%) and restrictive filling (23.5%) (Figure 17).

Figure 17 - Recruitment and final group classification of patients.



Statistical Analysis

Comparisons between groups for continuous normally distributed variables were made using Student's t-test and analysis of variance where appropriate. Non-parametric continuous data were analysed using Wilcoxon and Kruskall Wallace tests where appropriate. Differences between categorical variables were assessed using Chi-squared analysis. Stratified survival analysis (time to first event: death, admission or death and/or readmission) was performed using the Kaplan-Meier method. In multivariate models, Cox proportional hazards was used to adjust for the potential confounding effect of covariates, including age and LV ejection fraction. All tests were two-tailed and 5% significance level was maintained throughout. Procedures of the statistical analysis system SAS were employed in these analyses (SAS Institute, Cary, NC).

Results

Patients

One hundred and fifteen patients are included in this report. The mean age at entry to the study was 73 years (SD 10.8). Three quarters of the patients were classified as being NYHA functional class IV on admission but all patients improved sufficiently to be discharged from hospital. Heart failure was considered due to ischemic heart disease in 54%, and, while the remainder was classified as non-ischaemic, many of these patients had multiple potential causes of heart failure with the exact cause often being uncertain. 46% of all patients had a history of documented prior MI, 52% prior hypertension, and 29% diabetes. 52% had a prior admission for heart failure before the index admission. Most were receiving frusemide and 88% were receiving an ACE inhibitor. The average LV ejection fraction was 32% (SD13). Renal function was impaired with average creatinine clearance 48.9ml/min (SD 24) (normal range 90-140ml/min).

Mitral filling pattern

No patients had a normal filling pattern. Forty-six patients (40 %) were classified as abnormal relaxation, 42 (36.5 %) as pseudonormal and the remaining 27 (23.5 %) classified as restrictive filling (Table 16). There were no statistical differences in age, previous HF admissions, heart rate, sodium, creatinine, creatinine clearance or ACE inhibitor dose between the 3 groups. When comparing the abnormal relaxation group with the pseudonormal group, the LA area was smaller, the E:A ratio lower, the deceleration and isovolumic relaxation times longer. Comparing the abnormal relaxation group with the restrictive filling group, the systolic and diastolic blood pressures were higher, frusemide dose lower, LA area smaller, E:A ratio lower and deceleration and isovolumic relaxation times longer. The mitral A wave duration time was longer, but the pulmonary atrial reversal duration was not. Comparing the pseudonormal group with the restrictive filling group, both systolic and diastolic blood pressures were higher, E:A ratio was higher and deceleration time prolonged (Table 16).

Table 16 - Clinical and echocardiographic parameters at the time of discharge from hospital, after stabilisation with medication

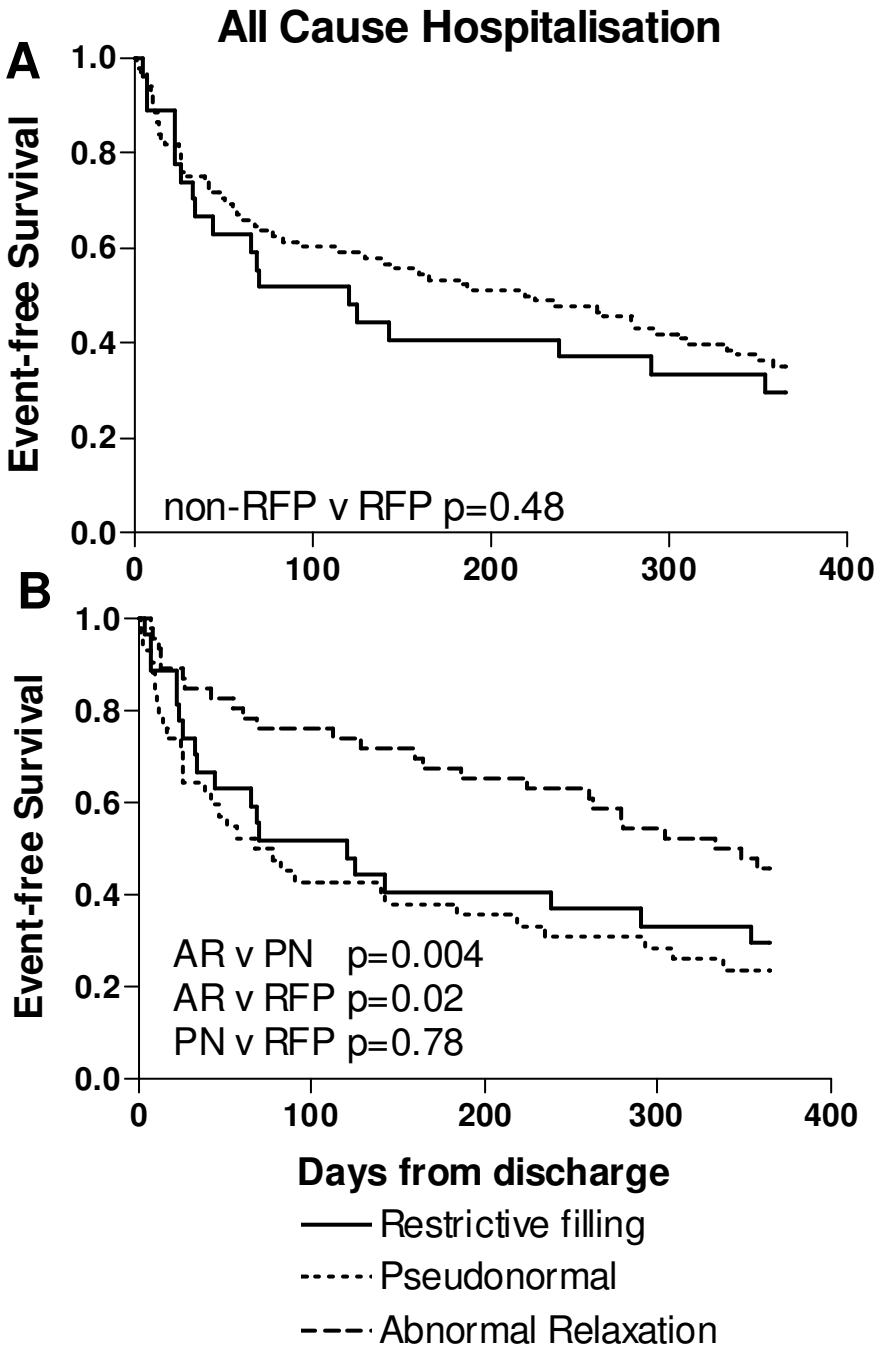
Variables	Abnormal relaxation	Pseudonormal filling		Restrictive filling	p
n (%)	46 (40%)	42 (36.5%)		27 (23.4 %)	
Age, (years)	73.5 ± 11.4	71.8 ± 9.8		69.6 ± 13.2	
NYHA class at discharge	1.7 ± 0.6	1.9 ± 0.5		2.0 ± 0.6	
Previous infarction (n (%))	24 (52%)	21 (51%)		13 (48%)	
Previous admissions (n)	1.1 ± 1.4	1.3± 1.8		1.3 ± 1.7	
Heart rate (bpm)	82.1 ± 13.2	78.2 ± 11.1		80.1 ± 11.1	
Systolic blood pressure (mmHg)	130.5 ± 22.7	128.0 ± 19.2		113.4 ± 19.3	# †
Diastolic blood pressure (mmHg)	71.8 ± 10.5	74.2 ± 12.2		63.7 ± 10.7	# †
Plasma sodium (mmol/l)	138.8 ± 3.5	139.2 ± 3.7		137.6 ± 6.9	
Plasma creatinine (mmol/l)	0.12 ± 0.03	0.13 ± 0.05		0.14 ± 0.06	
Creatinine clearance (ml/min)	49.6 ± 29.9	49.6 ± 19.8		49.2 ± 25.6	
Frusemide (mg)	87.1 ± 62.1	112.2 ± 86.7		155.6 ± 73.9	#
ACE inhibitors (mg)	9.4 ± 5.8	11.1 ± 6.6		10.6 ± 6.8	
LV end-diastolic volume (ml)	165.6 ± 71.8	181.0 ± 62.4		206.4 ± 83.2	
LV end-systolic volume (ml)	117.1 ± 66.2	125.9 ± 57.3		154.5 ± 75.4	
LV ejection fraction (%)	32.8 ± 13.6	32.0 ± 11.4		28.7 ± 12.5	
Left atrial area (cm^2)	24.3 ± 5.0	28.2 ± 4.3	*	28.2 ± 5.8	#
E:A ratio	0.7 ± 0.15	1.3 ± 0.3	*	2.5 ± 0.8	# †
Deceleration time (s)	0.269 ± 0.103	0.191 ± 0.053	*	0.132 ± 0.038	# †
A wave duration (s)	0.164 ± 0.024	0.153 ± 0.025		0.140 ± 0.024	#
Atrial reversal duration (s)	0.131 ± 0.024	0.155 ± 0.33		0.146 ± 0.037	
Isovolumic relaxation time (s)	0.073 ± 0.022	0.059 ± 0.017	*	0.053 ± 0.022	#

* $p < 0.05$ abnormal relaxation versus pseudonormal filling; # $p < 0.05$ abnormal relaxation versus restrictive filling; † $p < 0.05$ pseudonormal filling versus restrictive filling.
Values shown are mean ± standard deviation.
Abbreviations: ACE = angiotensin converting enzyme, E:A Ratio = ratio of early passive to late active mitral filling, LV left ventricle, NYHA = New York Heart Association class.

Time to first hospitalisation

During the twelve month follow-up period, 76 (66.1%) patients were readmitted to hospital. Readmission rates were similar between the non-restrictive group (57 readmissions, 64.8%) and the restrictive group (19 readmissions, 70.3%, p=0.48) (Figure 17A). Within the non-restrictive group there was a significant difference between the abnormal relaxation group (25 events, 54.3%) and the pseudonormal group (32 readmissions, 76.2%, p=0.0057) and a trend between the abnormal relaxation group and the restrictive group (19 readmissions, 70.3%, p=0.073), but no difference between the pseudonormal group (32 readmissions, 76.2%) and restrictive group (19 readmissions, 70.3%, p=0.52) (Figure 18B).

Figure 18- All-cause hospital admissions by non-restrictive versus restrictive filling (A) and abnormal relaxation, pseudonormal and restrictive filling (B)

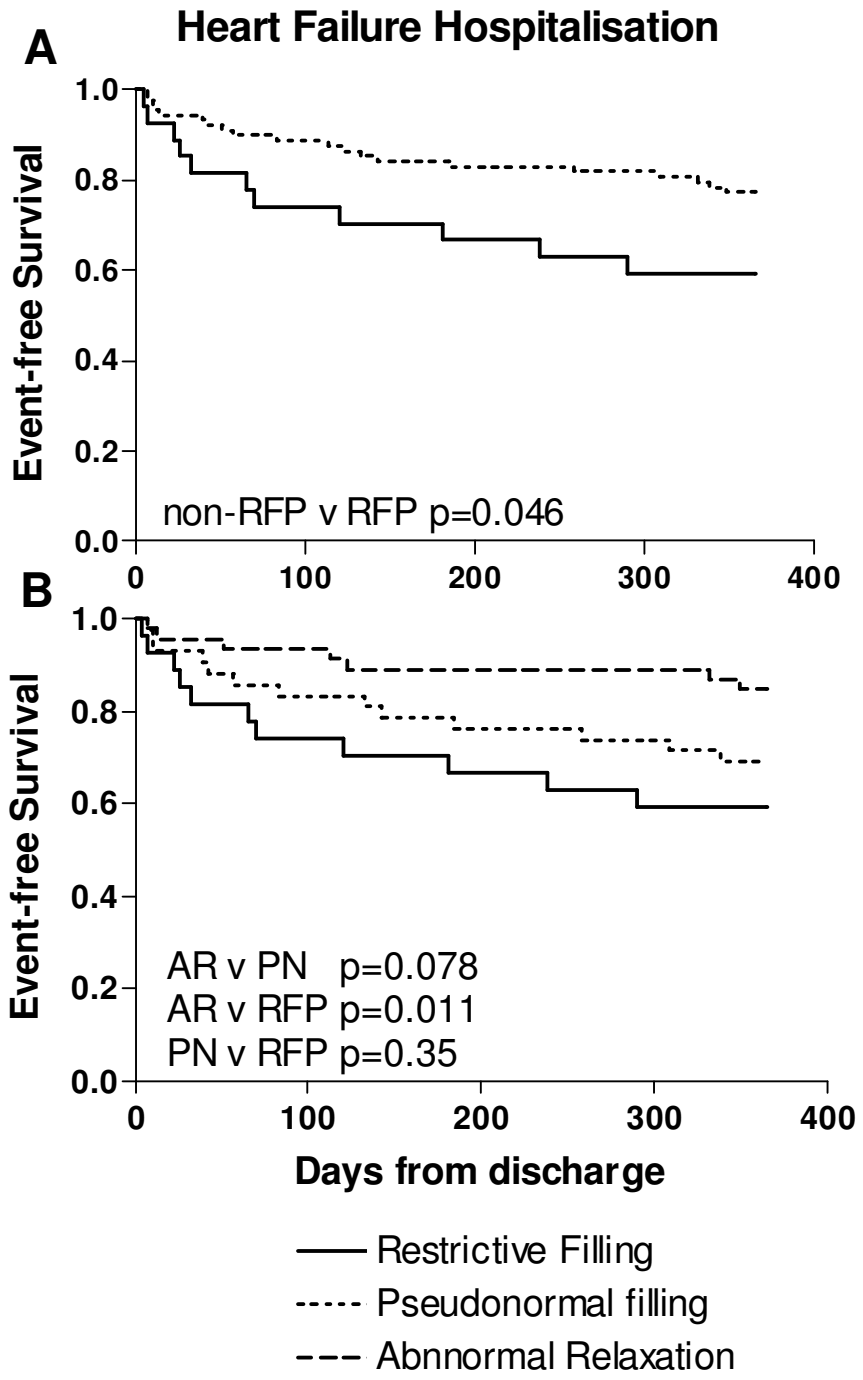


Kaplan Meier time to first event analysis.
Abbreviations: RF = restrictive filling, non-RF = non-restrictive filling, PN = pseudonormal filling, **AR = abnormal relaxation.**

Time to first heart failure hospitalisation

Of the 76 first readmissions to hospital, 31 (40.8%) were for exacerbation of HF. There were more readmissions for worsening heart failure in the restrictive group (11 HF readmissions, 40.7%) compared with the non-restrictive group (20 HF readmissions, 22.7%, p=0.046) (Figure 18A). Within the non-restrictive group, the abnormal relaxation group (7 HF admissions, 15.2%) had fewer HF admissions than the restrictive group (11 HF admissions, 40.7%, p=0.011) but not statistically different to the pseudonormal group (13 HF admissions, 30.9%, p=0.078). HF admissions were not different between the pseudonormal group (13 HF admissions, 30.9%). and the restrictive group (11 HF admissions, 40.7%, p=0.35) (Figure 19B).

Figure 19 - Hospital readmissions by non-restrictive versus restrictive filling (A) and abnormal, pseudonormal and restrictive filling (B)

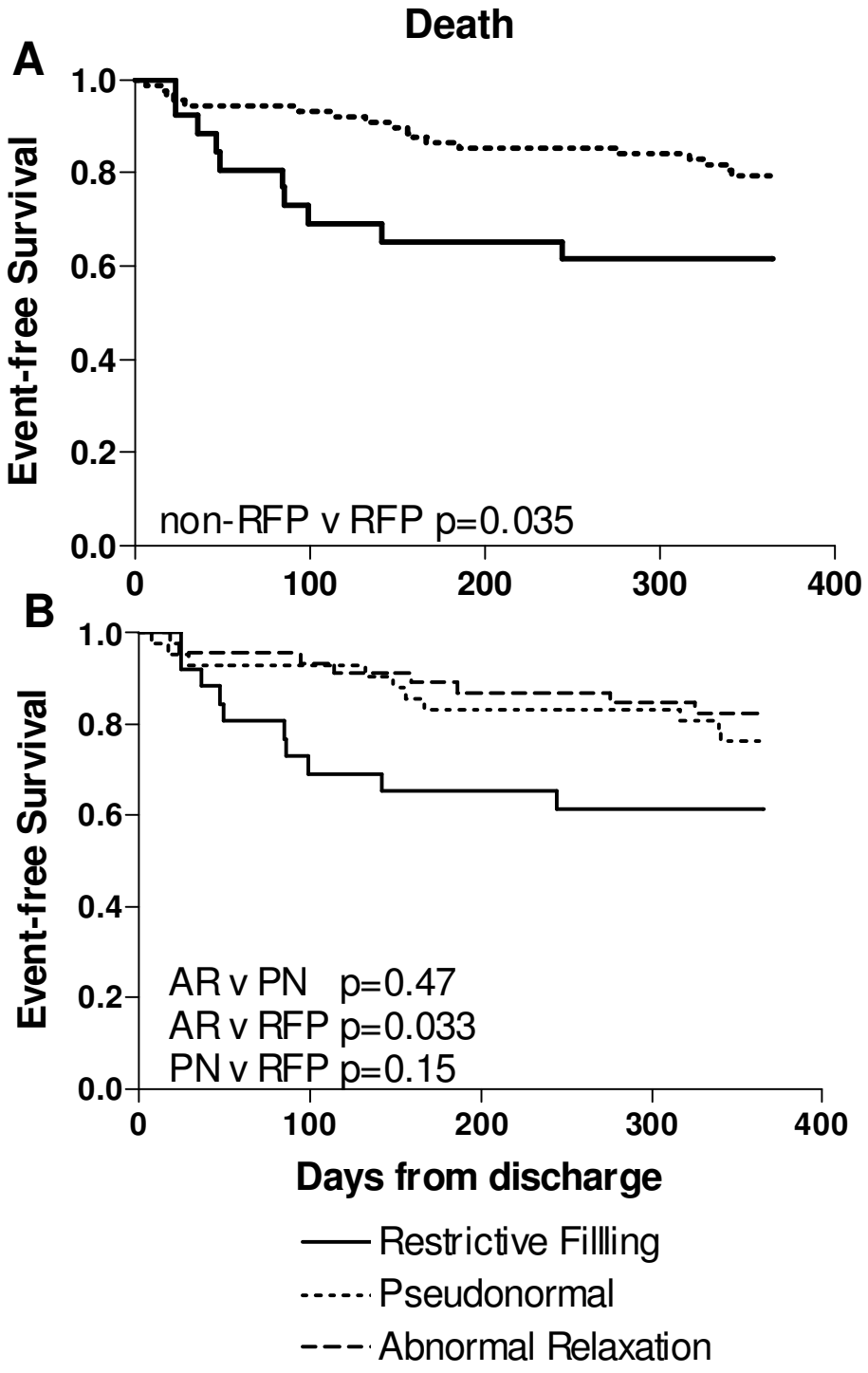


Kaplan Meier time to first event analysis.
Abbreviations: RF = restrictive filling, non-RF = non-restrictive filling, PN = pseudonormal filling, **AR = abnormal relaxation.**

One year all-cause mortality

During the twelve month follow-up period, there were 28 deaths (24.3%). Mortality was significantly different between the non-restrictive filling group (18 deaths, 20.5%) compared to the restrictive filling group (10 deaths, 37.0%, p=0.035) (Figure 19A). Within the non-restrictive group, mortality was lower in the abnormal relaxation group (8 deaths, 17.4%) compared with the restrictive group (10 deaths, 37.0%, p=0.033), but not different from the pseudonormal group (10 deaths, 23.8%, p=0.47). Survival in the pseudonormal group (10 deaths, 23.8%) was not statistically different from the restrictive group (10 deaths, 37.0%, p=0.15) (Figure 20B).

Figure 20 - All-cause death by non-restrictive versus restrictive filling (A) and abnormal, pseudonormal and restrictive filling (B)

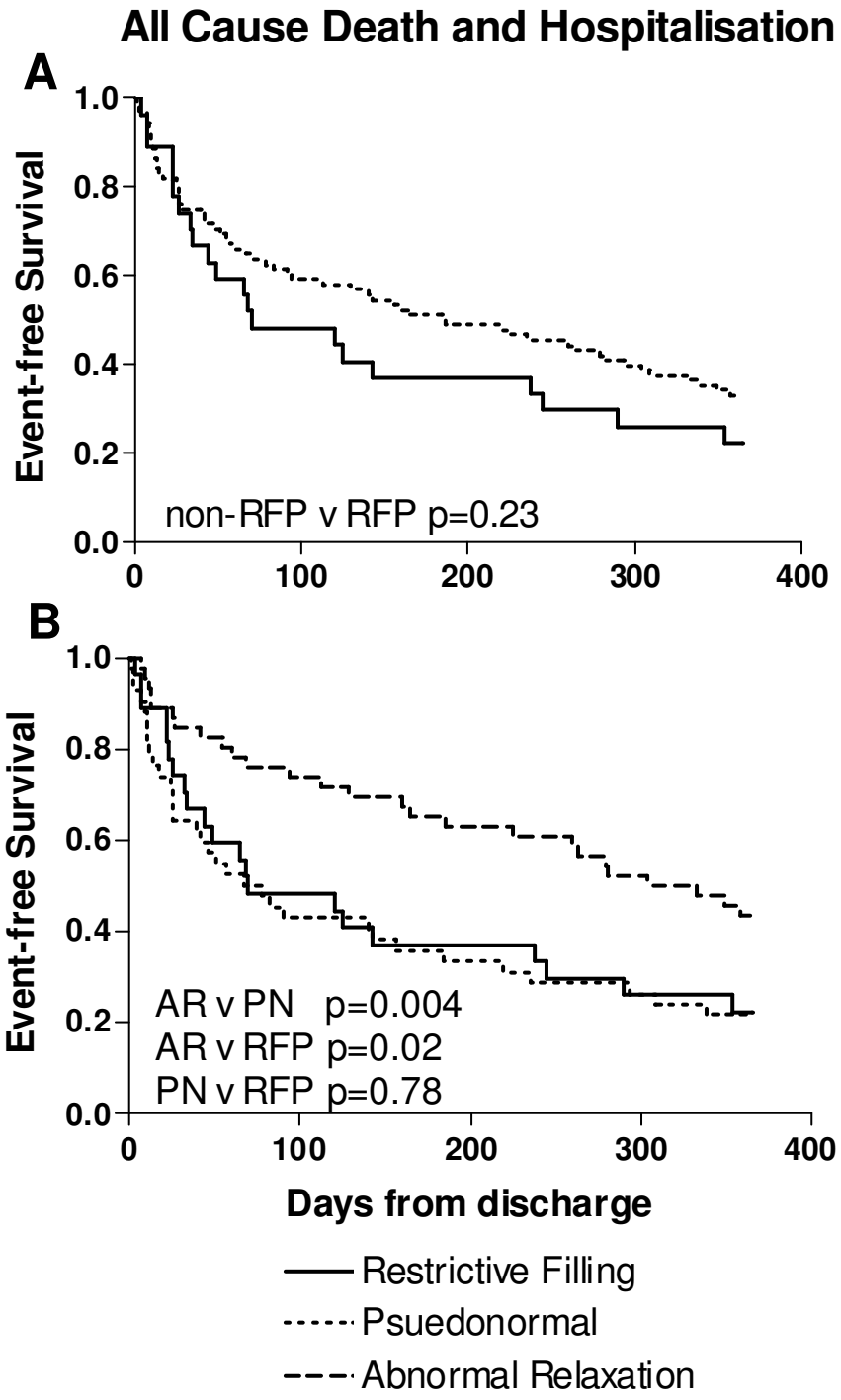


Kaplan Meier time to first event analysis.
Abbreviations: RF = restrictive filling, non-RF = non-restrictive filling, PN = pseudonormal filling, AR = abnormal relaxation.

All-cause mortality and readmission

During the twelve month follow-up period 80 (69.6%) patients either died or were admitted to hospital for any cause. There was no difference between the non-restrictive (59 events, 67.0%) and the restrictive group (21 events, 77.8%, p=0.23) for the combined end-point of death and/or readmission (Figure 21A). However, within the non-restrictive group there was a significant difference between the abnormal relaxation group (26 events, 56.5%) and the pseudonormal group (33 events, 78.6%, p=0.004) and the restrictive group (21 events, 77.8%, p=0.02), but no difference between the pseudonormal group (33 events, 78.6%) and restrictive groups (21 events, 77.8%, p=0.78) (Figure 21B).

Figure 21 - All-cause death/hospital readmission by non-restrictive versus restrictive filling (A) and abnormal, pseudonormal and restrictive filling (B)

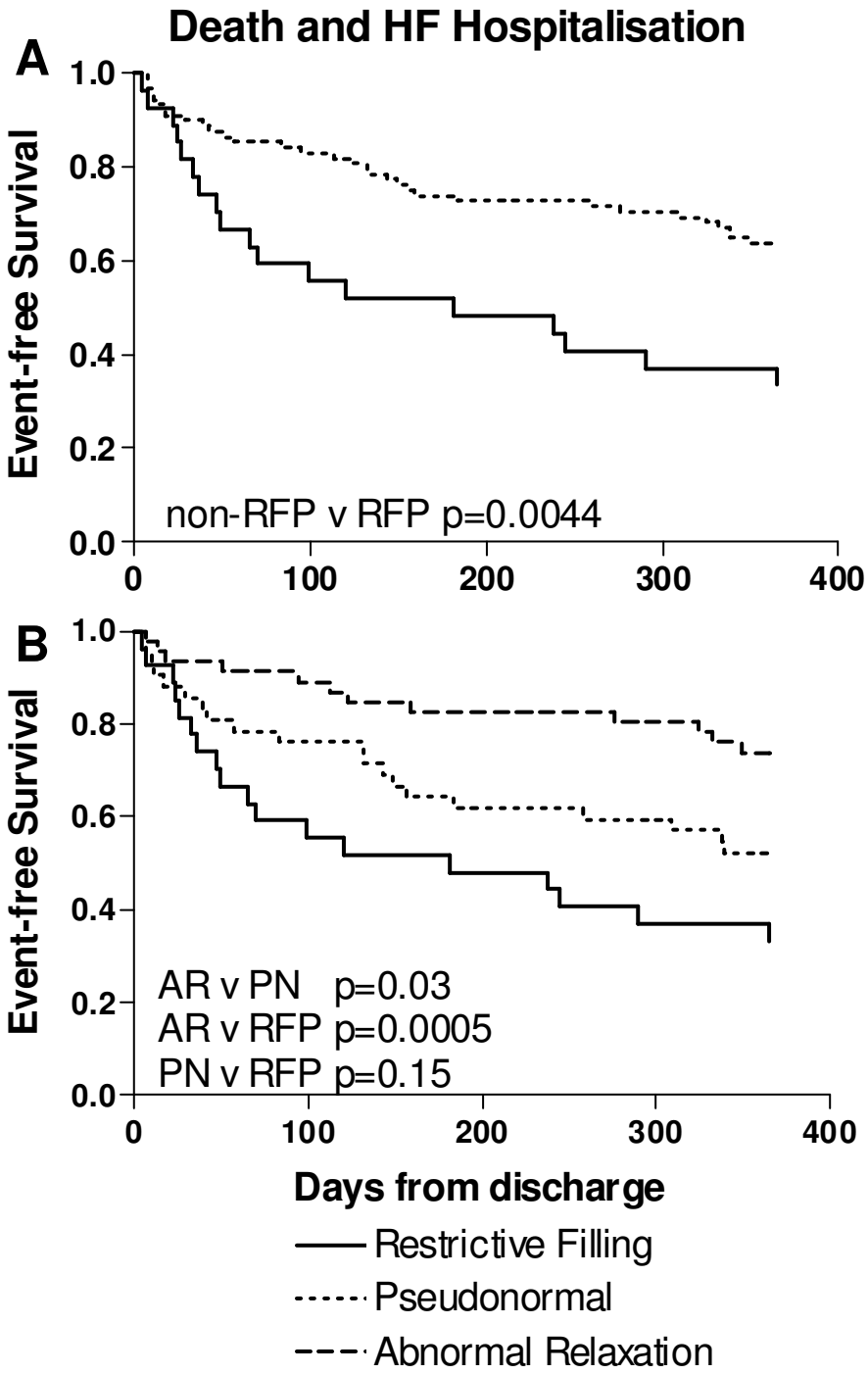


Kaplan Meier time to first event analysis.
Abbreviations: RF = restrictive filling, non-RF = non-restrictive filling, PN = pseudonormal filling, AR = abnormal relaxation.

All-cause mortality and heart failure readmission

During the twelve month follow-up period 59 (51.3%) patients either died or were admitted to hospital for exacerbation of HF symptoms. There was a significant difference between the non-restrictive 32 events, 36.4%) and the restrictive group (17 events, 63.0%, p=0.0044) for the combined end-point of death and/or HF readmission (Figure 22A). Within the non-restrictive group there was a significant difference between the abnormal relaxation group (12 events, 26.1%) and the pseudonormal group (20 events, 47.6%, p=0.03) and the restrictive group (17 events, 62.9%, p=0.0005), but no difference between the pseudonormal group 20 events, 47.6%) and restrictive group (17 events, 62.9%, p=0.15) (Figure 22B).

Figure 22 - All-cause death/HF hospital readmission by non-restrictive versus restrictive filling (A) and abnormal, pseudonormal and restrictive filling (B)



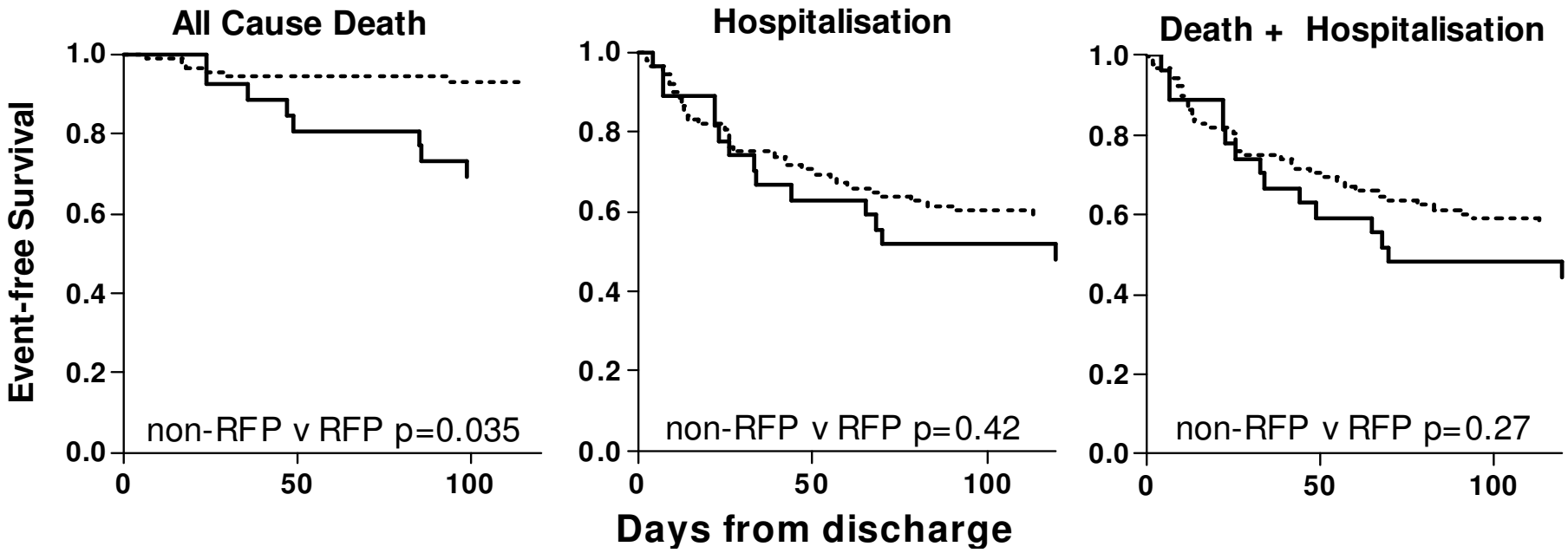
Kaplan Meier time to first event analysis.
Abbreviations: RF = restrictive filling, non-RF = non-restrictive filling, PN = pseudonormal filling, **AR = abnormal relaxation.**

Three month mortality or readmission

In the first three months following hospital discharge from hospital, there were 12 deaths (10.4%) and 47 readmissions (40.9%). Comparing the non-restrictive and restrictive groups, there was a significant difference in early mortality (5 (5.7%) v 7 (25.9%), p=0.0035) (Figure 23A) but no difference in readmission (34 (38.6%) v 13 (48.1%), p=0.42) (Figure 233B) or the combined endpoint of death and/or admission (34 (38.6%) v 14 (51.9 %), p=0.27) (Figure 23C).

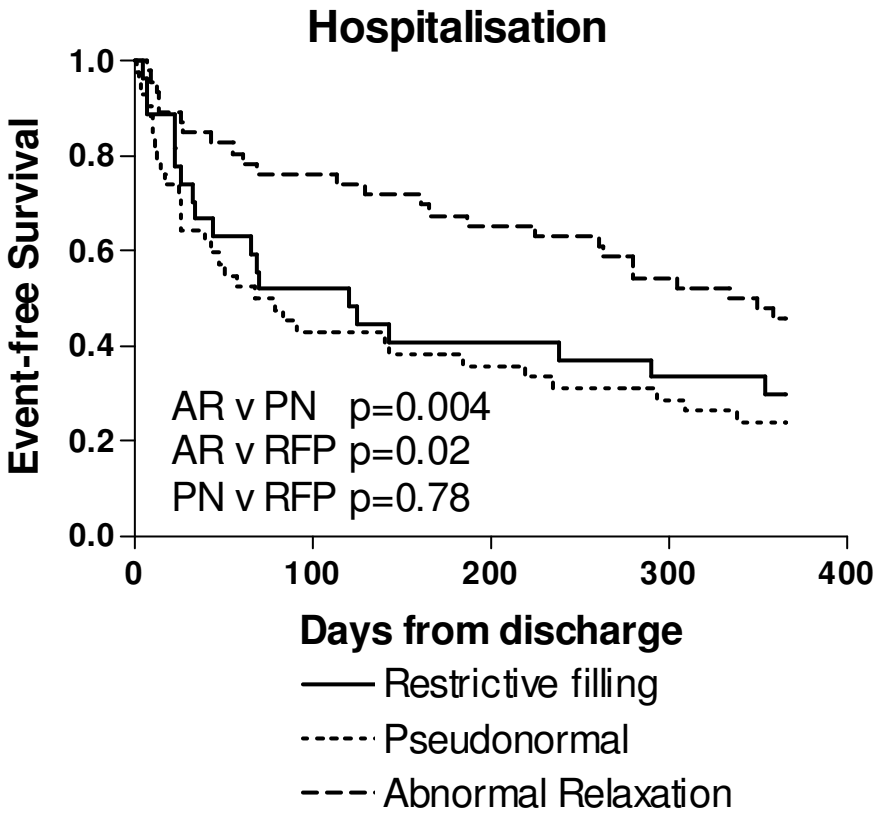
However, when the non-restrictive group were further divided into pseudonormal and abnormal, the abnormal relaxation group (11 admissions, 23.9%) had fewer hospital readmissions than the pseudonormal group (23 admissions, 54.7%, p=0.004) or the restrictive group (13 admissions, 48.1%, p=0.02) and the pseudonormal group (23 admissions, 54.7%) was not different to the restrictive group (13 admissions, 48.1%, p=0.78) (Figure 24).

Figure 23 – Three month survival plots for all-cause death, HF hospital readmission and combined mortality + readmissions (time to first event analysis) by non-restrictive versus restrictive filling



Kaplan Meier time to first event analysis. Abbreviations: RF = restrictive filling, non-RF = non-restrictive filling, PN = pseudonormal filling, AR = abnormal relaxation.

Figure 24 - Three month survival plots for hospital readmission (time to first event analysis) by mitral filling pattern



Kaplan Meier time to first event analysis.
Abbreviations: RF = restrictive filling, non-RF = non-restrictive filling, PN = pseudonormal filling, AR = abnormal relaxation.

Discussion

Patients with LV dysfunction and congestive heart failure have very poor prognosis.[2,3] Those who do survive have multiple readmissions to hospital with very high costs associated with their subsequent management.[4] End-systolic volume[114] and ejection fraction[112,115,116] are both very useful echocardiographic measurements for predicting survival in HF. However, once severe LV dysfunction is established, further prognostic differentiation is difficult. Previous work in this area has highlighted the need to differentiate patients with a restrictive filling pattern from those with a non-restrictive filling pattern, as the former is associated with poor survival[78,96,118-146] in HF.

To our knowledge, this is the first study to demonstrate that separation of the non-restrictive filling group using preload reduction provides additional prognostic information. In particular, the time to first readmission in patients with pseudonormal filling was comparable to that observed in patients with a restrictive filling pattern, and both were higher than that seen in patients with an abnormal relaxation pattern. Mortality in the patients with pseudonormal filling was intermediate between that observed in the abnormal relaxation group and the restrictive group, although not statistically different from either, which probably reflects the small number of events in each group. However, the pseudonormal group had hospital readmission rates as high as those observed in patients with the restrictive filling pattern, and both were nearly double that observed in the abnormal relaxation group. These data suggest that further differentiation of the HF patients with non-restrictive filling patterns provides important prognostic information, which may be useful for subsequent management. These data both complement and extend previous work in this area, which highlighted the need to differentiate restrictive from non-restrictive filling.

Restrictive versus non-restrictive filling in heart failure

Mitral valve E:A ratio and deceleration time are closely associated with mean left atrial pressure in patients with systolic dysfunction.[88] In patients with chronic heart failure and severely impaired LV function, deceleration time is the best predictor of pulmonary artery wedge pressure.[90,91] Deceleration time provides important prognostic information in addition to clinical parameters, especially when used to differentiate patients on the basis of restrictive and non-restrictive

filling.[78,96,118-147] Restrictive filling is correlated with NYHA functional class[268] and may be the single best predictor of cardiac death in patients with dilated cardiomyopathy.[121] Recently, in ischaemic cardiomyopathy patients, short deceleration time was related to myocardial viability and predicted improvement in ejection fraction post revascularisation.[140] Thus, deceleration time is important for differentiating restrictive from non-restrictive filling, but to date has not been useful for further differentiation of and risk stratification of the sub-groups within the non-restrictive filling group. Identification of the restrictive filling pattern by echo appears to be a surrogate for left atrial or left ventricular end-diastolic pressures.[16,88,90,95] By categorising patients according to filling pattern, one is identifying sub-groups in whom there is progressively higher mean left atrial pressure, thus it follows that if the pseudonormal filling group have higher LA pressures, higher event rates may be anticipated.

Comparison with previous studies

Despite an older, more generalised HF population, the current study demonstrated better survival in the non-restrictive group compared to the restrictive group in keeping with many other published studies.[78,96,118-146] In a larger study of patients with HF with longer follow-up similar differences in total mortality, hospital admissions for HF and a combined HF admission/death endpoint were demonstrated between the restrictive and non-restrictive group.[125] Deceleration time was also an important predictor of both death and a combined HF admission/death endpoint. In that study, short deceleration time, such as might be seen with restrictive filling, was the best single predictor of outcome. The study data were collected prior to the contemporary methods of echo assessment of diastolic function, and therefore the authors did not differentiate patients into pseudonormal or abnormal relaxation. Our data are in agreement with this study, but extends the findings and allows further differentiation of the non-restrictive group in particular.

One other study attempted to differentiate the non-restrictive filling group, by using contrast enhanced pulmonary venous Doppler.[137] Although the authors did not specifically separate patients into abnormal relaxation and pseudonormal filling, they found that the difference between atrial reversal duration and mitral A wave duration was an independent predictor of cardiac death or worsening heart failure. Among the non-restrictive filling group, a bigger difference between

atrial reversal duration and mitral A wave duration, which is associated with higher left atrial pressure, was associated with higher cardiac mortality.

Early readmissions

In the restrictive and pseudonormal filling groups, nearly two-thirds of the readmissions occurred in the first three months after the index HF admission, compared with the abnormal relaxation group, where only approximately one quarter of the readmissions occurred within 3 months. This suggests that correct identification of filling pattern may provide both short and medium-term prognosis.

Generalisability of results

Our study population included a mixed population of patients who were admitted to hospital for exacerbation of HF symptoms and are representative of those patients in a general hospital setting. Other studies of similar nature often included younger patients, referred for evaluation prior to heart transplantation, often with severely impaired systolic function.[78,122,125,127,130,139] These differences are reflected in the high event rate in our study compared to some previously reported studies. Because of the nature of the study, patients with tachycardia, atrial fibrillation or implantable pacemakers were excluded from this analysis and thus, these results may have limited generalisability in those groups.

Limitations

We included patients with mitral regurgitation and did not quantify the degree of regurgitation. Some studies have excluded patents on the basis of significant mitral regurgitation as it might lead to misleading results. However, this does not appear to be the case in dilated cardiomyopathy patients (ischaemic and non-ischaemic) where excellent correlation between mitral deceleration time and pulmonary venous recordings was seen even in patients with significant mitral regurgitation.[90]

Invasive measurements of LA pressure would have confirmed the hypothesis that these findings reflect higher LA pressure in each group, which is in turn associated with mortality. We believe there is considerable experimental data to support the hypothesis that pseudonormal filling is associated with higher LA pressure and likewise the restrictive filling pattern is as well.

Another limitation is the use of mitral filling pattern for assessment of diastolic filling. Heart rate, loading conditions and age affect mitral filling. Neither heart rate nor age was not significantly different between the groups. Cardiovascular medications may affect loading conditions. All of these subjects were on optimal medical therapy and had been stabilised in hospital prior to entry into the study. It is thus unlikely that major swings in preload would have affected our results. ACE inhibition was similar between the groups, as was B-blocker use. Diuretic use was incrementally higher in each of the groups: pseudonormal higher than abnormal relaxation and likewise restrictive higher than pseudonormal. If anything the higher diuretic use would have tended to lower LA pressure in those groups, and probably reflects the higher symptomatic status of those patients. Tissue Doppler and in particular the ratio of the MV inflow E velocity of the MV annular velocity (Ea) (E/Ea) [83,84] may have shown similar results and would potentially be a more powerful continuous variable. It also may be useful in patients with atrial fibrillation, who are by necessity excluded from the methodology used in the current study.

Conclusions

This study has demonstrated that in a population of older patients with HF the restrictive filling pattern is associated with poor survival and high hospital readmission rates within one year of an index HF admission. In addition, the pseudonormal pattern of mitral filling is also associated with readmission rates which are comparable to those observed in the restrictive filling group - the combined end-point of death or readmission was intermediate between that observed with restrictive filling and abnormal relaxation. Mitral filling pattern is probably a surrogate for LA pressure and the differentiation between the three groups in the current study is likely to reflect three progressive tertiles of LA pressure.

Restrictive mitral filling pattern has previously been shown to be a useful prognostic indicator and can easily detect those patients at highest risk. The current approach, which uses preload reduction, allows further differentiation of the non-restrictive filling group into those with intermediate risk from the patients with lower risk. This is a relatively easy addition to routine clinical echocardiography, which may provide important prognostic information in a wide range of patients with HF, which might otherwise have been overlooked. Importantly, most of the readmissions occurred within three months of discharge from hospital. Identifying these patients early may allow for more targeted management and potentially event reduction and cost saving.

Key Points:

- Diastolic filling pattern can be used to stratify heart failure patients in terms of risk of death and/or hospitalisation
- In particular when preload manipulation is used, it is possible to identify patients with pseudonormal filling, whose event rate is intermediate between the highest risk group (restrictive filling) and lowest risk group (abnormal relaxation)

Chapter 4 - The prognostic significance of restrictive diastolic filling associated with HF or MI: A meta-analysis.

Background

Echo-Doppler indices of diastolic function have been used to identify sub-groups of patients with altered risk in heart failure (HF) populations,[78,96,118-146] after acute myocardial infarction (AMI)[155-174] post coronary artery bypass grafting (CABG) [286,144] and in population studies.[162,287] Many of these Doppler studies evaluated the association of mitral filling pattern with prognosis, and specifically compared the restrictive filling pattern (RFP) with the non-restrictive filling patterns (non-RFP). Although many of these studies show significant increases in mortality with advanced filling patterns, the relative risk between the groups is varied because of the differences in baseline characteristics, number of events, follow-up times and statistical chance.

The aim of these meta-analyses was firstly to combine the results of all studies investigating the relationship between prognosis and echocardiographic diastolic measurements in order to gain an accurate estimate of the risk associated with advanced diastolic filling abnormalities. Primarily, evaluating the mortality associated with restrictive mitral filling pattern compared to the non-restrictive filling pattern in patients with HF and post AMI. Secondly, to evaluate the relationship between diastolic filling pattern and development of HF post AMI and recurrent hospital admissions in patients with HF. Thirdly, to determine the incremental prognostic relationship between different filling patterns in HF.

Methods

Identification of studies

Published studies were identified through online searches of several medical databases: Biological Abstracts, Clinical Evidence, Current Contents, Embase, Medline, Medline In-progress and PubMed, using the search terms: incidence, prognosis, outcome, mortality, clinical trials, echocardiography, ventricle, systolic, diastolic, HF, LV dysfunction and AMI. The citation lists of the identified papers were also reviewed. All authors were contacted and asked to provide further data or studies (published or unpublished). One additional unpublished study was identified this way.[169]

Criteria for study inclusion

From the online searches, we selected any study that included echocardiography, prognosis, HF, LV dysfunction and/or AMI. Each study was then reviewed according to a pre-determined protocol, which included information about patients, recruitment and follow-up (prospective, retrospective, consecutive recruitment, exclusions and reason), co-morbidity (NYHA classification, LV ejection fraction, aetiology), loss to follow-up, completeness of data (i.e. in how many patients the echo measurements were actually performed) (Table 17). Only the first three questions were compulsory for inclusion.

Table 17 - Study review questionnaire

Questions:	
Were the subjects enrolled retrospectively or prospectively?	**Prospective**
Were patients enrolled on the basis of their clinical syndrome?	**HF or AMI**
What is the endpoint?	**death, transplantation, HF admission, development of HF**
Setting	
How many patients enrolled at baseline?	
Were patients enrolled consecutively?	
How long was the average follow-up?	
How many patients were lost to follow-up?	
How was restrictive filling defined?	
How many patients in diastolic analysis?	
Main aetiology	
Average age	
male/female	
Average EF	
Were patients matched at baseline for other clinical variables?	
Included in Review?	Bold questions must be answered to be included
If not, why not?	
comments	

Definition of a prospective study

For the purposes of these analyses, we determined a prospective study to be one where patients were enrolled in a study and then followed up for a period of time. The diastolic analysis may have been retrospectively applied, but the patients needed to be recruited at the time point where follow-up began, rather then the time point where follow-up concluded. Retrospective cohort studies where patients were identified at the end of the follow-up period were thus not included. Most studies recruited consecutive patients, although this was not an inclusion criterion in order to allow the exclusion of subjects in whom data was incomplete, i.e. atrial fibrillation or suboptimal imaging.

Criteria for heart failure or myocardial infarction

Diagnostic criteria for HF or MI were clearly stated in most studies. Studies that enrolled patients on the basis of LV dysfunction only without a diagnosis of HF or MI were excluded.

Data collection

For many studies, the numbers of patients and events in each filling pattern group were identified in the publication. Every investigator was contacted by letter and/or email asking them to confirm the data we had extracted or provide data where the paper's content was insufficient. Authors were also asked to confirm that patients were included in one publication only and to identify sources of potential publication duplication. We also sought any additional references to either published or unpublished studies. For papers published in languages other than English, we obtained English translations and data directly from the authors or used numbers in the English language abstracts.{147,162,166,273] One paper reported pseudonormal and RFP together and these deaths were attributed equally between the two groups{161] and one author supplied unpublished data from a doctoral thesis[169] to supplement already published data.[173] In some HF studies, it was not possible to separate the deaths from transplantations.[147,160] Not all studies reported diastolic parameters as a primary endpoint. We contacted authors of any publications that included outcome data and comprehensive echocardiographic examinations at baseline to determine whether patients were able to be stratified according to diastolic filling grade.

Differentiation of restrictive filling

Restrictive filling was determined by the individual authors and clearly stated in the manuscript methods. These criteria were reviewed and considered to be acceptable and in accordance with internationally accepted standards, allowing for slight regional and institutional variation.

Statistical methods

The Cochrane Collaboration Program Review Manager 4.2.7 was used for analysis. For each study, patients were stratified according to the individual study criteria as restrictive or non-restrictive. The number of patients and the number of events allocated to each group were recorded. The odds ratio using a fixed effects model is presented, but a random effects model was

also evaluated. As the latter was not different from the former we only present the fixed effects model. Each study was weighted in the model according to sample size. Standard tests for heterogeneity were used including Chi^2 (presented) and funnel plots were examined for evidence of publication bias and none was observed.

Many of the HF studies included patients with non-ischaemic dilated cardiomyopathy only, thus the studies were subdivided by aetiology: non-ischaemic dilated cardiomyopathy and a mixed aetiology group (HF of any cause) according to the individual study recruitment strategies. HF end-points were all-cause mortality, a composite endpoint of death or transplantation, and readmission to hospital. For the MI analysis, all-cause mortality was the major endpoint under consideration, although sub-analyses of development of HF were also performed in this group. Further sub-analyses were performed to determine the effect of other diastolic filling patterns.

Results

Seventy-nine potential studies were identified, of which 43 studies were included in this analysis: 26 studies recruited HF patients and 17 studies recruited patients after AMI. Thirty-six studies were reviewed and subsequently excluded: 6 studies were retrospective cohort studies; in 9 studies patients were not selected on the basis of a clinical syndrome of HF or MI; 2 studies did not collect data about filling pattern; 2 studies reported other outcomes than those previously defined; 17 studies reported patients that were included in other patient cohorts and publications and the remaining two studies that we were unable to confirm or obtain data(Table 18).

Table 18 - Excluded Studies

Author	Year	Reason for Exclusion
Heart failure studies		
Pinamonti [120]	1993	Same patient cohort [127]
Shen [269]	1993	Same patient cohort [118]
Rihal [123]	1994	Retrospective
Werner [270]	1995	Same patient cohort [122]
Fuchs [271]	1995	Same patient cohort [122]
Werner [277]	1996	Same patient cohort [122]
Traversi [246]	1996	Same patient cohort [78]
Lipsitz [276]	1996	Retrospective
Dujardin [272]	1998	Retrospective
Florea [138]	1998	Not filling pattern
Rich [132]}	1999	Retrospective
Dini [256]	2000	Same patient cohort [259]
Dini [259]	2000	Same patient cohort [259]
Farris [142]	2002	Retrospective
Morales [141]	2002	Unable to confirm data
Sabharwal [145]	2004	Not filling pattern
Acute myocardial infarction studies		
Garcia-Rubira [278]	1997	Same patient cohort [159]
Poulsen [280]	2000	Same patient cohort [161]
Moller [279]	2000	Same patient cohort [156]
Poulsen [280]	2001	Same patient cohort [161]
Poulsen [282]	2001	Same patient cohort [161]
Moller [166]	2001	Same patient cohort [156]
Boccalandro [255]	2002	Retrospective
Szymanski [168]	2003	Unable to confirm data
Moller [285]	2003	Same patient cohort [156]
Schwammenthal [284]	2003	Same patient cohort [171]
Hillis [146]	2004	Same patient cohort [157]
Other aetiology		
Hurrell [129]	1998	Not HF / AMI
Lapu-Bula [274]	1998	Retrospective, not HF / AMI
Yong et al [257]	2001	Post CABG
Vaskelyte [286]	2001	Post CABG
Aurigemma [287]	2001	Population, Not HF / AMI
Alameda [261]	2002	Not HF or AMI
Kuperstein [258]	2003	Retrospective, not HF / AMI
Liu et al [114]	2003	Not HF or AMI
Wang [143]	2003	Not HF or AMI

Abbreviations: AMI = acute myocardial infarction, CABG = coronary artery bypass grafting, HF = heart failure

Heart failure

Study data (number of patients and events) were confirmed by 20 authors. Despite repeated attempts, confirmation was not possible for 7 studies.[121,124,126-128,141,273] Of these, 6 studies clearly reported numbers in the publication[121,124,126-128,273] and these unconfirmed numbers were used in the analysis, the remaining one study may have been eligible but was not included[141]. One author combined the results of two studies to exclude overlapping patients.[137,256] Thus, this report includes 3020 patients reported in 6 studies of non-ischaemic dilated cardiomyopathy (379 patients, 91 deaths) and 20 studies of HF of ischaemic or mixed origin (2641 patients, 593 deaths)(Table 19). The average follow-up time varied between the studies: one study was less than six months; seven were one year; fourteen were between 1 and 3 years and the remaining four studies had average follow-up of 3 or more years (Table 19).

Table 19 - Prospective prognosis studies using restrictive filling pattern classification in HF

First Author	Year	Author confirmed data	Country	Published Language	N	% IHD	EF %	FU	Events	Echo definition of restrictive filling
Idiopathic dilated cardiomyopathy										
Werner [122]	1994	yes	Germany	English	57	0	33	2.5	15 deaths 4 Tx	DT < 140 ms
Piszczek [126]	1996	Numbers in abstract	Poland	Polish	49	0	-	2	15 deaths	DT <115 ms
Sun [128]	1997	Numbers in paper	USA	English	41	0	30	1	6 deaths 2 Tx	DT < 110 ms
Pinamonti [127]	1997	Numbers in paper	Italy	English	110	0	25	4	28 deaths 13 Tx	DT <115 ms
Fruhwald [131]	1999	Yes	Austria	English	32	0	< 45	2	7 deaths 3 Tx	Non-Restrictive Restrictive
Cabell [185]	2002	Yes	USA	English	100	0	22	2.5	25 deaths	Non-Restrictive Restrictive
Mixed aetiology										
Shen [118]	1992	Yes	France	English	62	32	-	2.5	23 deaths 4 Tx	DT < 150 ms
Ortiz [119]	1993	Yes	Brazil	English	95	-	-	1	13 deaths	DT < 140 ms
Xie [121]	1994	Numbers in paper	USA	English	100	55	26	1	26 deaths	DT < 140 ms
Belardinelli [124]	1995	Numbers in paper	Italy	English	55	67	27	1	6 deaths 9 HF	Non-restrictive Restrictive
Giannuzzi [125]	1996	Yes	Italy	English	508	94	-	4	100 deaths	DT < 125 ms
Pozzoli [78]	1997	Yes	Italy	English	173	-	23	1.5	41 deaths 25 Tx 68 Hosp	Non-Restrictive Restrictive: Reversible Non-Reversible
Boni [273]	1998	Numbers in Abstract	Italy	Italian	35	46	-	1.5	6 deaths 1 Tx	High E:A, short DT
Temporelli [130]	1998	Yes	Italy	English	144	76	22	4	37 deaths 7 Tx	Reversible Non-Reversible
Yu [133]	1999	yes	China	English				1	33 deaths	
Akioka [135]	2000	yes	Japan	English	33	33	< 50	0.25	5 deaths 0 Tx	DT < 120 ms
Bettencourt [134]	2000	yes	Portugal	English	97	53	34	1.5	18 deaths 0 Tx 30 Hosp	DT < 130 ms
Dini [137,256]	2002	yes	Italy	English	207	68	32	2	44 deaths 0 Tx 37 Hosp	DT < 140 ms
Tabet [136]	2000	yes	France	English	85	18	< 45	1.5	14 deaths 12 Tx	DT < 145 ms
Hansen [139]	2001	yes	Germany	English	265	28	24	1.5	52 deaths 37 Tx	DT < 140 ms
Yong [140]	2001	yes	USA	English	40	100	28	1	5 deaths 3 Tx	DT < 150 ms
Whalley	2002	yes	New Zealand	English	115	54	32	1	28 deaths 76 Hosp	DT < 140 ms
Rossi [260]	2002	yes	Italy	English	243	75	31	3.5	60 deaths/Tx	DT < 140 ms
Yamamoto [96]	2003	yes	Japan	English	96	-	< 40	2.5	36 deaths	DT < 140 ms
Zheng [147]	2004	yes	China	Chinese	90	47	30	1.5	21 deaths 12 Tx	Restrictive filling index > 1

Abbreviations: DT = deceleration time of passive mitral filling velocity (E), EF = ejection fraction, FU = follow up, HF = HF, Hosp = hospital admission for heart failure, IHD = ischaemic heart disease, Tx = cardiac transplantation, Year = year of publication.

Restrictive filling and mortality

3020 patients are included in this analysis: 1241 (41.1 %) patients had a restrictive filling pattern and the remaining 1779 (58.9 %) had a non-restrictive pattern. There were 684 deaths: 452 (66 %) of the deaths of occurred in the restrictive group and 232 (34 %) of the deaths occurred in the non-restrictive group. The overall event rate was 22.6 %; 36.4 % in the restrictive filling group and 13 % in the non-restrictive filling group. The overall odds ratio for death associated with restrictive filling pattern was 4.32 (95% CI 3.57, 5.22), $p < 0.00001$. There was no significant heterogeneity between the studies ($p = 0.47$) (Figure 25). In two studies, transplants were included as deaths because the composite endpoint was initially reported and separation of events was not possible.[147,260]

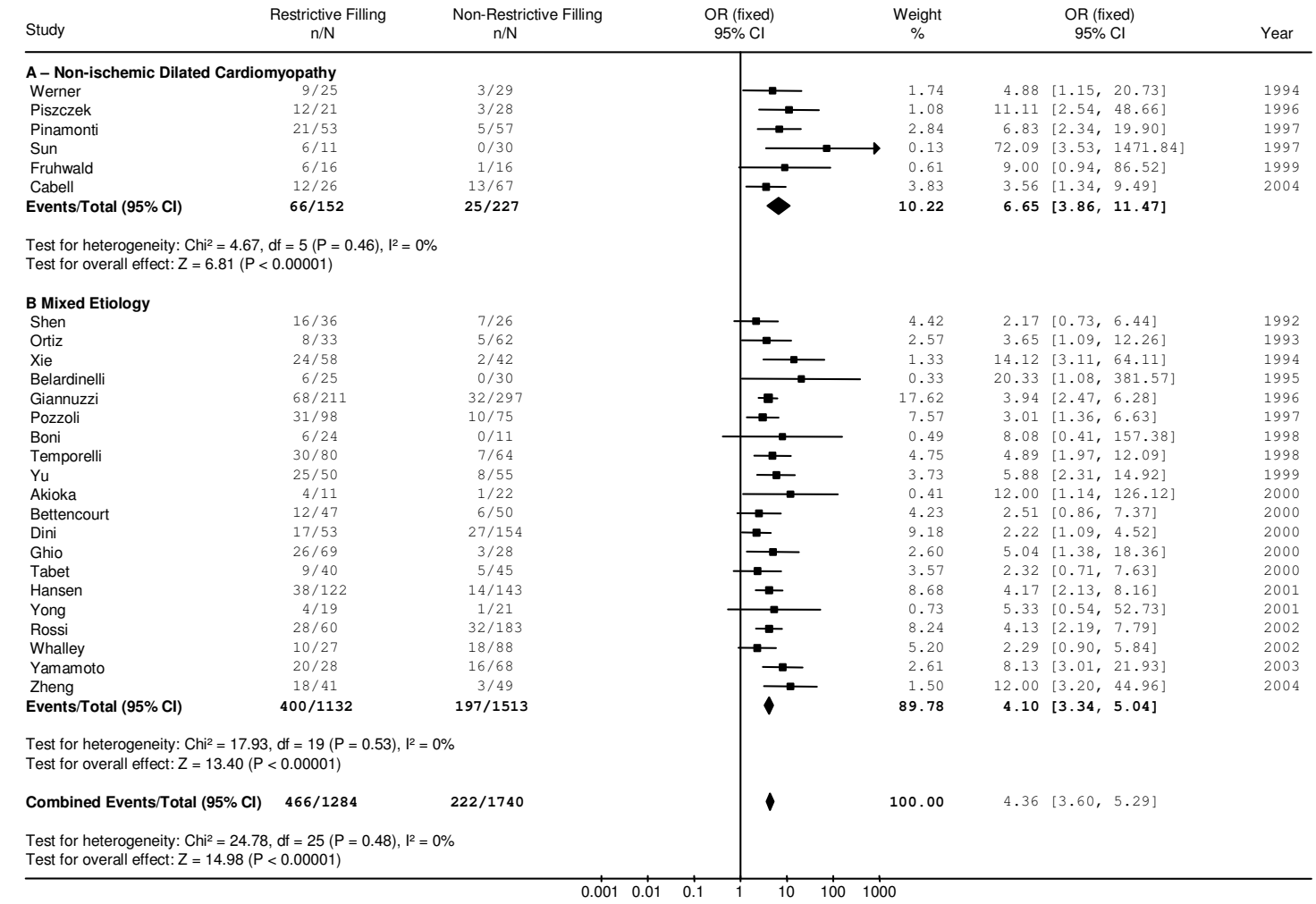
Non-ischaemic dilated cardiomyopathy

379 patients were included in this sub-analysis. 152 (40 %) patients had a restrictive filling pattern and the remaining 227 (60 %) patients had a non-restrictive pattern. There were 91 deaths in total: 66 (73 %) occurred in the restrictive group and 25 (27 %) in the non-restrictive group. The overall event rate was 24 %; 43 % in the restrictive group and 11 % in the non-restrictive group. The odds ratio for death associated with restrictive filling pattern was 6.65 (95% CI 3.86, 11.47), $p < 0.00001$. There was no significant heterogeneity within this group of studies ($p = 0.46$) (Figure 25A, *top*).

Ischaemic/mixed aetiology

2641 patients were included in studies of mixed aetiology. 1089 (47 %) patients had a restrictive filling pattern and the remaining 1552 (53 %) patients had a non-restrictive pattern. There were 593 deaths in total, 386 (65 %) in the restrictive group and 207 (35 %) of the deaths occurred in the non-restrictive group. The overall event rate was 22.4 %; 35.4 % in the restrictive group and 13.3 % in the non-restrictive group. The odds ratio for death associated with restrictive filling pattern was 4.05 (95% CI 3.30, 4.97), $p < 0.00001$. There was no significant heterogeneity within this group of studies ($p = 0.53$) (Figure 25B, *bottom*).

Figure 25 - Meta-analysis of all-cause mortality associated with restrictive filling in HF

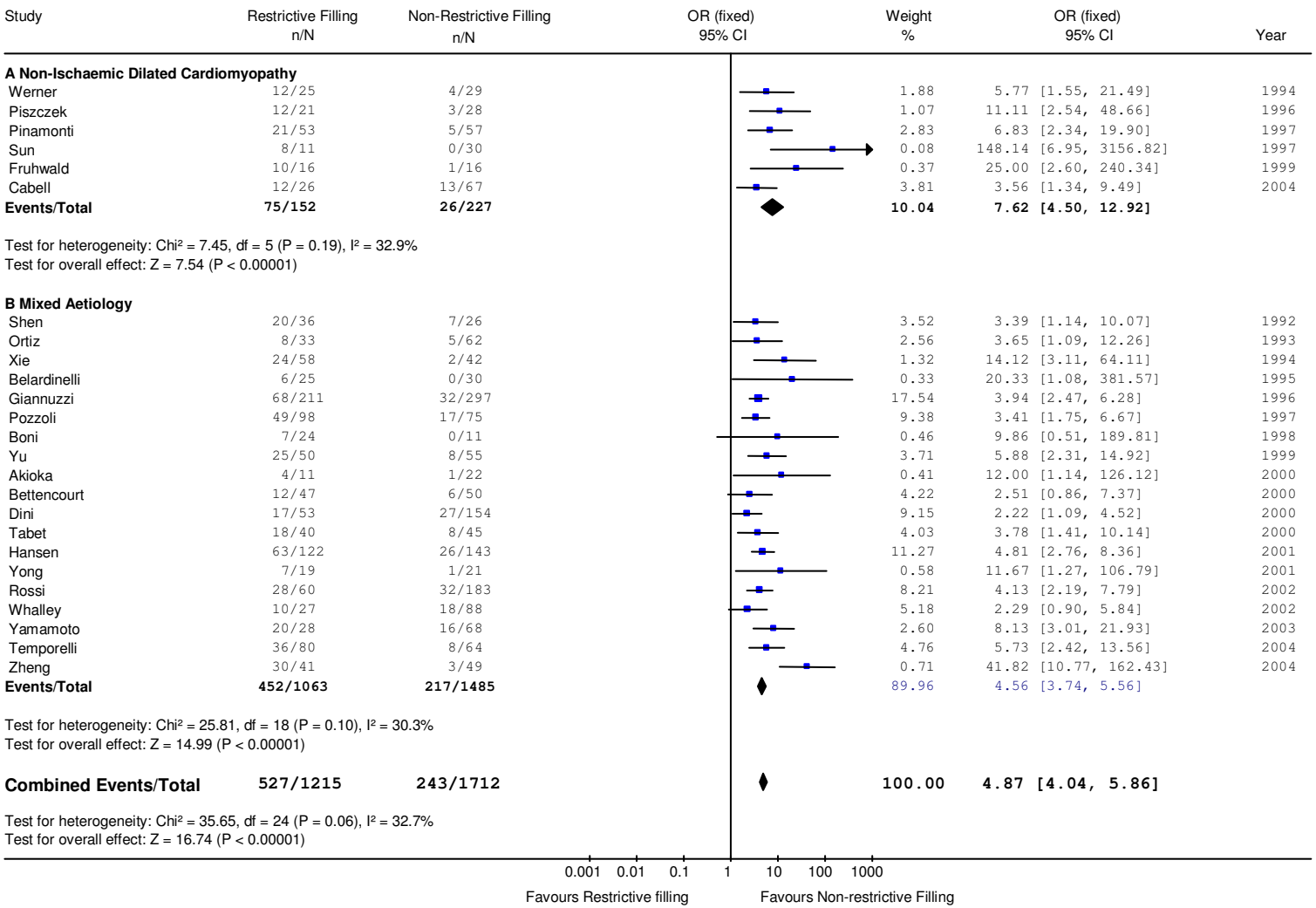


Fixed effects model, studies weighted according to sample size.
Abbreviations: CI = confidence interval, n = number of events, N number of patients, OR = odds ratio, Year = year of publication.

Restrictive filling and death and/or transplantation

Thirteen studies reported transplantation. There were 86 transplants in addition to 684 deaths previously reported: 87 transplants occurred in the restrictive group, and 98 in the non-restrictive group. The overall event rate was 26.3 %; 43.4 % in the restrictive group and 14.2 % in the non-restrictive group. The overall odds ratio for death and/or transplantation associated with restrictive filling pattern was 4.87 (95% CI 4.04, 5.86), $p < 0.00001$. There was no significant heterogeneity within this group of studies ($p = 0.06$) (Figure 26). Within the idiopathic group of studies, the odds ratio for death and/or transplantation associated with restrictive filling pattern was 7.62 (95% CI 4.50, 12.92), $p < 0.00001$ (Figure 26A, *top*). There was no significant heterogeneity within this group ($p = 0.19$). The odds ratio was 4.56 (95% CI 3.74, 5.56), $p < 0.00001$) in the mixed aetiology group and no significant heterogeneity was observed within this group ($p =0.10$) (Figure 26B, *bottom*).

Figure 26 - Meta-analysis of all-cause mortality and/or transplantation associated with restrictive filling in heart failure

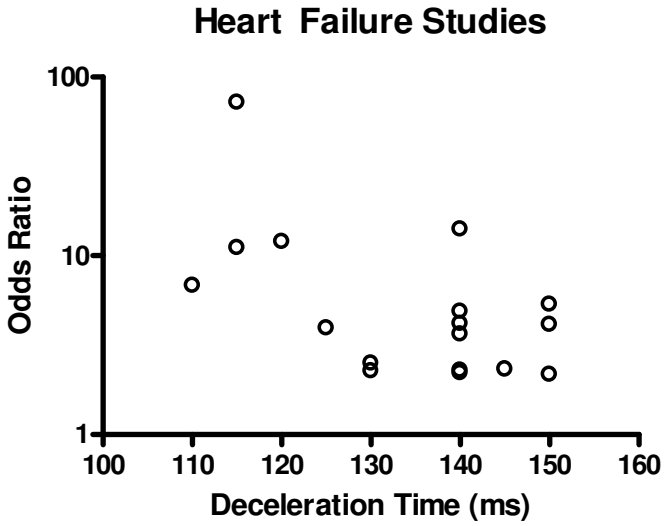


Fixed effects model, studies weighted according to sample size.
Abbreviations: CI = confidence interval, n = number of events, N number of patients, OR = odds ratio, Year = year of publication.

Criteria for detection of restrictive filling

The criteria for restrictive filling varied between studies, and usually included a shortened deceleration time (cut-off ranged from 110 to 150 ms) Studies which used very short deceleration time cut-offs tended to have higher odds ratio, however these studies were published earlier and used shorter deceleration time cut-offs than are routinely applied today. Within the range of deceleration times currently used (130-150 ms), no relationship was observed between the observed odds ratio for the individual study and the deceleration time cut-off used (Figure 27).

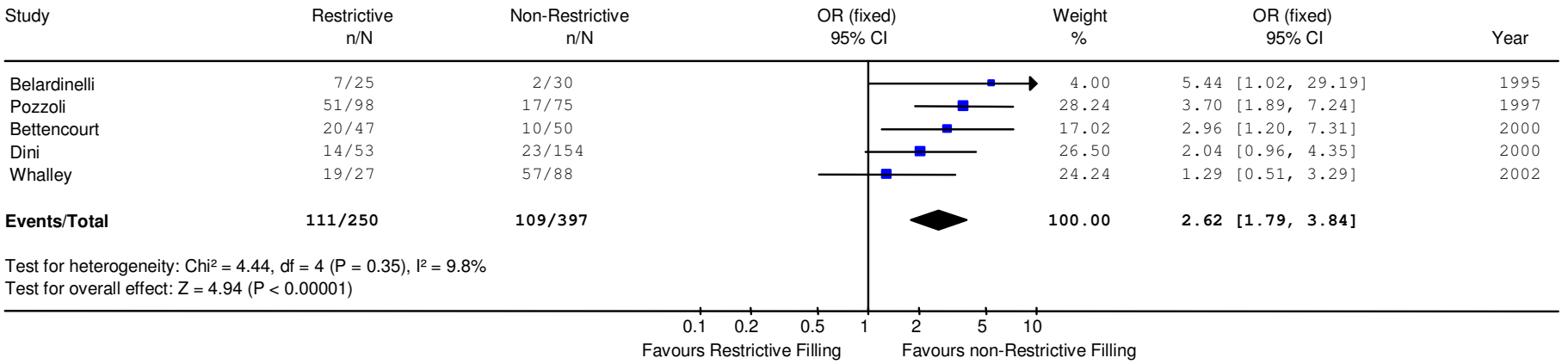
Figure 27 - Odds ratio according to different deceleration time criteria



Hospitalisation for heart failure

Five studies reported the number of patients hospitalised for worsening HF.[78,124,134,137,Whalley chapter 3] 647 patients and 220 hospitalisations are included in this sub-analysis. One hundred and eleven hospitalisations occurred in the 250 patients with restrictive filling pattern (event rate 44.4 %) and 109 hospitalisations occurred in the 397 patients with non-restrictive filling pattern (event rate 27.5 %), odds ratio 2.62 (95% CI: 1.79, 3.84 $p < 0.00001$). No heterogeneity was observed within this group of studies ($p=0.35$) (Figure 28).

Figure 28 Meta-analysis of hospitalisation in patients with heart failure



Fixed effects model, studies weighted according to sample size.
Abbreviations: CI = confidence interval, n = number of events, N = number of patients, OR = odds ratio, Year = year of publication.

Post Myocardial Infarction

Seventeen studies were eligible for this analysis.[155-174] Study data (number of patients and events) was confirmed by 12 of the authors. Despite repeated attempts, confirmation was not received for six studies. Of these, five studies clearly reported numbers in the publication and were included, leaving only one study which may have been eligible but was excluded.[168] One author provided additional data published in thesis form only,[169] which was merged with another publication with a slight patient overlap.[169] Thus, 17 studies were included in the final analysis.[155-167,169-174] This represents 3855 patients, in whom 580 deaths occurred (overall event rate 15 %) (Table 20). The average follow-up time varied between two weeks and five years: two studies were six months or less; five were one year; six were 1-3 years, and in the remaining four studies follow-up was 4-5 years.

Table 20 - Prognosis studies using or restrictive filling pattern classification post myocardial infarction

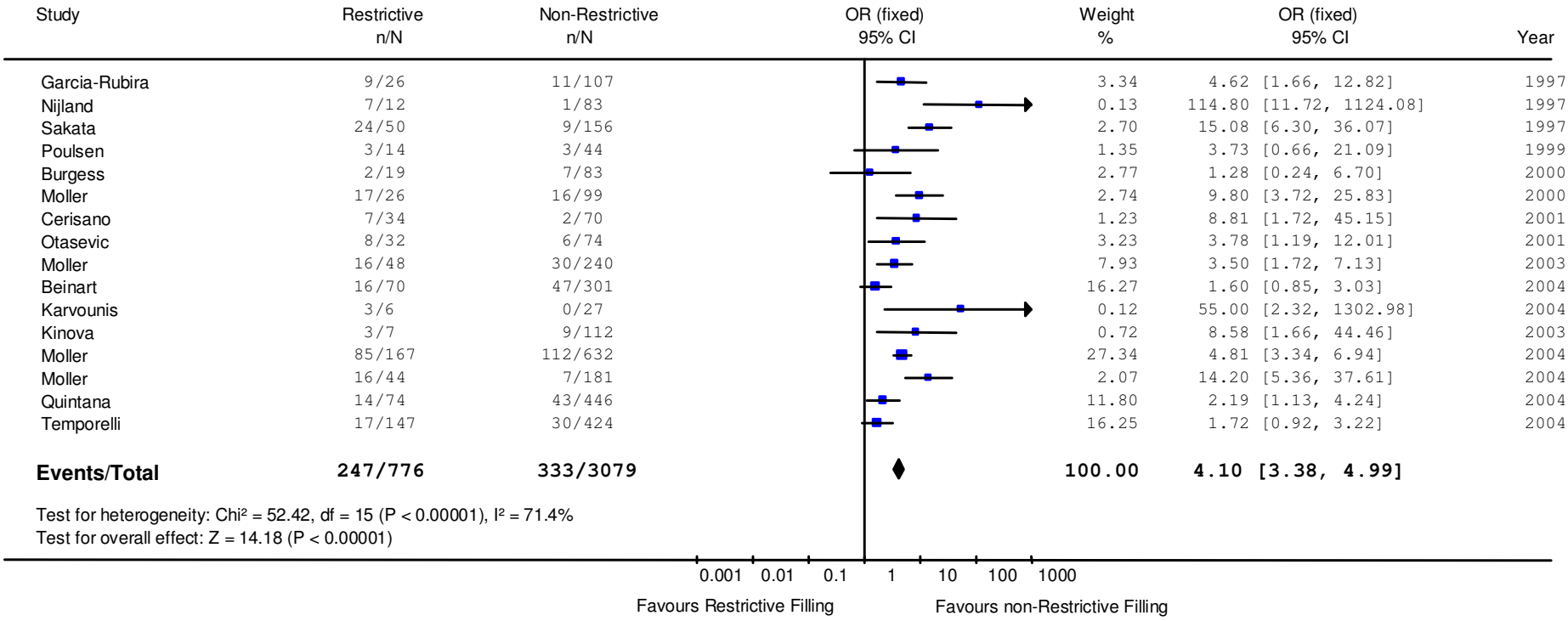
First Author	Year	Author confirmed data	Country	Published Language	N	FU years	Events	Echo definition of restrictive filling
Garcia-Rubira [159]	1997	Numbers in paper	Spain	English	133	In hospital	20 deaths 30 HF	Non-Restrictive Restrictive
Nijland [155]	1997	Numbers in paper	The Netherlands	English	95	3	8 deaths 5 HF	E:A > 2 and/or DT < 140 ms
Sakata [160]	1997	Numbers in paper	Japan	English	206	5	33 deaths	Low mitral A velocity
Poulsen [161]	1999	yes	Denmark	English	58	1	6 deaths 4 HF (MFP 2/3)	DT < 140 ms
Tsai [162]	1999	Numbers in abstract	Taiwan	Chinese	27	2.5	6 HF	DT < 125 ms
Burgess [163]	2000	yes	United Kingdom	English	102	1	9 deaths 14 HF	Non-Restrictive Restrictive
Moller [156]	2000	yes	Denmark	English	125	1	33 deaths	DT < 140 ms
Cerisano [164]	2001	yes	Italy	English	104	2.7	9 deaths 14 HF	DT < 130 ms
Otasevic [165]	2001	yes	Yugoslavia	English	106	4.9	14 deaths	DT < 150 ms
Brzezninska [166]	2002	Numbers in abstract	Poland	Polish	88	1	23 HF	E:A > 2 or DT < 140 ms
Moller [167]	2003	yes	Denmark Multi-centre	English	799	2.8	197 deaths	DT < 140 ms
Moller [157]	2003	yes	USA	English	288	1.25	46 deaths	DT < 140 ms
Beinart [171]	2004	Numbers in paper	Israel	English	395	5	63 deaths	DT < 140 ms
Kinova [169,173]	2004 2003	yes	Bulgaria	English	91	0.5	12 deaths 12 HF	DT < 140 ms
Karvounis [174]	2004	yes	Greece	English	33	1	3 deaths 7 HF	E:A > 2
Moller [170]	2004	yes	Europe multi-centre	English	225	2.3	23 deaths 25 HF	DT < 140 ms
Quintana [172]	2004	yes	Sweden	English	520	2.6	57 deaths	DT < 140 ms
Temporelli [158]	2004	yes	Italy	English	571	4	47 deaths	DT <130 ms

Abbreviations: DT = deceleration time of passive mitral filling velocity (E), E:A = ratio of early to late mitral filling, EF = ejection fraction, FU = follow-up, HF = heart failure, Year = year of publication.

Restrictive filling versus non-restrictive filling and death

3855 patients are included in this analysis: 776 (20 %) patients had a restrictive filling pattern and the remaining 3079 (80 %) had a non-restrictive pattern. There were 580 deaths in total: 247 (43 %) occurred in the restrictive group and 333 (57 %) occurred in the non-restrictive group. The event rate in the whole groups was 15.1 %; 31.8 % in the restrictive filling group, and 10.8 % in the non-restrictive group. The odds ratio for death associated with restrictive filling pattern was 4.10 (95% CI 3.38, 4.99), $p < 0.00001$ (Figure 29). There was significant heterogeneity within the group ($p < 0.00001$) however this was driven by two studies[115,174] with unusually high odds ratio due to lower event rates in the non-restrictive group. When these studies were excluded from the analysis no heterogeneity was observed ($p = 0.11$).

Figure 29 Metanalysis of the restrictive filling pattern post myocardial infarction

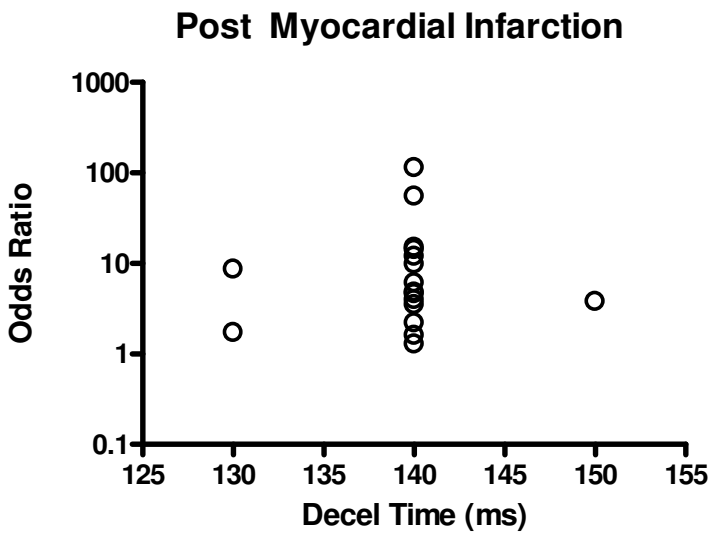


Fixed effects model, studies weighted according to sample size.
Abbreviations: CI = confidence interval, n = number of events, N = number of patients, OR = odds ratio, Year = year of publication.

Criteria for detection of restrictive filling

The criteria for restrictive filling varied between studies, and usually included a shortened deceleration time (cut-off ranged from 130 to 150 milliseconds). No relationship was observed between the observed odds ratio for the individual study and the deceleration time cut-off used although there was a wide spread of odds ratios around the most commonly used deceleration time of 140 ms (Figure 30).

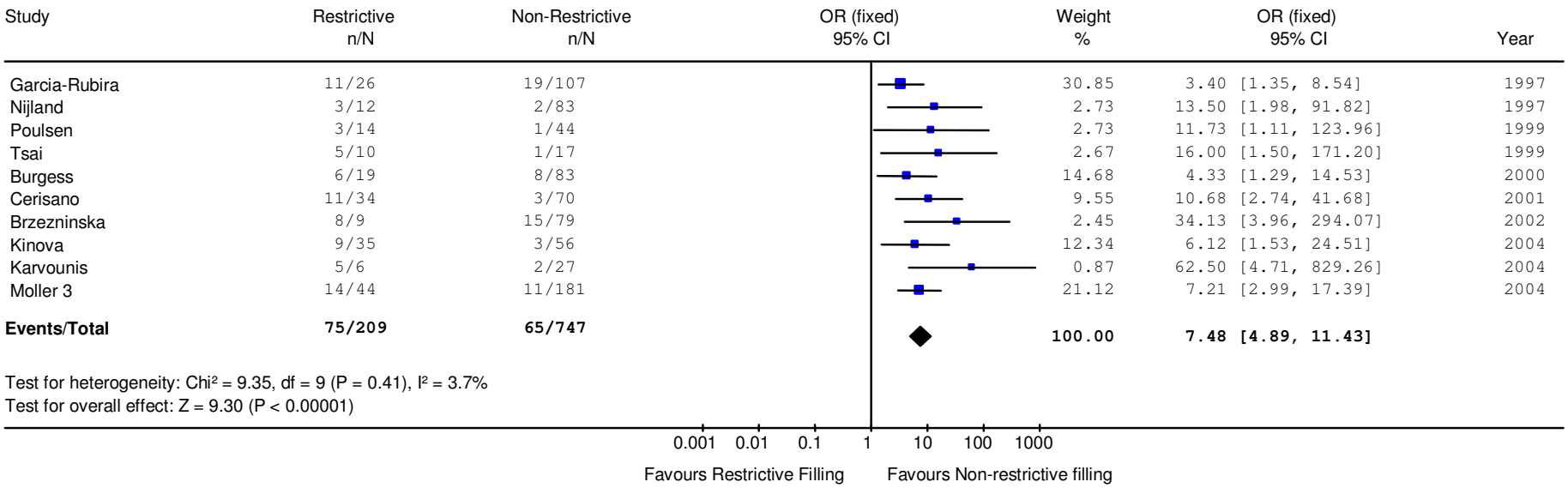
Figure 30 Odds ratio according to different deceleration time criteria



Development of heart failure

Ten studies reported the number of patients developing HF post MI.[155, 159,161-164,169,170,173,174] 956 patients and 140 episodes of HF are included in this sub-analysis. Seventy-five episodes of HF occurred in the 209 patients with restrictive filling pattern (event rate 35.9 %) and 65 episodes of HF occurred in the 747 patients with non-restrictive filling pattern (event rate 8.7 %), odds ratio 7.48 (95% CI: 4.89, 11.43, $p < 0.00001$). No heterogeneity was observed within this group of studies ($p=0.41$) (Figure 31).

Figure 31 - Meta-analysis of development of HF in post MI patients



Fixed effects model, studies weighted according to sample size.
Abbreviations: CI = confidence interval, n = number of events, N number of patients, OR = odds ratio, Year = year of publication.

Other Filling Patterns

Reversible restrictive filling versus non-reversible restrictive filling and mortality

Three studies compared reversible (responsive to preload reduction) and non-reversible restrictive filling pattern.[78,128,130] Data were available for 295 patients. 141 (48 %) patients had a non-reversible restrictive filling pattern and the remaining 154 (52 %) had a reversible restrictive pattern. 82 (85 %) of the deaths of occurred in the non-reversible restrictive group and 15 (15 %) of the deaths occurred in the reversible restrictive group. The odds ratio for death associated with non-reversible restrictive filling pattern was 13.74 (95% CI 7.13, 26.45), $p < 0.00001$ (Figure 32). There was significant heterogeneity in the group ($p = 0.001$), which is reflects of the small number of studies, patients and events, and the very different event rates and odds ratios within each of these patient populations.

Non-restrictive filling patterns

This analysis included 545 patients in five studies (one AMI and 4 HF cohorts). 187 (34 %) patients had a restrictive filling pattern, 140 (25.7%) had a pseudonormal filling pattern and the remaining 218 (40 %) had a normal or abnormal filling pattern. There were 193 deaths in total: 88 (46 %) in the restrictive group, 68 (35 %) and the remaining 37 (19 %) of the deaths occurred in the normal/abnormal relaxation group.

Restrictive filling compared to pseudonormal filling

There was no difference in mortality between the groups. The odds ratio for death associated with restrictive filling compared to pseudonormal filling pattern was 1.33 (95% CI 0.82, 2.18), $p = 0.25$ (Figure 33). There was significant heterogeneity within the group ($p = 0.003$) reflecting markedly different odds ratios (one negative, one positive and three neutral effects).

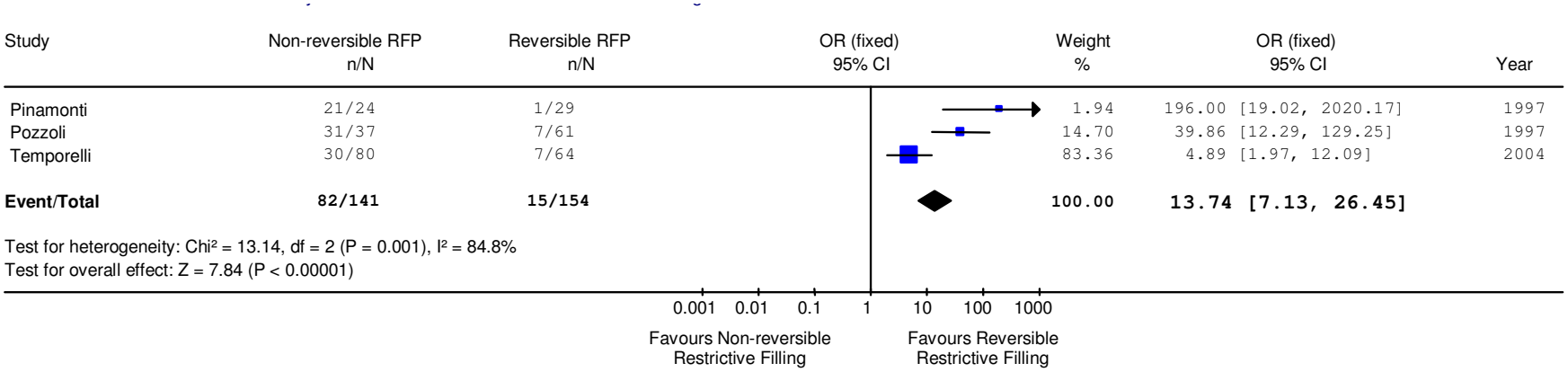
Pseudonormal filling versus abnormal relaxation or normal filling

The odds ratio for death associated with pseudonormal filling pattern compared to abnormal filling or normal filling was 2.75 (95% CI 1.84, 4.13), $p < 0.00001$ (Figure 34). There was no heterogeneity within the group ($p = 0.05$).

Restrictive filling versus abnormal relaxation or normal

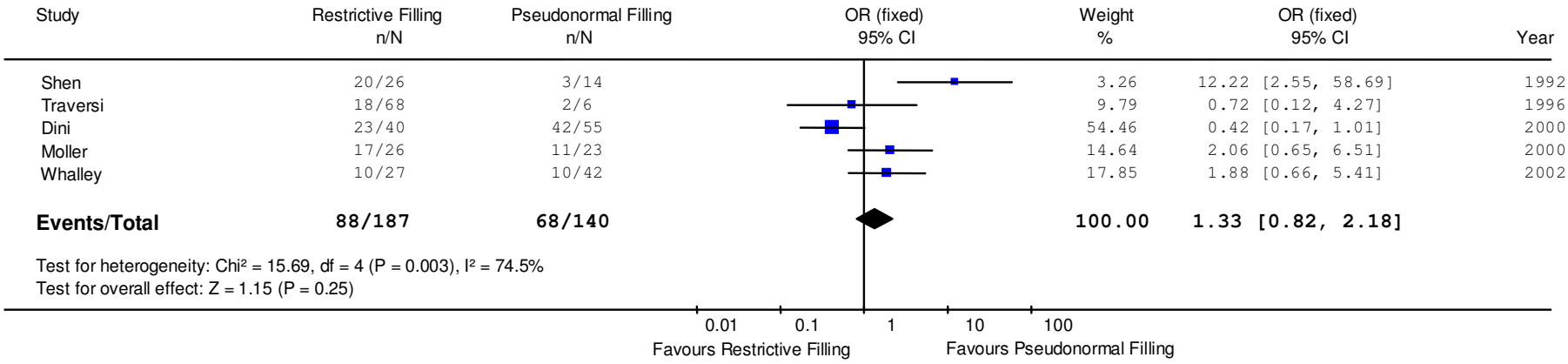
The odds ratio for death associated with restrictive filling pattern compared to abnormal relaxation or normal filling was 5.92 (95% CI 3.56, 9.85), $p < 0.00001$ (Figure 35). There was no significant heterogeneity within the group ($p = 0.20$).

Figure 32 - Meta-analysis of reversible restrictive filling pattern in heart failure



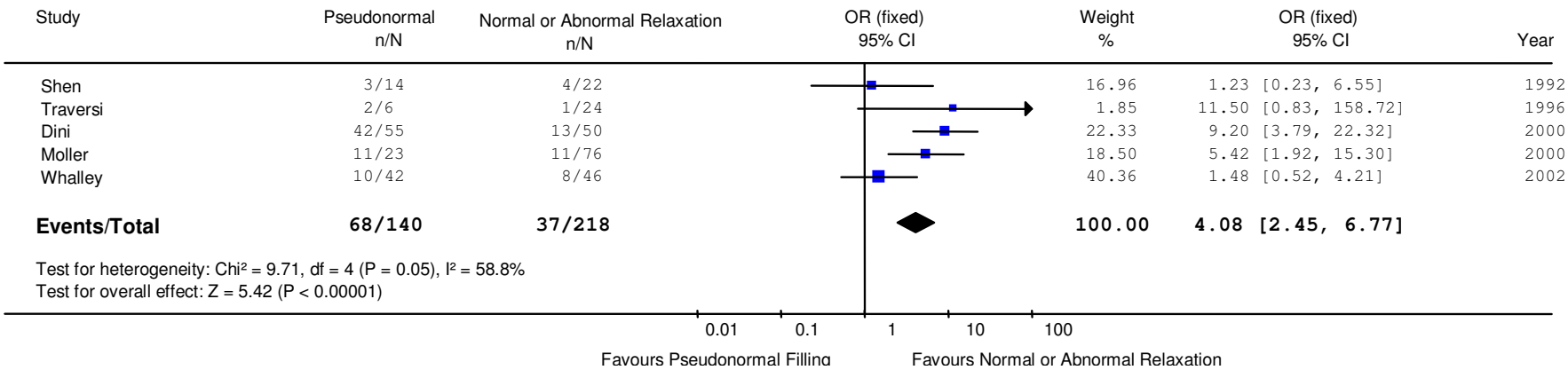
Fixed effects model, studies weighted according to sample size.
Abbreviations: CI = confidence interval, n = number of events, N number of patients, OR = odds ratio, Year = year of publication.

Figure 33 - Meta-analysis of pseudonormal compared to restrictive filling



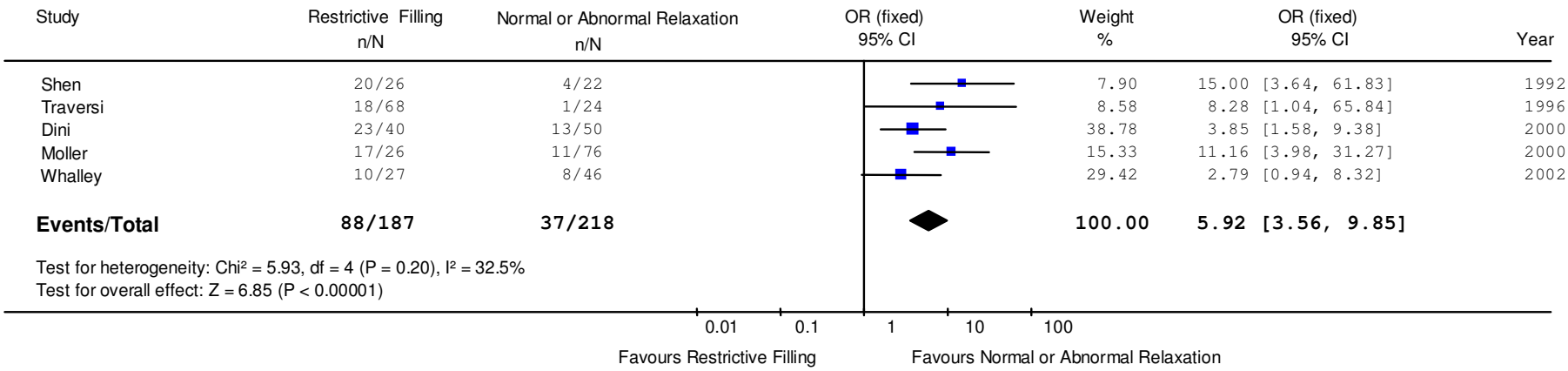
Fixed effects model, studies weighted according to sample size.
Abbreviations: CI = confidence interval, n = number of events, N number of patients, OR = odds ratio, Year = year of publication.

Figure 34 - Meta-analysis of pseudonormal filling compared abnormal relaxation or normal filling



Fixed effects model, studies weighted according to sample size.
Abbreviations: CI = confidence interval, n = number of events, N number of patients, OR = odds ratio, Year = year of publication.

Figure 35 - Meta-analysis of restrictive filling compared to abnormal relaxation or normal filling



Fixed effects model, studies weighted according to sample size.
Abbreviations: CI = confidence interval, n = number of events, N number of patients, OR = odds ratio, Year = year of publication.

Summary of survival according to filling pattern

There was a stepped, incremental relationship between survival and filling grade, with each grade associated with a slight increase in mortality, with the exception of the non-reversible restrictive filling pattern which was associated with a more than ten-fold increase in death when compared to the reversible restrictive filling pattern and the pseudonormal filling pattern which was not different to the restrictive group (Table 21).

Table 21 - Summary of meta-analysis odds ratios for all-cause mortality associated with different diastolic filling patterns.

Comparison	events/N	Odds Ratio	95 % CI
Restrictive filling v non-Restrictive filling (HF)	659/2894	4.29	3.53, 5.22
Restrictive filling v non-Restrictive filling (MI)	508/3855	4.10	3.38, 4.99
Restrictive v Abnormal Relaxation or Normal	125/405	5.92	3.56, 9.85
Pseudonormal v Abnormal Relaxation/Normal	105/368	4.08	2.45, 6.77
Restrictive filling v Pseudonormal filling	156/327	1.33	0.82, 2.18
Non-reversible Restrictive v Reversible Restrictive	97/295	13.74	7.13, 26.45

Abbreviations: CI = confidence interval, RFP = restrictive filling pattern

Discussion

The major thrust of these analyses has been to compare the presence of a restrictive filling pattern with all other non-restrictive filling patterns to predict prognosis in patients with HF and after AMI. Despite a difference in overall mortality rates within each group (HF: 22.8 %, AMI: 13.2 %), both HF and AMI patients with a restrictive filling pattern experienced a four-fold difference in mortality compared to those with non-restrictive pattern. Combined, these two analyses involved 6749 patients and 1167 deaths, representing a large number of events and thus statistically robust results. Restrictive filling pattern, or short deceleration time, is associated with higher left atrial pressure,[88,90-93,95,96] higher neurohormone level[99,135] and higher NYHA functional class.[268] Thus, it is not surprising that these patients have poor prognosis. Identification of a

restrictive filling pattern is a relatively simple examination that can be added to most clinical echocardiographic procedures without adding significant time to the study.

Many of the patients with restrictive filling pattern, and indeed many of the patients included in this review, will have important systolic impairment in addition to their diastolic abnormalities. It was beyond the realm of this review to determine the individual contribution of systolic and/or diastolic dysfunction because we did not collect individual patient data. However, in many studies and in several multivariate analyses the presence of restrictive filling pattern, characterised by high E velocity, low A velocity and shortened deceleration time, remains one of the strongest independent predictors of cardiovascular outcome.[125,127,130,134,136,137,139]

Heart failure

Heart failure is the end result of common conditions such as hypertension, ischaemic heart disease and diabetes, and patients with HF have very poor prognosis, even when optimally managed. This meta-analysis has demonstrated that stratification of patients on the basis of diastolic filling grade identifies several patient groups with differing survival. Echocardiography is often used in such patients to determine LV systolic function, despite the fact that many studies have failed to demonstrate an independent link between EF and outcome and the evidence linking diastolic filling grade with outcome. These studies have been performed in varied clinical situations: HF outpatient clinics, transplant assessment units and after acute admission and prior to hospital discharge. Some have recruited only patients with idiopathic dilated cardiomyopathies, whilst others have taken all patients with HF and consequently a mixed aetiology of HF. As a result, the patients and their associated event rates reported in individual studies vary greatly. This heterogeneity makes interpretation and generalisability of individual study results difficult and was the stimulus for this meta-analysis.

Despite the recruitment strategies and different patient characteristics within these studies, this meta-analysis has confirmed the very significant and clinically important finding that restrictive filling pattern is associated with very poor outcome in a wide range of HF patients. Identification of

patients with a restrictive filling is relatively easy to perform, especially given that most patients with either a definite diagnosis or a strong suspicion of HF will have an echocardiogram performed. This prognostic information will allow both clinicians and patients to better plan their future and may eventually lead to more targeted treatment of HF patients.

Whilst the relationship between restrictive filling and prognosis has been studied extensively, further classification of patients with non-restrictive filling patterns is also important. Separation of patients with pseudonormal filling from those with an abnormal relaxation pattern reveals a group of patients at intermediate risk of death and/or hospitalisation. Identification of this group of patients can be achieved by preload reduction, colour M-mode propagation velocity[82] or pulmonary venous Doppler. [137] In the current meta-analysis, pseudonormal filling was associated with nearly three times the risk as abnormal relaxation, but similar risk as than restrictive filling.

A clinically useful finding in this analysis is that non-reversible restrictive filling is associated with more than ten-fold worse prognosis than non-reversible restrictive filling. Several small studies have demonstrated that it is possible to alter the diastolic filling pattern of patients.[78,130,175,264] For example, Capomolla et al demonstrated that patients in whom diastolic filling was affected by preload manipulation (i.e. reversible restrictive or pseudonormal) were more tolerant of beta-blocker therapy (Carvedilol) and had better outcome.[175] Similarly, Pallazzouli et al report long-term reversal of the restrictive filling is more common in HF patients randomised to Carvedilol compared to placebo.[246] It might be reasonable to perform repeat echocardiography to determine if the filling pattern has changed over time, or with treatment. However, this has only been demonstrated in highly selected small groups of patients with impaired systolic function. And most importantly has not been tested in a randomised fashion, so caution needs to be applied when extrapolating to patients with HF and normal EF.

Recently, it has been demonstrated that changes in BNP during treatment of decompensated HF in hospital predicted subsequent outcome[288] and therefore supports the concept that BNP levels can be used to guide treatment of heart failure. Since, both neurohormonal activation (measured by

plasma BNP) [99,135] and echo Doppler parameters[16,74-76,80,81,83-85,87-96] are related to LV filling pressures, it is conceivable that echocardiography might be similarly useful for guiding therapy, but this remains unproven.

Post myocardial infarction

Like the HF analysis, restrictive filling pattern predicted death in patients after AMI. Unlike the HF analysis, there was significant heterogeneity between individual studies, which may be explained by the different outcome observed in individual studies, which may be explained by the changing medical management of acute AMI over the seven years that these studies were reported. Regional and temporal differences in access to drugs and interventions will have undoubtedly affected the outcomes in these studies individually. Despite this, the overall result provides clinically important information and highlights yet again the importance of assessing diastolic filling in patients after acute coronary events.

Left ventricular systolic impairment and clinical HF are common complications of AMI and undoubtedly explain some of the risk observed in the patients with restrictive filling pattern. Excluding the patients who are admitted with shock (the most severe form of post-infarct heart failure), HF is either present at admission or develops during hospitalisation in 20-30% of patients after suffering an acute infarction.[289-293] This number continues to rise after hospital discharge,[289] with approximately 40% of patients developing HF by six years.[293] Patients who develop HF in hospital are 3-4 times more likely to die, are older, more likely to be female, have more frequent comorbidity, such as diabetes and hypertension, and more complicated history than those who do not develop or have existing HF.[289-292]

LV systolic dysfunction was once considered to be one of the most important predictors of outcome and thus the primary goal of echocardiography after an acute coronary event was to assess LV systolic function. When EF is measured, patients with low EF experience higher mortality rates than those with preserved EF, but the patients in whom EF is not measured (the majority of patients in many acute coronary studies) experience similar mortality to those in whom EF is depressed.[293,294] Whilst it is true that many of the patients who develop HF have depressed

systolic function, the relationship between EF and outcome is biphasic, with increased risk in patients with hyperdynamic systolic function.[291] These two interesting findings may be explained by advanced diastolic filling abnormalities in this group of patients.

Patients with angiographically documented coronary artery disease but no detectable resting systolic dysfunction almost always have diastolic filling abnormalities when assessed by radionuclide techniques.[295] Often patients with advanced diastolic filling abnormalities and HF have small LV cavities that appear to contract normally but because of the reduced volume, the stroke volume is inadequate. In such patients, systolic function may have been assumed to be within normal limits. This hypothesis is supported by the many individual studies, and the current meta-analysis, that have demonstrated increased risk associated with restrictive filling pattern. However, this needs to be considered in the context of the tens of thousands of patients who suffer acute coronary events each year, and the minority (approximately 30%) that undergo comprehensive echocardiography.[291] The absence of EF measurements may also reflect the constraints of performing echocardiography in unstable patients in an acute setting, given all the other competing urgencies. In which case, the patients without EF measurements may be the sickest patients, however given that the majority (70%) of subjects do not have EF measurements performed, this seems unlikely.

The lack of performance of systolic echocardiographic measurements in the acute coronary setting probably reflects many of these factors and also the insensitivity of current systolic echocardiographic techniques. Most certainly, there is a paucity of comprehensive echocardiographic assessment in patients with acute coronary syndromes. Many of the studies included in this meta-analysis were individually very small, recruiting just hundreds rather than thousands of patients with subsequently small numbers of events. Nevertheless, several of the larger studies demonstrated that when both diastolic and systolic measurements were available systolic measurements offered little or no additional prognostic information over and above diastolic filling pattern.[158,167,171] In a multi-centre study of 799 subjects, wall motion score index (WMSI), diastolic filling pattern and the Tei index (a measure of global systolic and diastolic LV

function) all predicted outcome, but in a multivariate model, WMSI had no prognostic value.[167] In another study of 571 patients, pre-discharge restrictive filling pattern was a very strong predictor of death and LV end-diastolic index a weaker, but still significant predictor of death in Cox proportional hazards model.[158] These findings were confirmed in another smaller study (N=371) where restrictive filling pattern predicted death alongside other clinical factors and left atrial size, but not systolic function.[171] In marked contrast, in another multi-centre study of 520 patients, although restrictive filling pattern predicted death, it did not reach significance in a multi-variate model where WMSI, age, history of hypertension and diabetes did.[172]

It was not within the realm of this meta-analysis to evaluate the individual and multivariate contribution of all echocardiographic variables to overall risk. This would require a meta-analysis incorporating individual patient data from each study. Because of the similarity between the studies and the total number of patients, this approach might be able to discern the relative weighting of systolic and diastolic parameters and overall risk. An individual patient meta-analysis or large individual study (sample size 1000-2000 patients, 300-500 events) would potentially have the power to discriminate between the individual echo parameters. This would be an important study that might lead to understanding of both the development of HF and the risk factors for death in patients suffering acute coronary events. In turn, this may lead to enhanced medical management of these patients.

The presence of restrictive filling post AMI also predicted the development of HF after the index infarct. The importance of the assessment of diastolic filling pattern in the setting of AMI is often underrated. In this situation, the diagnostic role of echocardiography is of paramount importance: quantification of regional wall motion, infarct size, viable myocardium and structural trauma are all the first goal of echocardiography in patients with an acute coronary event. However, the findings of the many individual studies included in this meta-analysis and these results of the current meta-analysis would suggest that it may be equally important for prognostic purposes to accurately identify diastolic filling grades. This approach may offer a means of identifying those patients who are at highest risk of both mortality and developing HF after their acute coronary event.

Limitations

As with any analysis of this type, there are several limitations inherent within the process. The first of these is publication bias. We did not restrict our searches to English language publications and as a result have included several studies published in languages other than English and the studies originate from a wide variety of countries. We almost certainly will have omitted some unpublished data, which may or may not be in agreement with these results. Often unpublished studies are negative and the omission of such studies will mean that this risk estimate is exaggerated. We did contact all published authors to ask for any unpublished data and in some cases received additional data. In order to minimise the risk of publication bias we identified all studies that included prognosis and diastolic parameters, but not necessarily restrictive filing pattern and as a result included studies where diastolic filling was not a primary study endpoint. These authors were contacted and requested whether it was possible to breakdown their data based on restrictive versus non-restrictive filling. This approach, we believe, will have minimised publication bias. This is supported by the lack of heterogeneity in most analyses and the examination of funnel plots.

A further bias might be duplication of patients. Because of the nature of our search strategy outlined above, we did identify several publications that contained duplicate patients but reported different echocardiographic variables. In consultation with all authors, we were able to identify several studies where patients were duplicated and thus excluded and therefore minimise this potential bias.

Overall, we believe this rigorous methodological approach has minimised these potential sources of bias and error.

Lastly, the criteria used by individual investigators for classification of restrictive filling varied slightly. In many cases, this was predetermined by the investigators to be the best cut-off for detecting at-risk subjects. This may have influenced the results but we do not think this was the case for two reasons. Firstly, the variation was only slight and secondly the analysis of odds ratio

as a function of deceleration time cut-off showed no relationship within the range of deceleration time used by most studies and thus no bias.

The size of the risk estimates and confidence intervals around the risk estimates in the two main results of this meta-analysis, in conjunction with the sample size, would suggest that these potential sources of error although possible are likely to have minimal effect on the overall risk estimates. Meta-analysis is commonly used to combine the results of randomised controlled trials, but is also applicable to observational data in the way we have done. We followed published guidelines for this.

Conclusions

The assessment of diastolic filling grade confers important prognostic information in both HF patients and after AMI. In this study, over 40% of HF patients and 20% of AMI patients displayed a restrictive filling pattern, which was associated with the worst outcome. This prognostically important finding is thus not a rare phenomenon in these patient groups. In addition, incremental prognosis is associated with each intermediate grade of diastolic filling. The findings of this study would support comprehensive echocardiographic assessment of diastolic filling pattern in both patient groups and this important prognostic information should be considered alongside other important echocardiographic and clinical findings when managing such patients.

Key Findings:

- Restrictive filling pattern is associated with a four-fold increase in mortality in both HF and MI patients
- There is a stepped relationship between the different diastolic filling patterns: patients with normal filling or abnormal relaxation have the best survival, pseudonormal intermediate, but closer to restrictive filling and non-reversible restrictive filling is more than ten times worse than reversible restrictive filling
- Restrictive filling pattern also predicts development of HF post AMI and hospitalisation in patients with HF

Acknowledgements:
The following authors kindly confirmed their published data or provided additional data for use in these analyses:

Dr Kaname Akioka, Yoshikawa, Japan; Dr Paulo Bettencourt, Porto, Portugal; Dr Malcolm Burgess, Brisbane, Australia; Dr Christopher Cabell, Durham, USA; Dr Giampaolo Cerisano, Florence, Italy; Dr Alain Cohen-Solal, Clichy, France; Dr Frank Dini, Pisa, Italy; Dr Viorel Florea, London, England; Dr Friedrich Fruhwald, Graz, Austria; Dr Alexander Hansen, Heidelberg, Germany; Dr Haralambos Karvounis, Thessaloniki, Greece; Dr Elena Kinova, Sofia, Bulgaria; Dr Jacob Møller, Odense, Denmark; Dr Sherif Nagueh, Texas, USA; Dr Aleksandar Neskovic, Belgrade, Yugoslavia; Dr Ioannis Nouskas, Thessaloniki, Greece; Dr Takashi Oki, Tokushima, Japan; Dr Andrea Rossi, Verona, Italy; Dr Patricia Pellikka, Rochester, USA; Dr Miguel Quintana, Stockholm, Sweden; Dr Pier Temporelli, Veruno, Italy; Dr Christophe Tribouilley, Amiens, France; Dr Gerald Werner, Goettingen; Germany; Dr Cheuk-Man Yu, Hong Kong, China; Dr Zhelan Zheng, Hangzhou, China.

Chapter 5 - Complementary role of echocardiography and brain natriuretic peptide for diagnosis of HF and determining prognosis in symptomatic breathless patients in the community.

Background

Given the high events rates associated with heart failure (HF) and the widely available treatments, early diagnosis is important. Although the diagnosis of HF is based upon clinical findings, echocardiography is often used and indeed advocated in patients with HF to determine aetiology, to document the degree of ventricular dysfunction and determine reversible or treatable causes of HF.[7] Recently published guidelines for HF diagnosis from both the American College of Cardiology/American Heart Association[8] and the European Society of Cardiology[9] include an objective measure of ventricular dysfunction. Thus, clinicians are increasingly relying upon echocardiography to confirm a clinical suspicion of HF and as a result, there is a call for open access echocardiography to be available to primary care physicians to aid their diagnosis of HF without consultation with a cardiologist.[10] Whether echocardiography is requested by a primary care physician or a cardiologist, the goal remains similar - to establish the underlying anatomy and pathology and to assess both systolic and diastolic function.

Neurohormones, and in particular brain natriuretic peptide (BNP), are also useful markers of heart failure. BNP is released from the heart in response to wall stress. In healthy individuals, low levels of BNP are detectable and higher BNP levels have been detected in patients with HF and other cardiac disease.[297-301] BNP level increases proportionally with left ventricular (LV) dysfunction[302,303] and is closely related to both diastolic and systolic LV function.[303-305] BNP does however increase with increasing age[307-309] and renal impairment,[310] and is higher in women.[307,308,309,311] As a result, BNP has poor positive predictive value, but high negative predictive value and is most powerful as a “rule-out” test.

BNP significantly improves the diagnosis of HF in dyspnoeic patients in the emergency room.[97,312-317] However, there are limited data regarding the role of BNP for diagnosing HF in the community and most are only observational studies.[318-320] The Natriuretic Peptides in the Community study (NPC) was the first prospective, randomised controlled trial to demonstrate the improved diagnostic accuracy of NT-proBNP (NT-proBNP) measurement in elderly patients with HF symptoms in primary care.[321]

Prognosis of symptomatic patients in the community

Diastolic echocardiographic measurements can provide important prognostic information about death and/or readmission in patients with established HF,[78,96,118-147] especially the differentiation of restrictive filling patterns (E:A ratio >2, short deceleration time) from non-restrictive patterns as shown in the previous meta-analyses. Within the non-restrictive filling group, further differentiation of the patients with pseudonormal filling reveals a group at intermediate risk of death and/or hospitalization.[118,137,156,246] These indices also predict development of HF[155,159,161,162,163,164,166,169,173,174] and death[155-174] after acute myocardial infarction.

More recently, pulsed wave tissue Doppler imaging (TDI) has been used to assess diastolic function. In particular, the ratio of mitral E velocity to annular E velocity (E/Ea) is related to filling pressure.[83-85,96,97] and these newer tissue Doppler measurements may also be useful for predicting cardiac events. In HF patients with impaired systolic function, the systolic annular velocity (Sa) predicts all cause mortality.[96] In a study of patients undergoing echocardiography, but not specifically with HF, Ea predicted death over a mean of 23 months.[143] In another study, E/Ea > 15 added important prognostic information to clinical data and EF, by predicting death in patients post myocardial infarction in patients with reduced EF (<40%) and normal EF (>40%).[146]

Similarly, neurohormones have been used to predict outcome in HF patients. An elevated BNP level is associated with mortality, hospitalisation and worsening HF.[322-328] Most of these prognostic studies have been performed in cohorts of patients with established HF - either referred to a transplant clinic, admitted to hospital for exacerbation of symptoms, or attending specialist HF clinics. The current study was performed in the community and included elderly, symptomatic patients without a previous diagnosis of HF. These are the people in whom echocardiography is increasingly being relied upon to aid the confirmation of a clinical diagnosis of HF.

The aim of the current study was to evaluate the role of echocardiography for diagnosis of HF in symptomatic patients in the community and to compare this with NT-proBNP. Secondly, we wanted to evaluate the prognostic role of both echocardiography and NT-proBNP measurements for predicting subsequent hospitalisation in these patients.

Methods

Subjects

Three hundred and five symptomatic patients (dyspnoea and/or oedema) were recruited from 92 primary care practices and the Auckland area.[321] After providing informed consent, patients attended Auckland Hospital for a study visit where cardiological assessment, electrocardiography, chest X-ray, blood collection for NT-proBNP measurement and transthoracic echocardiography were performed. The study was approved by the Auckland District Health Board Ethics Committee and all patients provided written informed consent.

Panel standard diagnosis of heart failure

The diagnosis of HF was made by an expert panel of three cardiologists and one general physician who were independent of all study procedures and were blinded to the NT-proBNP result. The panel reviewed all clinical data for each patient including ECG, chest X-ray and echocardiogram in order to determine whether the clinical syndrome of HF was present using the European Society of Cardiology Working Group on Heart Failure diagnostic criteria.[329] To meet the case definition of HF, patients were required to have appropriate symptoms (dyspnoea or fluid retention) with clinical signs of pulmonary or peripheral congestion in the presence of an underlying abnormality of cardiac structure and function. If doubt remained, a beneficial response to treatment was considered.

BNP assay

Blood was collected using standard venepuncture technique into tubes containing EDTA. Samples were centrifuged and frozen at –70^{o}C. NT-proBNP was measured by radioimmunoassay at the CardioEndocrine Research Laboratory, Christchurch, New Zealand.[302]

Echocardiography methods

All patients were examined lying on their left side and images were digitally obtained (Philips HDI-5000, Phillips Ultrasound, Bothell, WA). Detailed echocardiographic methods have been described in chapter 2. Briefly, a full clinical echocardiographic examination was performed including: parasternal M-mode recordings, biplane Simpson's left ventricular volumes and ejection fraction (EF); left atrial area (apical four-chamber view); mitral valve pulsed wave Doppler; pulmonary venous Doppler and isovolumic relaxation time (IVRT). Mitral valve inflow Doppler was then recorded during the Valsalva manoeuvre. All echocardiographic images were obtained according to a standardised protocol by specially trained research sonographers, without knowledge of the patients' clinical details.

Pulsed wave tissue Doppler

In addition to the standard echocardiography techniques described, pulsed wave tissue Doppler was also performed by placing a 5 mm sample volume on the medial and lateral aspects of the mitral valve annulus. The signal was optimised and recorded at 100 mm/s sweep speed. The average of both measurements was used.

Echocardiographic measurements

Triplicate measurements of all variables were made. Measurements were made according to standard methods and included: i) 2-dimensional and m-mode measurements: left ventricular end-diastolic dimension (LVEDD), left ventricular end-systolic dimension left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV), left atrial area; ii) Doppler measurements: mitral valve peak early filling velocity (E), peak late filling velocity (A), deceleration time (DT) of the mitral E wave, A wave duration (A dur), IVRT; pulmonary venous peak systolic velocity (S), peak diastolic velocity (D), atrial reversal velocity (AR), atrial reversal duration (AR dur); iii) tissue Doppler measurements: mitral annular E velocity (Ea), mitral annular A velocity (Aa), mitral annular S velocity (Sa). The following variables were calculated: E:A ratio = E velocity/A velocity, AR dur – A dur, stroke volume (SV) = LVEDV – LVESV, ejection fraction (EF) = SV/LVEDV x 100%; E:Ea ratio.

Differentiation between diastolic filling patterns

After the baseline measurements were made, each subject was classified into one of the following categories of filling patterns:

- Normal filling: E:A ratio 1.0-2.0 and deceleration time 0.15 – 0.23 s

- Abnormal relaxation: E:A ratio < 1.0 and deceleration time > 0.23 s

- Pseudonormal filling: E:A ratio 1.0-2.0 and deceleration time 0.15 – 0.23 s, but E:A ratio < 1.0 and deceleration time > 0.23 s with Valsalva and/or pulmonary atrial duration: A wave duration ratio >1.2

- Restrictive filling: E:A ratio > 2.0 and deceleration time < 0.15 s.

Statistical analysis

Comparisons between groups for continuous normally distributed variables were made using Student's t-test and analysis of variance where appropriate. Non-parametric continuous data were analysed using Wilcoxon and Kruskall Wallace tests where appropriate. Differences between categorical variables were assessed using Chi-squared analysis. ANOVA was used to determine between group differences when there were more than two groups and post-hoc Tukey's test for within group differences.

Diagnostic Accuracy

Receive operating characteristic (ROC) curves were used to determine the diagnostic capability of each echocardiographic parameter and NT-proBNP. Echocardiographic parameters are grouped according to whether they are principally diastolic or systolic parameters. The area under the ROC curve (AUC) was calculated using trapezoidal method and high order functions were plotted.

Survival Analysis

Medical charts and general practice computer databases were reviewed to collect data regarding each patient's vital status and number of hospitalisations with diagnosis at discharge. For any patients who had died during the follow-up period, a death certificate was obtained to verify the cause of death. Stratified survival analysis (time to first event: death, admission or death and/or readmission) was performed using the Kaplan-Meier method. Where more than two categorical groups were tested (eg. NT-proBNP level or diastolic filling pattern) Chi square was used to test overall significance. All tests were two-tailed and 5% significance level was maintained throughout. Procedures of the statistical analysis system SAS were employed in these analyses (SAS Institute, Cary, NC).

Multivariate Predictors of Hospitalisation
In multivariate models, Cox proportional hazards was used to adjust for the potential confounding effect of covariates, including age and LV ejection fraction.

Analysis by NT-proBNP Level
Both the sensitivity analysis and survival analysis were performed in different patient sub-groups based upon the NT-proBNP level: less then 50 pmol/l (heart failure diagnosis unlikely), 50-150pmol/l (heart failure diagnosis uncertain) and >150 pmol/l (heart failure diagnosis likely). This was done in order to compare the role of echocardiography within these groups of patients and to reflect the likely clinical scenarios in which physicians might use both echocardiography and NT-proBNP.

Survival Analysis by Different Systolic and Diastolic Criteria
Survival analysis was performed according to systolic function (EF < 45%) and diastolic function: diastolic filling pattern (restrictive filling, non-restrictive filling (pseudonormal and abnormal filling)[121] and using established E/Ea criteria (<8, 9-14 and >15)[84] and </>11.[83]

Results

Baseline characteristics

The mean age of the group was 72 years (range 40 to 95 years) and 65% were female. 118 patients (49%) presented with dyspnoea only, 38 (12%) with oedema only and 149 (49%) with both symptoms. Seventy-seven patients (25%) reached the expert panel diagnostic threshold for HF. The HF group were similar age and had similar symptoms as the non-HF group, but had more ischaemic heart disease (IHD), diabetes and atrial fibrillation (AF) compared to the non-HF group. In addition, they had lower blood pressure, cardiomegaly, raised jugular venous pressure and higher NT-proBNP levels (Table 22).

Table 22 - Baseline demographics and clinical characteristics of patients

	Not heart failure N = 228	Heart failure N = 77	p
Demographics			
Number of patients, n (%)	228 (75 %)	77 (25 %)	-
Mean age (years)	71 ± 11.1	74 ± 12.2	0.16
Female, n (%)	159 (71 %)	39 (51 %)	-
Male, n (%)	69 (30 %)	38 (49 %)	0.004
Symptoms			
Dyspnoea only, n (%)	90 (39 %)	28 (36 %)	-
Oedema only, n (%)	34 (15 %)	4 (5 %)	-
Both dyspnoea and oedema, n (%)	104 (46 %)	45 (58 %)	0.05
Previous medical history			
Hypertension, n (%)	122 (53 %)	37 (48 %)	0.5
Previous myocardial infarction, n (%)	18 (8 %)	26 (34 %)	< 0.0001
Type 2 diabetes, n (%)	24 (10 %)	22 (28 %)	< 0.0001
Asthma/chronic airways disease, n (%)	34 (15 %)	9 (12 %)	0.57
Angina, n (%)	65 (28 %)	32 (42 %)	0.04
Atrial fibrillation, n (%)	12 (5 %)	23 (30 %)	0.0019
Admitted to hospital within previous year, n (%)	53 (23 %)	20 (26 %)	0.32
Clinical findings on examination			
Heart rate (bpm)	74 ± 15	73 ± 16	0.75
Systolic BP (mmHg)	148 ± 22	140 ± 24	0.007
Diastolic BP, mmHg, mean (SD)	80 ± 14	76 ± 17	0.024
Third heart sound, n (%)	17 (7 %)	30 (39 %)	< 0.0001
NT-proBNP (pmol/L) median (IQR)	36 (20, 61)	183 (103, 319)	< 0.0001
Cardiothoracic ratio (%)	0.50 ± 0.06	0.58 ± 0.08	< 0.0001
Jugular venous pressure (cm) median (IQR)	1 (0, 2)	5 (3, 5)	< 0.0001

Values are mean ± standard deviation. Student's t-test (unpaired, two-way) used to test between group differences.
Abbreviations: Aa = mitral annular late velocity, Ea = mitral annular early velocity, E:A ratio = mitral E velocity/ mitral A velocity, E:Ea ratio = mitral E velocity/Ea, FS = fractional shortening, NT-pro-BNP = N-terminal pro-brain natriuretic peptide, Sa = mitral annular systolic velocity.

Echocardiographic measurements

Excluded Patients

Not all echocardiographic variables were obtained in all subjects due to both patient and imaging constraints. Left ventricular volumes could not be measured in 27 subjects, but EF was estimated in 16 of these subjects, leaving only 11 (3.6%) subjects in whom EF was not assessed. Seventy-four patients did not have complete Diastolic measurements (mitral and tissue Doppler): 35 (11.4 %) due to atrial fibrillation, 13 (9.7 %) due to tachycardia and fused mitral Doppler, 6 (4.4 %) who had a permanent pacemaker and 20 (6.6 %) who had incomplete measurements. This left 228 (74.8 %) patients in whom complete Doppler assessment was possible at baseline and 77 subjects that were excluded from the complete diastolic analyses. Of these, 50 (22%) of the patients without HF and 30 (39%) of the patients with HF were excluded.

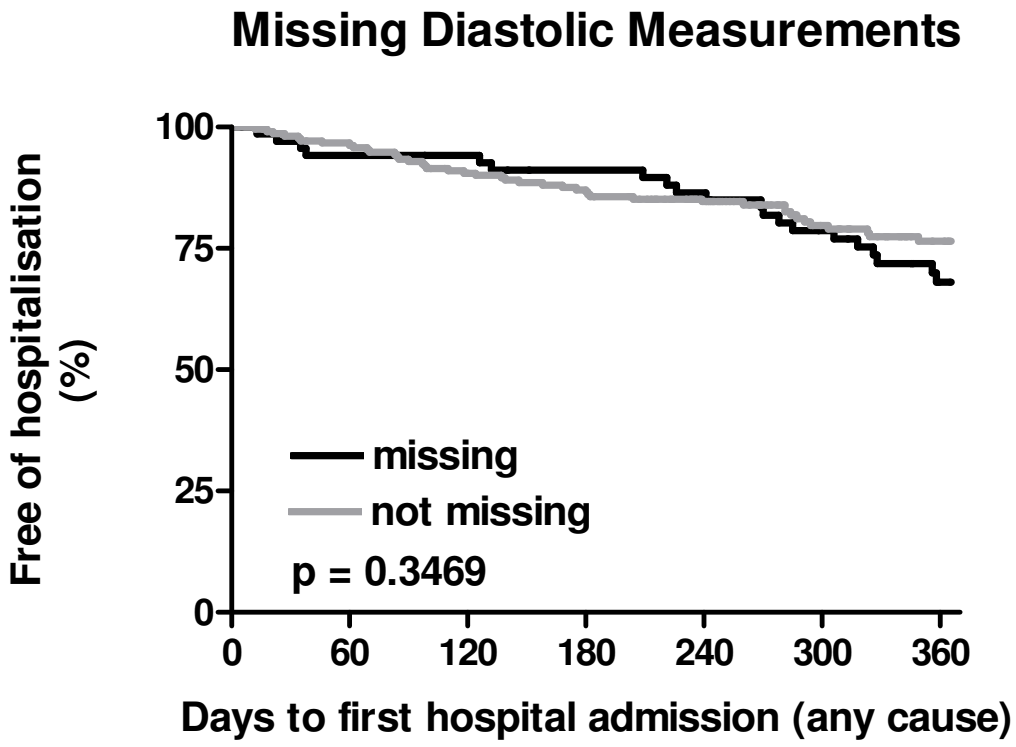
Comparing the 77 excluded patients, with those in whom complete diastolic measurements were available, there were no significant differences detected in NT-proBNP level, age, heart size or systolic function (Table 23). In addition, the readmission rates were similar between those excluded (21 admissions, event rate 28 %) and those included (47 admissions, event rate 20 %): hazard ratio 0.7762 (95% CI: 0.4363, 1.3338), p= 0.3469 (Figure 36)

Table 23 - Characteristics of patients excluded from and included in the diastolic analyses

	Missing	Not missing	p
Number of patients	77	228	-
NT-proBNP (pmol/l)	136.3 ± 149.1	111.4 ± 185.8	0.11
Age (years)	69.1 ± 74.9	70.3 ± 73.1	0.34
LV end-diastolic volume (ml)	90.3 ± 33.8	92.8 ± 35.9	0.64
LV end-systolic volume (ml)	41.9 ± 27.7	40.6 ± 27.5	0.76
FS (%)	30.6 ± 7.9	31.9 ± 8.5	0.41
Ejection fraction (%)	55.2 ± 10.7	58.4 ± 11.8	0.06
Stroke volume (ml)	49.4 ± 14.2	52.7 ± 16	0.24

Values are mean ± standard deviation. Student's t-test (unpaired, two-way) used to test between group differences.
Abbreviations: FS = fractional shortening, NT-proBNP = N-terminal pro-brain natriuretic peptide.

Figure 36 - Time to first hospitalisation in those patients with diastolic data and those without



Patients With and Without Heart Failure

Patients with HF had larger hearts (larger LV volumes, LA area and higher LV mass), impaired systolic function (lower FS, EF and Sa) and advanced diastolic filling abnormalities and elevated filling pressures (short deceleration time, higher E:A and E:Ea ratios (Table 24).

Table 24 - Echocardiographic parameters in patients with and without heart failure

	No heart failure N = 228	Heart failure N = 77	p
Heart size			
LV end-diastolic volume (ml)	83.6 ± 25.4	119.4 ± 58.7	< 0.0001
LV end-systolic volume (ml)	32.7 ± 16.3	66.7 ± 46.0	< 0.0001
Left atrial area (cm^2)	20.7 ± 5.0	26.1 ± 6.0	< 0.0001
LV mass (g)	177.6 ± 56.7	229.7 ± 90.4	< 0.0001
LV systolic parameters			
Fractional shortening (%)	34.3 ± 7.7	23.9 ± 9.7	< 0.0001
LV ejection fraction (%)	61.1 ± 10.0	47.2 ± 14.7	< 0.0001
Stroke volume (ml)	51.3 ± 15.3	54.1 ± 22.5	0.26
Systolic annular velocity (Sa) (cm/s)	5.8 ± 1.9	7.7 ± 1.7	< 0.0001
LV diastolic parameters (N=228 with complete data)			
E wave velocity, msec	52.0 ± 17.1	62.9 ± 22.5	<0.0001
A wave velocity, msec	69.1 ± 17.2	58.3 ± 24.7	<0.0001
Deceleration time, msec	215.0 ± 59.7	175.1 ± 74.8	0.0002
Isovolumic relaxation time, msec	83.5 ± 18.7	80.0 ± 28.6	0.41
Annular E velocity (Ea) (cm/s)	6.7 ± 2.3	5.0 ± 2.7	0.0006
Annular A velocity (Aa) (cm/s)	10.6 ± 2.4	7.1 ± 3.6	< 0.0001
E/Ea ratio	10.4 ± 7.7	19.7 ± 24.1	0.0006
E/A ratio	0.77 ± 0.30	1.29 ± 0.84	< 0.0001
Mitral filling pattern			
Normal	12 (5)	6 (8)	Overall effect 0.004
Abnormal relaxation	169 (74)	24 (32)	
Pseudonormal	32 (14)	4 (5)	
Restrictive	0	7 (9)	

Values are mean ± standard deviation. Student's t-test (unpaired, two-way) used to test between group differences. Abbreviations: Aa = mitral annular late velocity, Ea = mitral annular early velocity, E:A ratio = mitral E velocity/ mitral A velocity, E:Ea ratio = mitral E velocity/Ea, FS = fractional shortening, NT-proBNP = N-terminal pro-brain natriuretic peptide, Sa = mitral annular systolic velocity.

Diagnostic Accuracy

In the whole group (n=305) NT-proBNP was the most sensitive and specific parameter for diagnosing HF (area under the curve (AUC) = 0.82), however both FS and Sa were comparable (AUC = 0.81 and 0.76, respectively) (Figure 37). Most diastolic variables performed poorly, with the exception of LA area (AUC = 0.75). When the analysis was restricted to just those patients with elevated NT-proBNP > 50 pmol/l (n=161), FS performed slightly better than NT-proBNP (AUC 0.81 and 0.79, respectively) (Figure 38). However, when the analysis was restricted to those patients in whom NT-proBNP was inconclusive (NT-proBNP between 50 and 150 pmol/l) the diagnostic accuracy of NT-proBNP was poor (AUC = 0.64) and FS (AUC = 0.79), Sa (AUC = 0.70) and EF (AUC = 0.79) were superior (Figure 39). No diastolic parameters performed well within this sub-analysis.

Figure 37 - Receiver operating characteristic curves for NT-proBNP, systolic and diastolic echocardiographic variables (all patients, N=305)

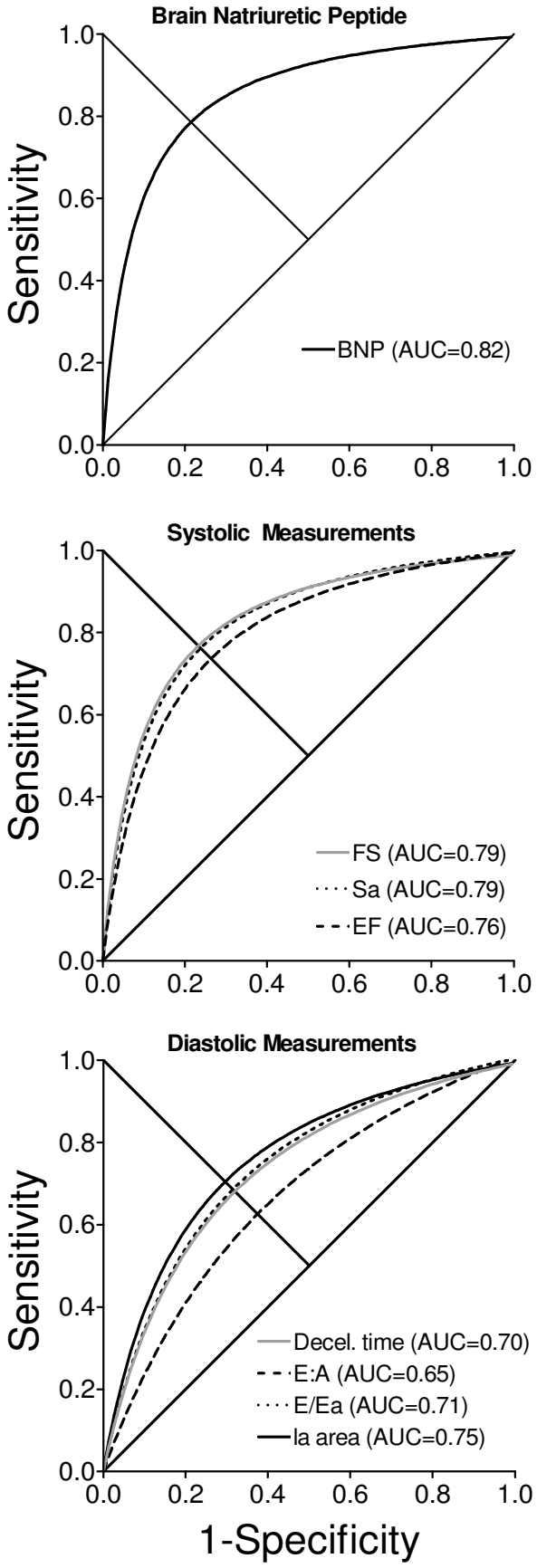


Figure 38 - Receiver operating characteristic curves for NT-proBNP, systolic and diastolic echocardiographic variables (Patients with NT-proBNP > 50 pmol/l, N=161)

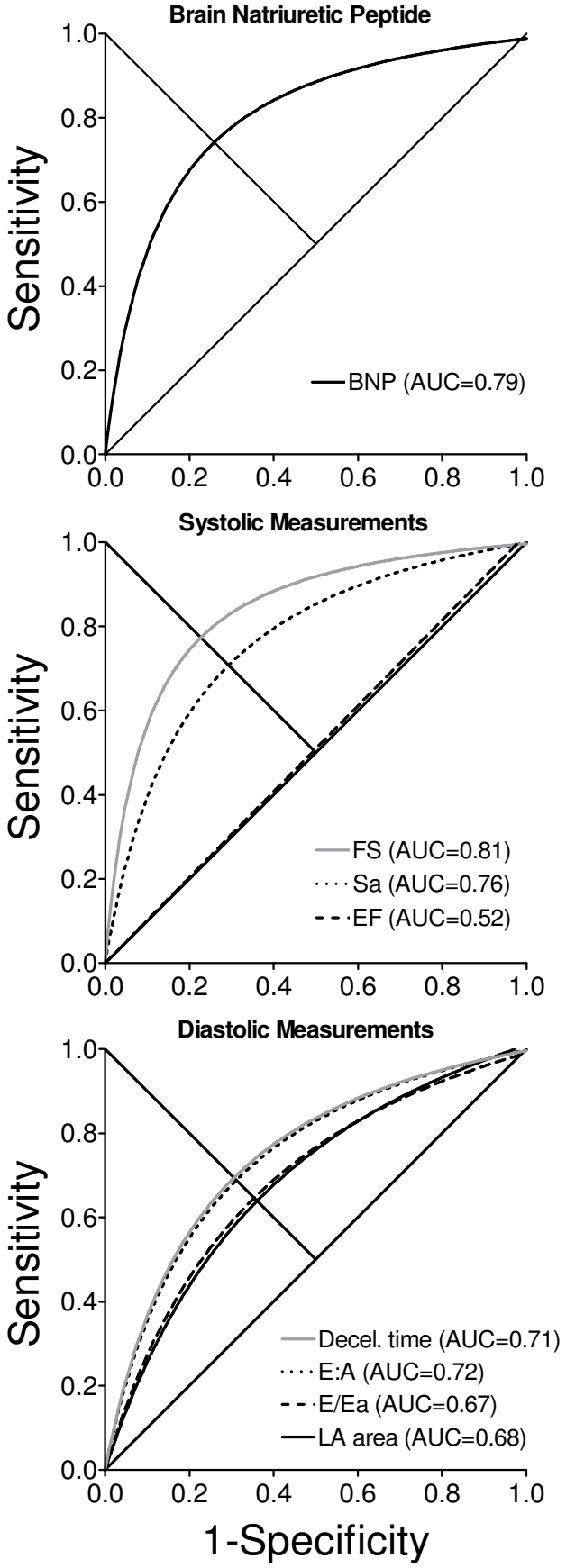
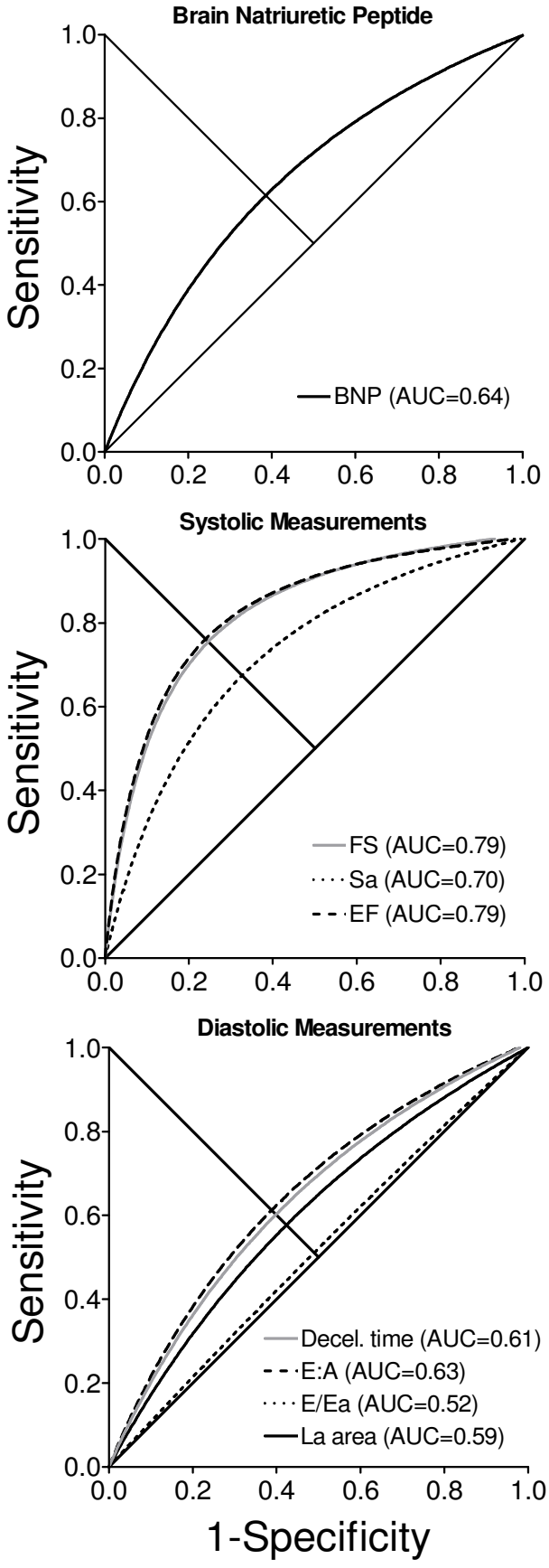


Figure 39 - Receiver operating characteristic curves for NT-proBNP, systolic and diastolic echocardiographic variables (Patients with NT-proBNP 50 - 150 pmol/l, N=98)



Time to first hospitalisation

Vital status was unavailable for 6 patients with HF and 16 without HF. During the twelve month follow-up period, 68 (22.3 %) patients were admitted to hospital (total admissions = 139). Patients with a diagnosis of HF had more hospitalisations than those in whom HF was ruled out (p=0.009). Of the total 139 admissions, the most common reasons for admission were: cardiovascular but not HF (33), HF (17), orthopaedic (16) and chronic respiratory illness (13). The remaining 52 were for a variety of different reasons. Time to first event analysis is presented by NT-proBNP level, ejection fraction, diastolic filling pattern and E/Ea ratio.

Brain Natriuretic Peptide

One hundred and forty-five patients had an NT-proBNP level $\leq$ 50 pmol/l indicating HF was an unlikely diagnosis, 63 had an NT-proBNP level >150 pmol/l indicating HF was the likely diagnosis and the remaining 98 patients had NT-proBNP levels in the uncertain diagnostic range between 50 and 150 pmol/l. Higher NT-proBNP level was associated with older age, larger LV volumes, reduced FS, EF and Sa (all consistent with depressed systolic function), larger LA area, higher E velocity, lower A velocity, lower Ea and Aa velocities, shorter deceleration time, higher E/Ea and E:A ratios (suggestive of advanced diastolic filling abnormalities and elevated filling pressure)

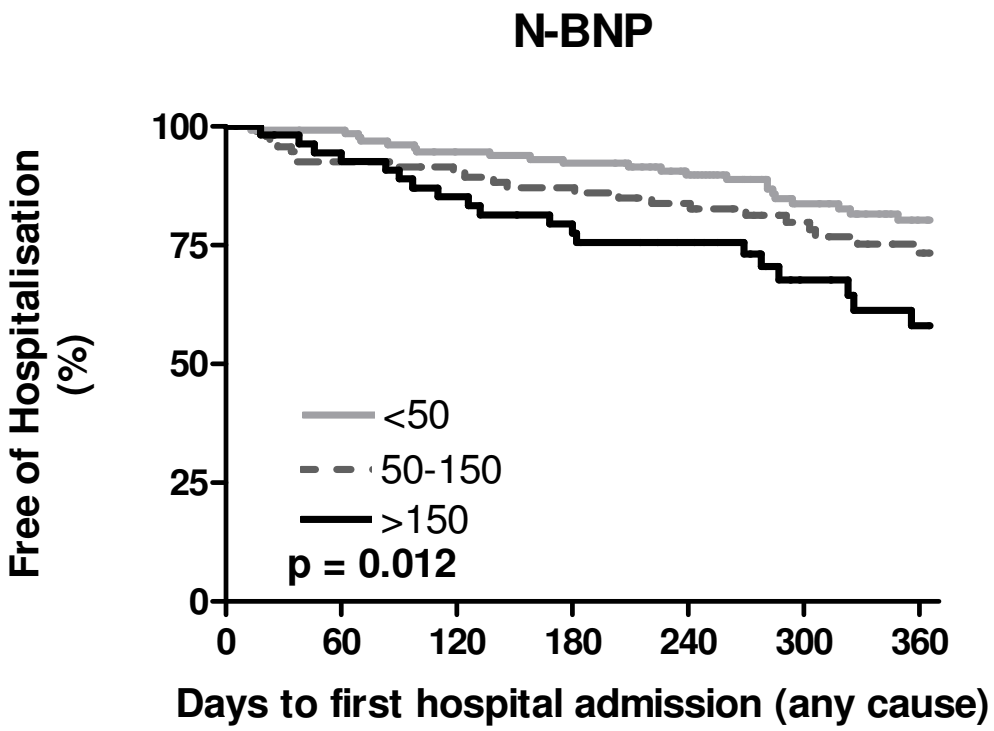
Table 25 - Characteristics of patients according to NT-proBNP level

	N- BNP ≤ 50 pmol/l	NT-proBNP 50 - 150 pmol/l	NT-proBNP > 150 pmol/l	ANOVA
Number of patients	144	98	63	-
NT-proBNP (pmol/l)	24.1 ±12.6	89.2 ± 27.7	374.9 ± 313.1	< 0.0001
Age (years)	66.8 ± 10.5	75.3 ± 10.2	77.9 ± 10.3	< 0.0001
LV end-diastolic volume (ml)	85.1 ± 25.9	91.9 ±42.9	110.1 ± 53.4	0.0003
LV end-systolic volume (ml)	32.7 ± 17.9	40.3 ± 28.7	61.9 ± 45.4	< 0.0001
LV systolic parameters				
FS (%)	34.3 ± 8.3	32.0 ± 8.7	25.8 ± 10.0	< 0.0001
Ejection fraction (%)	62.0 ± 9.9	57.7 ± 12.4	47.3 13.9	< 0.0001
Stroke volume (ml)	52.7 ± 14.7	52.6 ± 19.8	49.4 19.0	0.465
Sm (cm/s)	8.04 ± 1.7	7.09 ± 1.4	5.16 ± 1.82	< 0.0001
LV diastolic parameters				
E velocity (cm/s)	50.0 ± 13.6	53.9 ±16.1	67.5 ± 26.6	< 0.0001
A velocity (cm/s)	69.7 ± 14.9	69.7 ± 19.6	53.0 ± 25.5	< 0.0001
Deceleration time (s)	218.2 ± 55.6	208.7 ± 65.6	171.6 ± 76.3	0.004
Left atrial area (cm^2)	19.7 ± 4.2	23.2 ± 5.7	26.3 ± 5.9	< 0.0001
Ea (cm/s)	6.95 ± 2.3	6.14 ± 2.2	4.74 ± 2.8	< 0.0001
Aa (cm/s)	11.1 ± 2.1	9.9 ± 2.8	5.79 ± 2.7	< 0.0001
E/Ea ratio	8.87 ± 2.9	12.1 ± 9.8	23.8 ± 27.1	< 0.0001
E:A ratio	0.74 ± 0.24	0.84 ± 0.45	1.45 ± 0.95	< 0.0001

Values are mean ± standard deviation. ANOVA was used to test the relationship between the three groups.
Abbreviations: Aa = mitral annular late velocity, Ea = mitral annular early velocity, E:A ratio = mitral E velocity/ mitral A velocity, E:Ea ratio = mitral E velocity/Ea, FS = fractional shortening, NT-proBNP = N-terminal pro-brain natriuretic peptide, Sa = mitral annular systolic velocity.

There was a tiered relationship between hospitalisation and NT-proBNP level (p = 0.012). When comparing patients with NT-proBNP ≥ 150 mmol/l with all others, higher NT-proBNP was associated with worse outcome (20 admissions, event rate 32 %) than NT-proBNP < 150 mmol/l (48 admissions, event rate 20 %) hazard ratio 2.084 (95% CI: 1.297, 4.815, p=0.0062). NT-proBNP ≥ 50 mmol/l was associated with worse outcome (41 admissions, event rate 25 %) than NT-proBNP < 50 mmol/l (25 admissions, event rate 17 %), hazard ratio 1.825 (95% CI: 1.093, 2.937, p=0.0207) (Figure 40).

Figure 40 - Time to first hospitalisation by NT-proBNP level



Ejection Fraction

Forty-five subjects had an EF ≤ 45% and this was associated higher NT-proBNP level, larger LV volumes, smaller stroke volume, reduced FS, EF and Sa (all consistent with depressed systolic function), larger LA area, higher E/Ea and E:A ratios (suggestive of advanced diastolic filling abnormalities and elevated filling pressure) (Table 25).

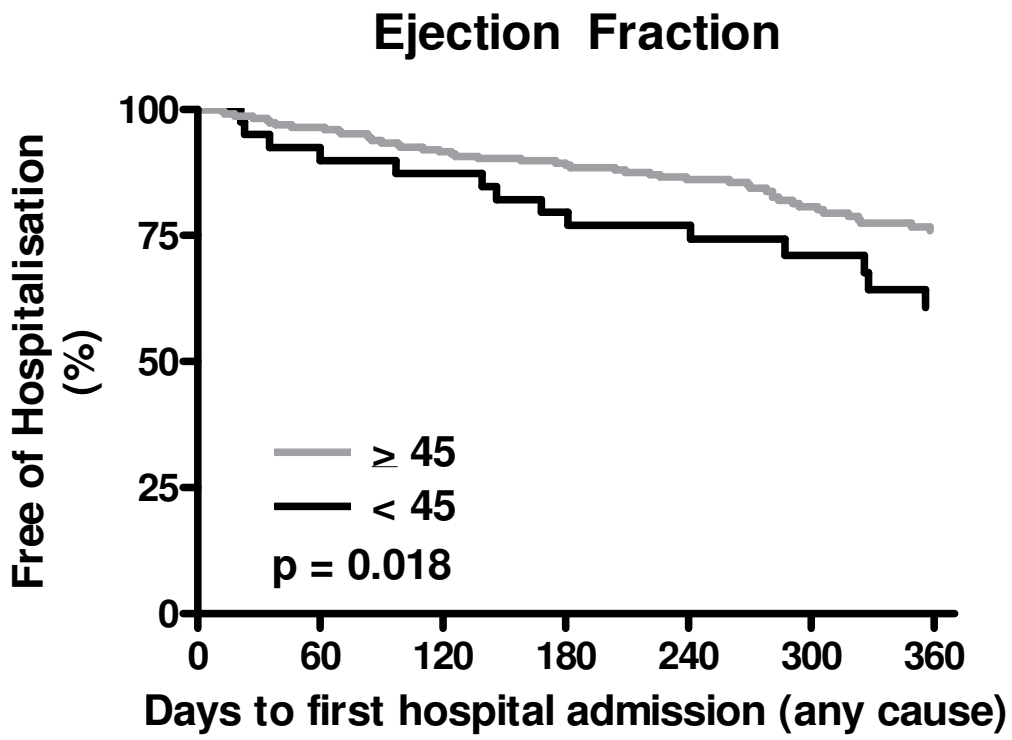
Table 26 - Characteristics of patients with depressed systolic function (≤ 45 %) compared to those with normal function (EF > 45 %)

	EF < 45 %	**EF ≥ 45**	**t-test**
Number of patients	45	246	-
NT-proBNP (pmol/l)	229.3 ± 348.1	152.8 ± 89.3	0.01
Age (years)	71.3 ± 9.87	71.8 ± 11.9	0.78
LV end-diastolic volume (ml)	131.2 ± 60.3	84.9 ± 28.8	< 0.0001
LV end-systolic volume (ml)	86.3 ± 47.4	33.0 ± 15.4	< 0.0001
LV systolic parameters			
FS (%)	19.1 ± 6.8	33.8 ± 8.0	< 0.0001
Ejection fraction (%)	34.9 ± 7.8	60.7 ± 11.5	< 0.0001
Stroke volume (ml)	46.5 ± 18.8	53.0 ± 16.8	0.03
Sa (cm/s)	5.3 ± 1.6	7.45 ± 1.57	< 0.0001
LV diastolic parameters			
E velocity (cm/s)	54.5 ± 17.6	54.7 ± 19.0	0.96
A velocity (cm/s)	62.6 ± 28.3	67.8 ± 17.2	0.11
Deceleration time (s)	186.0 ± 71.8	208.9 ± 63.7	0.05
Left atrial area (cm^2)	24.1 ± 5.9	21.8 ± 5.7	0.03
Ea (cm/s)	4.2 ± 2.02	6.70 ± 2.35	< 0.0001
Aa (cm/s)	7.6 ± 3.3	10.3 ± 2.80	< 0.0001
E/Ea ratio	17.6 ± 10.7	10.8 ± 2.80	0.002
E:A ratio	1.2 ± 0.92	0.83 ± 0.44	0.04

Values are mean ± standard deviation. Student's t-test (unpaired, two-way) used to test between group differences. Abbreviations: Aa = mitral annular late velocity, Ea = mitral annular early velocity, E:A ratio = mitral E velocity/ mitral A velocity, E:Ea ratio = mitral E velocity/Ea, FS = fractional shortening, NT-proBNP = N-terminal pro-brain natriuretic peptide, Sa = mitral annular systolic velocity.

Patients with depressed LV systolic function (< 45 %) had higher rates of hospitalisation (14 admissions, event rate 31 %) compared to patients with EF ≥ 45% (51 admissions, event rate 21 %), hazard ratio 1.90 (95% CI: 1.146, 4.349, p=0.018) (Figure 41).

Figure 41 - Time to first hospitalisation by ejection fraction



Restrictive Filling Pattern

Twelve subjects (5.8%) displayed RFP at baseline and this was associated higher NT-proBNP level, larger LV volumes, reduced FS, EF and Sa (all consistent with depressed systolic function), larger LA area, higher E velocity, lower A velocity, short deceleration time, low tissue Doppler velocities and higher E/Ea and E:A ratios (consistent with advanced diastolic filling abnormalities and significantly elevated filling pressure) (Table 26).

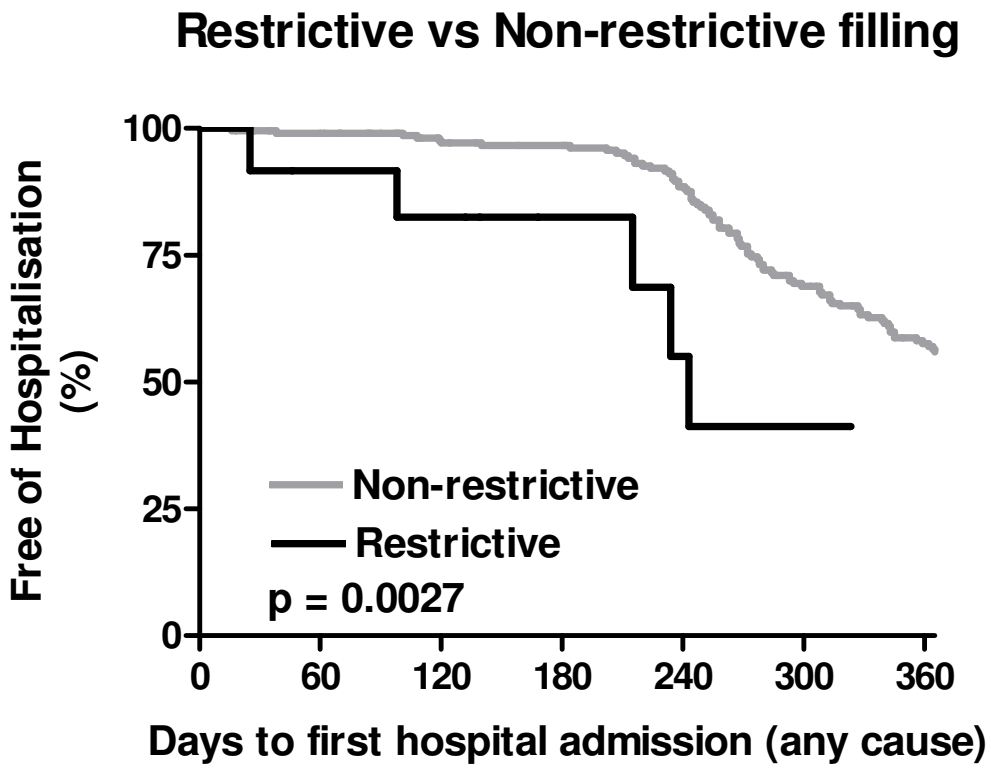
Table 27 - Characteristics of patients with restrictive mitral filling pattern compared to patients with non-restrictive pattern

	Restrictive Filling	Non-restrictive Filling	t-test
Number of patients	12	216	-
NT-proBNP (pmol/l)	229.3 ± 348.1	76.4 ± 119.8	< 0.0001
Age (years)	76.4 ± 6.98	71.2 ± 10.3	0.07
LV end-diastolic volume (ml)	117.7 ± 41.2	89.6 ± 34.5	0.007
LV end-systolic volume (ml)	69.9 ± 50.2	37.5 ± 25.7	< 0.0001
LV systolic parameters			
FS (%)	19.5 ± 8.7	33.9 ± 8.3	< 0.0001
Ejection fraction (%)	43.2 ± 21.0	59.8 ± 11.4	< 0.0001
Stroke volume (ml)	51.3 ± 18.2	52.7 ± 15.7	0.78
Sa (cm/s)	5.3 ± 1.6	7.52 ± 1.81	< 0.0001
LV diastolic parameters			
E velocity (cm/s)	77.5 ± 19.5	50.5 ± 13.9	< 0.0001
A velocity (cm/s)	34.7 ± 14.1	68.9 ± 17.4	< 0.0001
Deceleration time (s)	127.7 ± 40.5	218.3 ± 59.4	< 0.0001
Left atrial area (cm^2)	26.7 ± 5.7	20.9 ± 4.9	< 0.0001
Ea (cm/s)	3.28 ± 2.52	6.45 ± 2.32	< 0.0001
Aa (cm/s)	3.77 ± 1.20	10.3 ± 2.62	< 0.0001
E/Ea ratio	41.4 ± 39.6	10.8 ± 2.80	< 0.0001
E:A ratio	2.5 ± 0.82	0.77 ± 0.31	< 0.0001

Values are mean ± standard deviation. Student's t-test (unpaired, two-way) used to test between group differences. Abbreviations: Aa = mitral annular late velocity, Ea = mitral annular early velocity, E:A ratio = mitral E velocity/ mitral A velocity, E:Ea ratio = mitral E velocity/Ea, FS = fractional shortening, NT-proBNP = N-terminal pro-brain natriuretic peptide, Sa = mitral annular systolic velocity.

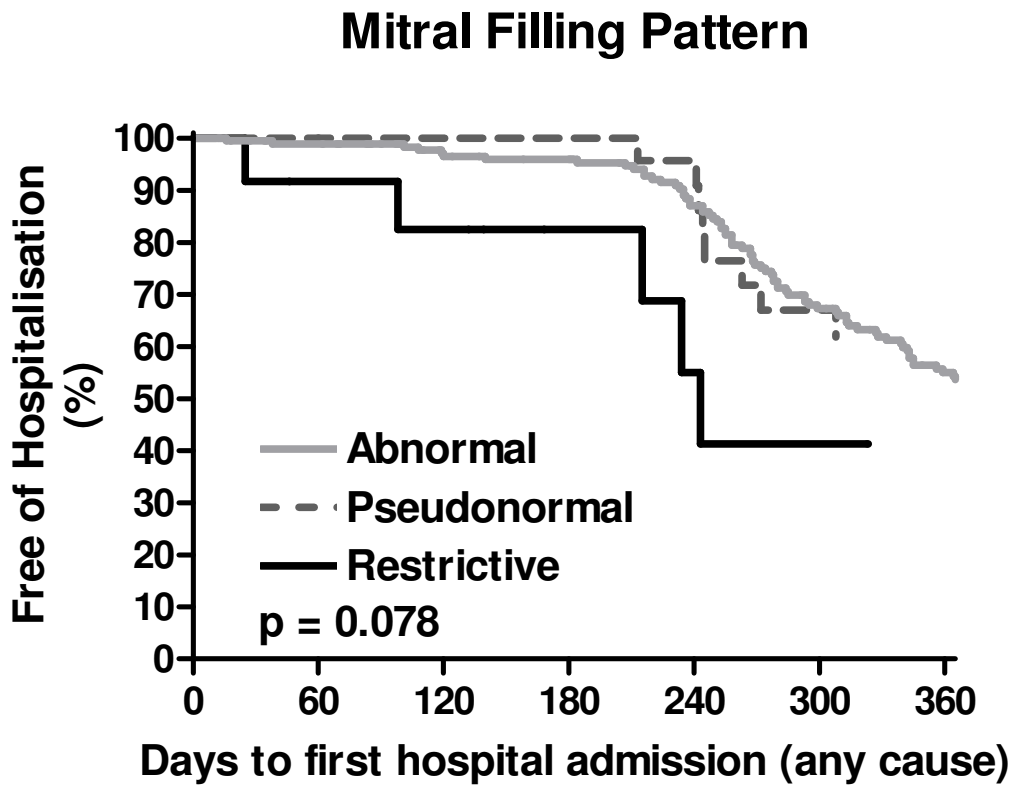
Patients with RFP had higher rates of hospitalisation (5 admissions, event rate 33 %) compared to patients with non-RFP (47 admissions, event rate 19 %), hazard ratio 2.97 (95% CI: 1.956, 25.22, p=0.0028) (Figure 42)

Figure 42 - Time to first hospitalisation by restrictive and non-restrictive filling pattern



Both pseudonormal filling and abnormal relaxation were different to the restrictive filling group (p = 0.0078) but no difference was seen between the pseudonormal filling and abnormal relaxation groups (Figure 43).

Figure 43 - Time to first hospitalisation by diastolic filling pattern



E/Ea ratio

E/Ea ratio ≤ 8, 8-15, > 15

E/Ea ratio was ≤ 8 in 77 (34 %) subjects, between 9 and 15 in 112 (49 %) subjects, and ≥ 15 in 39 (17 %) subjects. Higher E:Ea ratio was associated higher NT-proBNP level, older age, larger LV volumes, reduced FS, EF and Sa (all consistent with depressed systolic function), larger LA area, short deceleration time, higher E:A ratio and lower tissue Doppler velocities (consistent with advanced diastolic filling abnormalities and significantly elevated filling pressure) (Table 27).

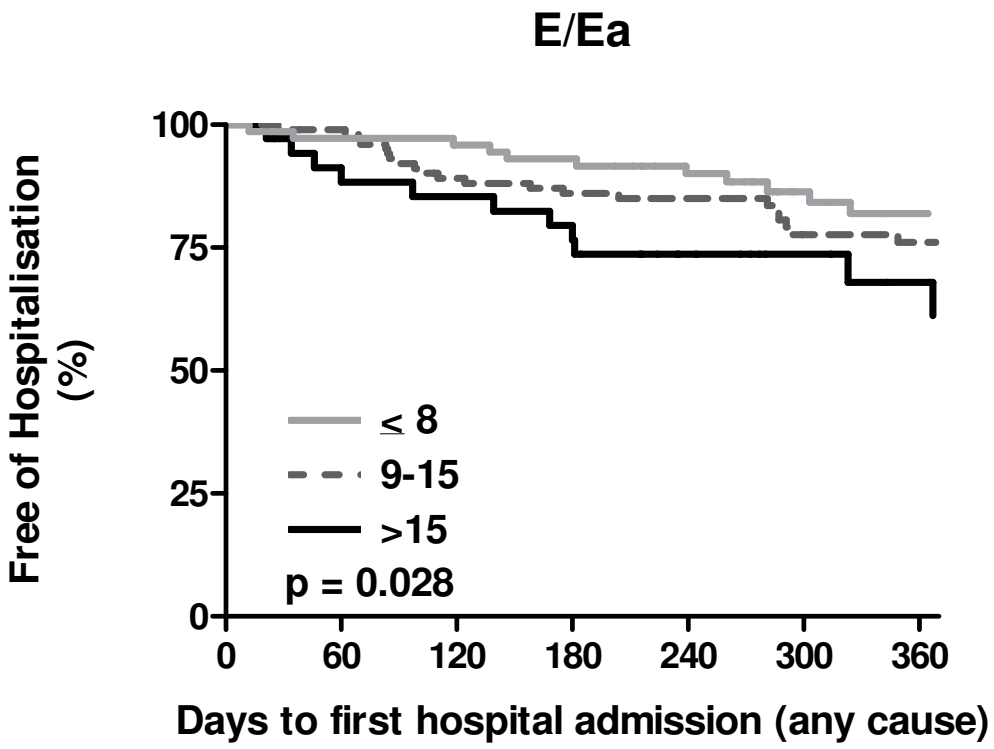
Table 28 - Characteristics of three groups of E/Ea ratio

	E/Ea < 8	**E/Ea 8 – 15**	**E/Ea > 15**	**ANOVA**
Number of patients	77	112	39	-
NT-proBNP (pmol/l)	52.4 ± 56.8	79.5 ± 97.7	315.4 ± 399.7§**	< 0.0001
Age (years)	69.7 ± 11.4	71.96 ± 10.9	75.1 ± 10.3§**	0.043
LV end-diastolic volume (ml)	86.2 ± 28.3	88.9 ± 36.97	117.2 ± 55.5§**	0.0002
LV end-systolic volume (ml)	33.97 ± 16.3	36.7 ± 27.4	65.3 ± 45.2§**	< 0.0001
LV systolic parameters				
FS (%)	33.3 ± 8.1	33.6 ± 8.4	25.2 ± 11.2§**	< 0.0001
Ejection fraction (%)	61.1 ± 9.1	60.7 ± 11.5	46.8 ± 16.8§**	< 0.0001
Stroke volume (ml)	52.3 ± 16.8	52.6 ± 15.7	53.6 ± 23.2	0. 934
Sa (cm/s)	8.05 ± 1.76	7.45 ± 1.57*	5.36 ± 1.72§**	< 0.0001
LV diastolic parameters				
E velocity (cm/s)	45.9 ± 11.3	54.2 ± 15.7	61.2 ± 18.2§**	< 0.0001
A velocity (cm/s)	63.6 ± 14.0	68.8 ± 16.3	68.7 ± 32.2	0.17
Deceleration time (s)	225.1 ± 59.5	203.2 ± 58.8	198.5 ± 79.3**	0.037
Left atrial area (cm^2)	20.6 ± 5.52	21.7 ± 4.7	23.0 ± 6.4	0.093
Ea (cm/s)	7.76 ± 2.0	6.29 ± 1.97	3.28 ± 1.43§**	< 0.0001
Aa (cm/s)	10.8 ± 2.43	10.2 ± 2.56	7.14 ± 3.81§**	< 0.0001
E/Ea ratio	6.64 ± 0.90	10.43 ± 1.72 *	29.9 ± 26.7§**	< 0.0001
E:A ratio	0.75 ± 0.30	0.84 ± 0.42	1.20 ± 0.92 §**	< 0.0001

Values are mean ± standard deviation. ANOVA was used to determine the effect between groups.
Abbreviations: Aa = mitral annular late velocity, Ea = mitral annular early velocity, E:A ratio = mitral E velocity/ mitral A velocity, E:Ea ratio = mitral E velocity/Ea, FS = fractional shortening, NT-proBNP = N-terminal pro-brain natriuretic peptide, Sa = mitral annular systolic velocity.

There were 12 hospitalisations in the group with E/Ea ≤ 8 (16 % event rate), 23 hospitalisations in the group with E/Ea 9-15 (event rate 21 %) and 11 hospitalisations in the group with E/Ea > 15 (event rate 28 %) (Chi^2 =0.028). The hazard ratio for E/Ea ≥ 15 was 2.230 (95% CI: 1.284, 6.507, p = 0.0103) and for E/Ea > 8 was 1.61 (95% CI: 0.874, 2.771, p = 0.1334) (Figure 44).

Figure 44 - Time to first readmission by E/Ea ratio



E/Ea ratio ≤ or > 11

Seventy-five subjects had an E/Ea > 11. Higher E:Ea ratio was associated higher NT-proBNP level, larger LV volumes, reduced FS, EF and Sa (all consistent with depressed systolic function), larger LA area, higher E velocity, shorter deceleration time, higher E:A ratio and E/Ea ratios and lower tissue Doppler velocities (consistent with advanced diastolic filling abnormalities and significantly elevated filling pressure) (Table 28).

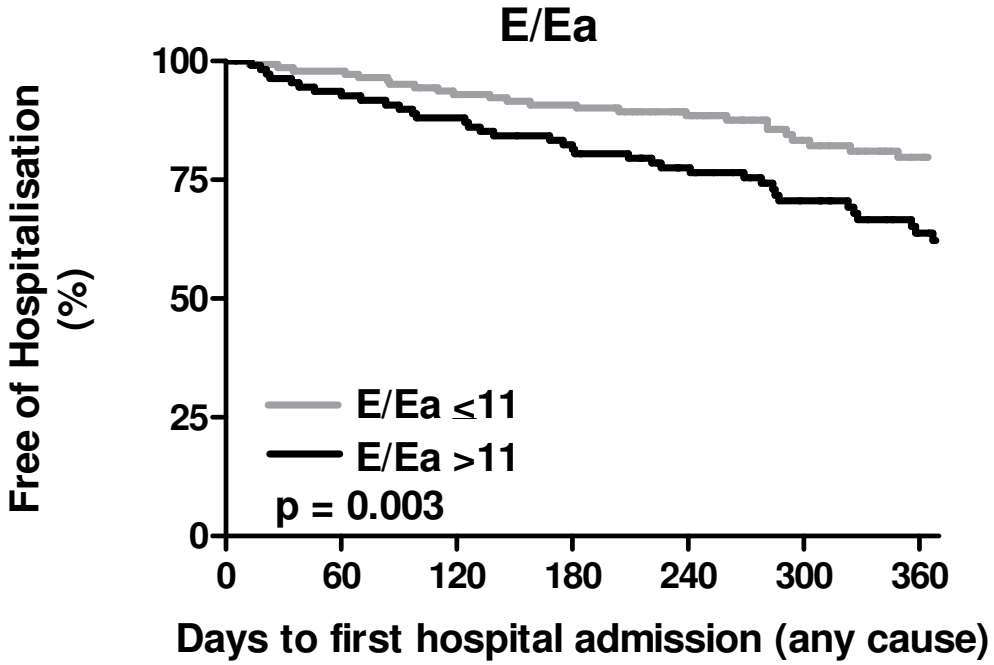
Table 29 - Characteristics of patients with E/Ea < 11 and those with E/Ea ratio > 11

	E/Ea ≤ 11	**E/Ea > 11**	**t-test**
Number of patients	153	75	-
NT-proBNP (pmol/l)	60.3 ± 77.8	213.4 ± 313.6	< 0.0001
Age (years)	73.7 ± 10.4	70.8 ± 11.3	0.10
LV end-diastolic volume (ml)	86.4 ± 31.2	106.0 ± 50.6	0.0008
LV end-systolic volume (ml)	34.2 ± 22.3	53.9 ± 39.4	< 0.0001
LV systolic parameters			
FS (%)	33.8 ± 8.2	28.2 ± 10.5	0.0002
Ejection fraction (%)	61.8 ± 10.4	51.6 ± 14.9	< 0.0001
Stroke volume (ml)	52.2 ± 15.4	53.6 ± 21.0	0.58
Sm (cm/s)	7.84 ± 1.69	5.3 ± 1.6	< 0.0001
LV diastolic parameters			
E velocity (cm/s)	48.7 ± 12.6	60.6 ± 18.4	< 0.0001
A velocity (cm/s)	66.3 ± 15.2	68.5 ± 25.9	0.42
Deceleration time (s)	213.7 ± 58.3	201.7 ± 73.1	0.19
Left atrial area (cm^2)	21.0 ± 5.3	22.7 ± 5.4	0.04
Ea (cm/s)	7.15 ± 2.03	4.48 ± 2.17	< 0.0001
Aa (cm/s)	10.6 ± 2.39	8.27 ± 3.59	< 0.0001
E/Ea ratio	8.03 ± 1.69	21.6 ± 21.0	< 0.0001
E:A ratio	0.77 ± 0.33	1.08 ± 0.76	< 0.0001

Values are mean ± standard deviation. Student's t-test (unpaired, two-way) used to test between group differences. Abbreviations: Aa = mitral annular late velocity, Ea = mitral annular early velocity, E:A ratio = mitral E velocity/ mitral A velocity, E:Ea ratio = mitral E velocity/Ea, FS = fractional shortening, NT-proBNP = N-terminal pro-brain natriuretic peptide, Sa = mitral annular systolic velocity.

There were 26 hospitalisations in the group with E/Ea ≤ 11 (17 % event rate) and 20 hospitalisations in the group with E/Ea > 11 (event rate 27 %), hazard ratio 2.011 (1.270, 3.292, p = 0.003) (Figure 45).

Figure 45 - Time to first readmission by E/Ea ratio ≥ 11



Multi-variate predictors of hospitalisation

Using the Cox proportional hazards model, only NT-proBNP predicted hospitalisation in the whole group (p=0.002). If NT-proBNP was removed from the model, the only independent predictor of hospitalisation was E/Ea (p=0.003). In the sub-group of subjects (N=98) where the NT-proBNP level was uncertain (NT-proBNP 50 -150 pmol/l) and thus neither ruled out HF nor gave a certain diagnosis, NT-proBNP did not predict survival in the multivariate model, but E/Ea did (p=0.028)(Table 29).

Table 30 - Stepwise multivariate predictors of hospitalization

Patients	Variable	Model Chi Square	P value
Model: Hospitalisation = NT-proBNP, EF, FS, E:A, E/Ea, LA area, deceleration time, Sa, age,			
All patients (n=204)	NT-proBNP	8.2	0.0041
Patients with NT-proBNP $\leq$ 50 (n=105)	no variables in model		
Patients with NT-proBNP 50- 150 (n=66)	E/Ea	6.2	0.0126
Patients with NT-proBNP $\geq$ 150 (n=33)	no variables in model		
NT-proBNP not in model: Hospitalisation = EF, FS, E:A, E/Ea, LA area, deceleration time, Sa, age			
All patients (n=204)	E/Ea $\geq$ 11	6.2	0.0129
Simplified Model: Hospitalisation = NT-proBNP, age, EF, E/Ea			
All patients (n=204)	NT-proBNP	11.6	0.0007

Abbreviations: E:A = ratio of early (E) to late (A) mitral filling, E:Ea = ratio of early mitral filling (E) to early mitral annular velocity (Ea), EF = ejection fraction, FS = fractional shortening, LA = left atrial, NT-proBNP = N-terminal pro-brain natriuretic peptide, Sa = mitral annular systolic velocity.

Discussion

The role of echocardiography for diagnosis of heart failure in primary care

The findings of this study support a role for both echocardiography and neurohormone assay in the management of symptomatic patients in the community. NT-proBNP and echocardiographic evidence of systolic dysfunction were similarly accurate when used to diagnose HF, but NT-proBNP is more readily available and also more than one fifth the cost of a standard echocardiogram. Of interest, however, is the finding that when NT-proBNP fell into the inconclusive range (50-150 pmol/l) echocardiography was superior. NT-proBNP in this range is neither sensitive nor specific. This is especially true in this group of subjects who are elderly and have frequent co-morbidity. NT-proBNP does increase with age,[306-308] thus making it difficult to be certain of the implications of a mildly elevated level.

None of the diastolic parameters were found to be useful for diagnosing HF. This may be explained in part by the fact that complete diastolic measurements were not available in 25% of the subjects, although there were no major differences between the subjects with and without data. Despite not being diagnostically discriminative, these diastolic parameters were linked to prognosis in the follow-up arm of the study. There was no difference in prognosis between the groups with and without baseline diastolic data. Thus it seems unlikely that the missing data would have been solely responsible for lack of diagnostic importance.

The failure of diastolic parameters to diagnose HF may also reflect the inherent bias of the European Society of Cardiology diagnostic guidelines,[103,329] which require objective evidence of cardiac dysfunction and were developed prior to the widespread introduction of tissue Doppler echocardiography and certainly prior to the publication of its clinical relevance. At the time of this study, tissue Doppler was only just beginning to emerge and it is likely that the expert panel did not utilise this information in the same way that a similar panel would today. This is supported by the fact that some diastolic parameters (left atrial size, E/Ea, Ea) were correlated with NT-proBNP at baseline. And E/Ea predicted hospitalisations in both the patients with HF and those without. Further, the mean E/Ea in the non-HF group was 9.6 which is higher than might be anticipated for a healthy population and 19 patients in this group had an E/Ea ratio of > 15, indicating significant

elevation of LV filling pressure. Of the patients with E/Ea > 15, approximately 10% had an EF > 50% which may have been regarded as normal cardiac function by the panel. It is not unusual for patents with diastolic HF to have normal EF, but reduced stroke volume due to small cavity size of the LV.

The non-HF group also had a higher percentage of women than the HF group and patients with confirmed diastolic heart failure are often older and more likely to be women.[102,330] It is relatively easy to diagnose structural abnormalities or systolic impairment, but it is more challenging to diagnose diastolic HF if one is to use the European Society of Cardiology Working Group guidelines.[104] Thus, rather than concluding that diastolic parameters failed to diagnose heart failure, it might be more appropriate to say that they failed to diagnose *systolic* heart failure in the current study. It is likely that a number of patients with diastolic heart failure were unrecognised by the expert panel. This is supported by the fact that prognosis was linked to baseline E/Ea even in those patients in whom HF was ruled out.

Predicting future hospitalisations

To our knowledge this is the first study to demonstrate the prognostic power of diastolic echocardiography in breathless patients in the community. In this study, E/Ea, an echocardiographic surrogate of LA pressure was closely linked to future hospitalisations. Many other traditional echocardiographic variables, such as EF and mitral filling pattern, as well as NT-proBNP also predicted hospitalisation, but in multivariate analysis, E/Ea was the only independent predictor of event-free survival in those patients in whom NT-proBNP was inconclusive. Certainly these factors are inter-related. The group of subjects with the highest E/Ea ratio had much higher NT-proBNP levels and also more systolic dysfunction. Thus, E/Ea is not merely reflecting diastolic filling abnormalities, but gives an overall view of LV function. E/Ea was more discriminative that diastolic filling pattern in this study as three distinct groups were identified each with associated and incremental event-free survival rates. In this study, we did not demonstrate separation between the pseudonormal filling group and abnormal relaxation group as we have in our previous work. This may be explained by the different clinical status and small number of patients with restrictive filling pattern in the current study. Our previous study (Chapter 3) involved patients with established HF who had all had a least one prior admission to hospital. The current study is at the other end of

the disease spectrum and there were in fact only a few (12) patients in this category. E/Ea which is a continuous variable may also be a better predictor than filling pattern which lacks power since it is a categorical variable and misclassification could dilute associations (regression/dilution bias). Lastly, E/Ea can be used in patients where conventional Doppler methods are challenging such as AF and supraventricular tachycardia, where the relationship between E:Ea and filling pressure has been validated.[85]

E/Ea has been correlated with filling pressures in several studies[83-85,96,97] and has been previously linked to prognosis in patients with established cardiovascular disease[143,146]. Unlike the mitral inflow velocities, this ratio is less affected by loading conditions and does not pseudonormalise. Of particular interest in the current study, is the fact that E/Ea even predicted hospitalisation in those patients in whom HF was ruled out. This may be explained in two ways. Firstly, that the expert panel diagnosis of HF was biased towards systolic impairment and thus missed some cases of diastolic HF. This is certainly likely. The second explanation is that the E/Ea reflects overall health status. E/Ea is related to left atrial pressure and thus some of the non-HF patients may have had some degree of increased filling pressure. This is supported by the fact that both E/Ea,[83-85,96,97] and deceleration time[74,88,90-93,95] are both related to LV filling pressure, it is conceivable that the use of these parameters has identified a group of patients with elevated filling pressures but who do not have definite HF. Deceleration time is also associated with higher neurohormonal activity[99,135] and as such both may be surrogates for LA pressure.

Echocardiography in general practice

Echocardiography is currently not widely available to general practitioners who are primarily responsible for diagnosing and managing patients with HF such as those in the current study. Whilst there has been a call to increase general practitioners' access to echocardiography [105] and anecdotally this appears to aid diagnosis, open access echocardiography has not been rigorously trialled and thus the added benefits remain uncertain. In addition, there is concern about

the general practitioners' abilities to interpret complex echocardiography reports and measurements into meaningful clinical information.

The choice of echocardiographic measurements is of interest. A simple measure of systolic dysfunction such as FS appeared to perform equally well as EF. However, the advantage of EF measurements is that they do incorporate wider areas of myocardium and are certainly more accurate when regional wall motion abnormalities exist. Tissue systolic velocity (Sa) was also accurate in the current study, but this is a difficult measurement because as a new measurement, there is a paucity of data regarding normal values. In addition, not all echocardiography centres are proficient and comfortable with performance and interpretation of TDI. In terms of diastolic measurements are concerned, LA size and E/Ea appear to be important, but again these are not often performed despite there being a significant amount of data supporting their use.

Limitations

The findings of this study and implementation of echocardiography for diagnosis and prognosis in community-based patients may be subjects to some measurement bias arising from the delay between onset of symptoms, presentation at the general practitioner and the further delay to echocardiography. In the current study, this may have resulted in some resolution of HF symptoms (perhaps in response to early initiation of HF therapy). Further, because a number of patients presented in rhythms that made complete diastolic assessment difficult, a number of patients were necessarily excluded from some analyses. However, this reflects the "real world" nature of implementing this approach in the community in a group of patients with frequent co-morbidity and fluctuating haemodynamic status.

Conclusions

This study has demonstrated the very Complementary roles of neurohormone assay and echocardiography for management of symptomatic patients in the community. Whilst, both echocardiography and NT-proBNP were equally efficacious for diagnosing HF, the latter is clearly more easily applied and considerably cheaper for large population use. A two-tiered approach is probably indicated: NT-proBNP assay first and echocardiography in those patients where NT-

proBNP is clearly elevated (>150 pmol/l) and in those in whom it is only mildly elevated (50-150 pmol/l). Echocardiography will not aid diagnosis in those patients with very elevated NT-proBNP levels, but will provide important anatomical information to aid aetiological diagnosis may identify remedial conditions and will add significant prognostic information.

When NT-proBNP falls into the indeterminate range (50-150 pmol/l) and is thus deemed inconclusive with regard to diagnosing HF, echocardiography is essential for achieving correct and appropriate diagnosis of HF. Diagnosis of HF is the primary goal of echocardiography in the community and the prognostic information obtained an added bonus, the added value of which may only appear as treatments are further evaluated.

Key Findings:

- The diagnosis of heart failure in the community may be optimised by using NT-proBNP as a first test to “rule-out” heart failure, and then echocardiography in patients with intermediate NT-proBNP levels to diagnose HF and in elevated NT-proBNP to assess aetiology and identify potentially remediable causes.
- Systolic measurements (EF, FS and Sa) are the main diagnostic variable in this cohort of elderly symptomatic community-based patients
- Echocardiography, especially the assessment of diastolic function is useful for identifying patients at highest risk of subsequent hospitalisation
- E/Ea appears to be one of the best discriminative variables for prognosis

Chapter 6 – Conclusions

Key findings from this research

Heart failure is the clinical manifestation of symptoms that arise from pathological and/or physiological alterations in cardiac function. Principally, a reduction in the forward output of the left ventricle (LV) and elevated ventricular filling pressure. Both of these may be estimated non-invasively by echocardiography, which is an important tool that assists physician management of patients with heart failure. It allows physicians to be confident in their diagnosis and also identifies patients at highest risk of subsequent events (death and/or hospitalisation). Advances in ultrasound imaging have led to a number of new techniques that can optimise the diagnostic and prognostic utility of echocardiography in HF. This thesis has explored several of these contemporary methods used to assess left ventricular function and found that these methods can enhance the reproducibility and accuracy of echocardiography, which in turn improves diagnostic and prognostic accuracy. The methods investigated in this thesis are not experimental techniques at the cutting-edge of technology, but are simple, validated techniques that are available to most practitioners and thus most patients. Many of these techniques are not currently applied routinely however. Table 31 summarises the key findings from each chapter.

Table 31 - Key findings from each chapter

1 - The Role of Echocardiography in the Contemporary Management of Chronic Heart Failure
• Heart failure, which is increasing in prevalence, is associated with significant mortality and morbidity and is a leading cause of cardiovascular morbidity, hospitalisation and death • Echocardiography can provide essential information for physician management of heart failure patients by providing important aetiological and diagnostic information • Echocardiography may also assist with prognosis in patients with heart failure • Echocardiography in patients with HF should be comprehensive and extend beyond the assessment of LV systolic function • Assessment of diastolic filling should be considered in all patients with high clinical suspicion of HF and those patients with established systolic impairment • Current echocardiographic techniques lack the precision required for repeat assessment of systolic function in individual patients
2 - Quantification of Left Ventricular Function in Heart Failure - Effects of Measurement Variability
• Assessment of systolic function in patients with heart failure is optimised by the use of harmonic imaging and not enhanced with the use of transpulmonary contrast agents • Assessment of diastolic filling is optimised by the use of preload manipulation to correctly identify true diastolic filling patterns
3 - Predicting Future Hospitalisations and Mortality in HF Patients After Hospital Discharge
• Diastolic filling pattern can be used to stratify heart failure patients in terms of risk of death and/or hospitalisation • When preload manipulation is used, it is possible to identify patients with pseudonormal filling, whose event rate is intermediate between the highest risk group (restrictive filling) and lowest risk group (abnormal relaxation)
4 - The Prognostic Significance of Restrictive Diastolic Filling Associated with HF or MI: A Meta-Analysis.
• Restrictive filling pattern is associated with a four-fold increase in mortality in both HF and MI patients • There is a stepped relationship between the different diastolic filling patterns: patients with normal filling or abnormal relaxation have the best survival, pseudonormal intermediate, but closer to restrictive filling and non-reversible restrictive filling is more than ten times worse than reversible restrictive filling • Restrictive filling pattern also predicts development of HF post AMI and hospitalisation in patients with HF
5 - Complementary Role of Echocardiography and Brain Natriuretic Peptide for Diagnosis of HF and Determining Prognosis in Symptomatic Breathless Patients in the Community.
• The diagnosis of heart failure in the community may be optimised by using NT-proBNP as a first test to “rule-out” heart failure, and then echocardiography in patients with intermediate NT-proBNP levels to diagnose HF and in elevated NT-proBNP to assess aetiology and identify potentially remediable causes • Systolic measurements (EF, FS and Sa) are the main diagnostic variables in this cohort of elderly symptomatic community-base patients • Echocardiography, especially the assessment of diastolic function is useful for identifying patients at highest risk of subsequent hospitalisation • E/Ea appears to be one of the best discriminative variables for prognosis

Assessment of systolic function

Cardiac output and more specifically LV output (stroke volume and ejection fraction) has become the main goal of echocardiographic assessment in patients with HF. Reduced ejection fraction (EF) has become synonymous with HF and thus a pre-requisite for diagnosis. However, EF is notoriously difficult to reliably assess using echocardiography, and the findings of our research suggest that this is especially true in patients with HF, even in the setting of optimised, modern ultrasonic imaging. We have found that tissue harmonics imaging improves endocardial definition and hence measurement of systolic function in HF patients, whilst other new 2D echo methodologies (i.e. contrast opacification) may offer little improvement in terms of reproducibility of EF measurements.

Harmonics imaging improves endocardial visualisation because it increases the quality and number of segments visualised[28] and thus improves interpretation and measurement. Contrast echocardiography also improves endocardial visualisation and thus the accuracy and reproducibility of measurements in other patient groups[46,47] but not in HF patients in this research. This is primarily because the passage of contrast through the lungs is slower in HF patients and thus when the contrast finally arrives in the LV it is diluted in the large ventricular blood volume. The result is inferior chamber opacification.

In this research, harmonic imaging reduced the limits of agreement for intra-observer, inter-observer and test-retest variability to within +/- 10% but no further improvements were observed with contrast. Importantly, the coefficient of variation for 2D EF measurements was 5% in the control subjects, but twice that in the HF patients and reflects the variation inherent in the population and also the potential for improvement. Contrast offered no further improvement.

This is not to say that all contrast agents may not be efficacious in HF patients. Newer contrast agents, which have not yet been studied in HF patients, may perform better and be proven beneficial in this area. Further, if reliable myocardial contrast echocardiography becomes widely

available, it may be useful for identifying reversible perfusion abnormalities and thus offer both diagnostic and prognostic advantages over 2D echocardiography.

Assessment of diastolic function

The non-invasive assessment of diastolic filling and estimation of filling pressures is now routinely applied in clinical cardiology.[70] However, although it is easy to distinguish between the most advanced filling pattern (restrictive filling) from the normal or mildly abnormal (abnormal relaxation) filling patterns, the differentiation of the intermediate phases (pseudonormal and reversible restrictive filling) is difficult. This research has evaluated a simple technique (preload reduction) and found that it improves the detection of these intermediate filling phases. Importantly preload reduction is easy to apply in everyday settings, does not require sophisticated echocardiographic equipment and will be available on handheld ultrasound devices, where tissue Doppler imaging is currently unavailable.

Echocardiography is widely used by clinicians to evaluate patients with HF or HF symptoms to derive an objective measure of cardiac dysfunction in line with published HF diagnostic guidelines. A contemporary echocardiographic assessment should include LV volumes, a measure of systolic function (EF or WMSI) and a complete diastolic haemodynamic Doppler evaluation. The diastolic assessment should include mitral valve pulsed wave Doppler at rest and during preload reduction to assess mitral filling pattern and its reversibility and tissue Doppler imaging to assess left atrial pressure.

Each progressive diastolic grade reflects a higher level of filling pressure elevation and in turn a level of prognostic risk. The relationship between filling pressure and diastolic parameters has been established in patients with very impaired systolic function[16,88,93,95] and near normal function.[75,89,94] From this and other research, each diastolic filling grade is associated with worse prognosis in patients with varied underlying systolic function.[78,96,118-145,155-174] The accurate determination of diastolic filling grade should be the goal of echocardiography regardless of the associated systolic function.

Echocardiography predicts outcome in patients with heart failure

Patients admitted to hospital for exacerbation of symptoms have very poor long-term outlook and echocardiography can be used to estimate prognosis in this setting. As in other similar studies,[78,96,118-145] we have demonstrated striking differences between patients with non-restrictive filling and restrictive filling in terms of long-term prognosis. What has not previously been documented is the relationship between the intermediate pseudonormal filling pattern, determined by preload reduction, and outcome.

Once admitted to hospital, these patients often have severely depressed systolic function and because of the homogeneity associated with EF measurements in this group, EF may lose its discriminative effect. These patients often have dilated ventricles and lower EF, which are both associated with poor and long-term outlook, but within this group the addition of diastolic filling pattern was able to discriminate three groups of patients on the basis of filling pattern (abnormal relaxation, pseudonormal, restrictive filling) that experienced incrementally worse outcome (death and all hospitalisation). The different filling patterns observed may reflect incrementally higher left ventricular filling pressures and thus the observed differences in prognosis may be related to filling pressure. This is supported by other invasive studies demonstrating the relationship between diastolic echocardiographic measurements and filling pressures.[16,74-76,78,79,81,83,85,87-97]

Meta-analyses of diastolic filling and prognosis

Although many studies have shown a relationship between filling pattern and prognosis, these studies have included patients of varied backgrounds (aetiology, age, clinical status and history), had different follow-up times and thus found variable results. In order to further evaluate and obtain a representative overall measure of the size of the survival deficit associated with restrictive filling, we performed several meta-analyses. These analyses demonstrated, with remarkable consistency across 43 studies (26 HF patients and 17 acute MI patients), that the presence of a restrictive filling pattern was associated with an approximately four-fold risk of death. Further, within the restrictive filling group, a more than ten-fold risk of dying was observed in patients in whom the pattern was not reversible (not responsive to preload manipulation or pharmacotherapy). There was a stepped prognostic response for each of the diastolic filling patterns.

In addition to the mortality data, these analyses have also revealed a relationship between restrictive filling and HF readmissions in those patients with HF and development of HF in those patients post AMI. The restrictive filling was observed in over 40 % of the HF subjects included in these analyses and 20 % of the patients in the acute AMI studies. This represents a significant number of patients and events. Further, the event rates were moderately high in both groups of patients: average mortality: HF 23 %, AMI 15 %; HF admission (HF patients) 28 %, new onset HF (AMI) 15 %.

These meta-analyses are limited by the absence of data related to systolic function and other clinical variables. Such an analysis would require obtaining individual patient data, which would allow multivariate analysis of many risk factors not just echocardiographic variables. However, studies included in this meta-analyses recruited patients with varied levels of systolic dysfunction: some studies were restricted to patients with severely depressed systolic function, while others were not. Despite this, the results were homogeneous across all of the included studies and thus may apply in a wide variety of patients with varied degrees of systolic impairment. Importantly, only studies that included prospective follow-up were included, most studies recruited consecutive patients and the total number of events and patients was large.

The role of contemporary echocardiography for diagnosis of heart failure

Elderly people often present to their general practitioner with symptoms of breathlessness or oedema and because of frequent co-morbidity the diagnosis of HF can be difficult. Community-based physicians have limited access to echocardiography[105,108] and as a result must rely upon clinical findings to make their diagnosis. Brian natriuretic peptide is a very specific test for HF and in particular when negative (rules out HF) and a sensitive diagnostic test at very high levels (confirms HF diagnosis).[321] This research has demonstrated that echocardiography may not offer additional benefit in these two groups with regard to HF diagnosis, but is in fact superior to BNP when BNP levels fall into a “grey zone” or intermediate level. Of course, echocardiography may still be required in patients with very elevated BNP levels in order to determine aetiology and identify correctable pathological causes of HF. Thus, a two-tiered approach to HF diagnosis in the

community might involve measurement of BNP as a first step, with targeted echocardiography in those patients with elevated BNP levels. This would be very cost-effective, given that BNP assay is considerably less expensive that echocardiography, is more widely available and many of these patients (approximately 75%) have other causes for their symptoms.

This community–based study also allowed us to evaluate the prognostic capability of both NT-proBNP and echocardiography in these elderly, symptomatic patients. As in many HF studies, we found that diastolic echocardiographic parameters predicted future hospitalisations in all patients, even those without a final diagnosis of HF. This probably reflects elevated filling pressures in these symptomatic patients but without definitive HF. The development of HF and elevation of filling pressures is likely to be a continuum. Since the symptoms of HF in these elderly patients may have multiple causes, expert physician judgement is required to determine the likelihood of the whole clinical scenario being related to HF or not. Many of these subjects, who were determined to not have HF on this occasion, may develop HF in the future. The advanced diastolic filling pattern may simply reflect an individual's position along the elevated filling pressure/HF continuum.

The role of contemporary echocardiography in heart failure management

Echocardiography is the imaging modality of choice in patients with HF because of its moderate cost, ready availability and extraordinary diagnostic and prognostic power. Echocardiography may allow clinicians to determine which patents will fare worst, to identify those patients who may benefit the most from newer or more intensive treatments, or simply allow patients to better plan for their remaining years. Many of the contemporary medical therapies have been shown to be beneficial in clinical trials in patients with EF < 35- 40%, including ACE-inhibitors,[186-191] beta-blockers[192] and spironolactone.[193] Because many treatments have only been extensively proven in patients with low EF, echocardiography is often used to determine the indication for many HF therapies. Whilst the efficacy of many treatments in patients with higher EF remains uncertain, EF appears to have replaced HF as the treatment goal. Many clinicians have become focused on the need to quantify EF before initiating treatment. It is nonsensical to suggest that an EF of 43% does not warrant treatment, but a measurement of 38% does. Both indicate a significant degree of LV dysfunction, but given the poor precision of echocardiography to measure EF in individual patients such an approach does not recognise the limitations of these data.

This approach arises principally from the early ACE inhibitor mortality studies, in which significant risk reduction was demonstrated in patients with HF and LV impairment. Ten years on, the HOPE study has shown that ACE inhibitors are effective in reducing mortality in high risk patients with vascular disease, regardless of baseline EF[194] and also prevent the development of HF in these patients.[195] This low EF recruitment approach has been successfully reapplied with a number of agents, including beta-blockers[192] and spironolactone,[193] and cardiovascular devices.[198,199] As a clinical trial recruitment strategy, selecting homogeneous groups of subjects with the most benefit to be gained from the treatment is understandable. However this approach results in physician uncertainty about how to treat the remainder of their patients.

In HF, a significant proportion of patients may have a normal EF but still have significant symptomatic compromise. Since mortality is similar in HF patients with normal or depressed EF[109] and patients with normal EF and HF have worse prognosis that non-HF subjects in the community[196] these patients may benefit from treatment. Conversely, data for the Digitalis Investigation Group, suggest that while decreases in EF below 45 % are associated with increased mortality, increased EF (above 45%) is associated with similarly high mortality[115]. Further, the CHARM-Preserved trial showed a beneficial morbidity effect of Candesartan over placebo in patients with baseline EF > 40 %.[197] If other therapies are proven to be equally efficacious then the use of arbitrary EF cut-off values should lose favour. Since it is LA pressure that primarily causes symptoms, it might be reasonable to use surrogates of LV filling pressure as a goal for therapy considering the body of prognostic evidence is accumulating for these measures. BNP has been used successfully to guide therapy in HF[288] by using it as the target to which treatment is titrated. A similar approach using echocardiographic surrogates of filling pressure might be similarly useful.

Advances in imaging technology and techniques have changed the role of echocardiography from a purely diagnostic imaging tool evaluating systolic pump function to a powerful tool that non-invasively assesses the diastolic filling properties of the heart and evaluates left ventricular filling

pressures. In addition to identifying pathological and physiological components of HF, echocardiography may also help physicians to identify patients with the worst prognosis.

Future directions

Despite being a relatively old technique (50 years) echocardiography continue to evolve. Rapid advances in technology and research will lead to a wide range of exciting new techniques being widely available to many practitioners. The challenge will be to present the data in a meaningful way, not an incomprehensible collection of Greek symbols and numerals. Busy clinicians require information that is diagnostic, prognostic and easily incorporated into clinical management. All of the echocardiography information regarding LV size, diastolic and systolic function, left atrial size and function, valve disease, coronary artery disease and the pericardium needs to be considered in totality alongside the patient's clinical findings.

Echocardiography has always played a pivotal role in the medical management of patients with HF. Given the projected increases in numbers of patients with HF, this seems unlikely to change. Other techniques, such as magnetic resonance imaging, may assess LV volumes and EF more accurately than echocardiography and provide other informative data but at present the costs remain too high for widespread application and cannot be applied to patients with implantable devices. The challenges for the future include providing adequate echocardiography services for managing patients with HF in the community and reaching consensus on the definition on ventricular dysfunction. Many HF patients will be managed in the community by primary care physicians and thus as access to echocardiography increases, it is imperative that echocardiography provides proven and understandable measures of ventricular function.

Assessment of systolic function

The American Society of Echocardiography guidelines for quantification of the LV by echocardiography include assessment of LV volumes, EF, mass and wall motion score.[11] Currently, there is variability regarding the degree of volume/systolic function quantification which is reported by echo providers and the clinicians applying the results may have limited understanding of more advanced methods. Many echocardiography reports provide detailed information about

regional wall motion abnormalities but rarely calculate wall motion score index. Wall motion score index is closely correlated with EF[24-26] and linked to prognosis.[24] Nearly all echo reports provide fractional shortening measurements and a qualitative assessment of overall LV function (mild, moderate, severe impairment) but these are hard to interpret by non-echo doctors given that all the clinical and trial data are based upon EF.

Newer techniques such as tissue Doppler imaging and strain rate imaging will allow us to detect changes in systolic function at an earlier stage of disease. As our understanding of LV function and dysfunction grows, hopefully we will overcome our very natural desire to classify people as diastolic or systolic heart failure on the basis of a single measurement.

Three-dimensional echocardiography

Three dimensional (3D) echocardiography makes fewer geometric assumptions about the LV shape and therefore may offer significant benefits over current 2D methods. In particular, the recent introduction of real-time 3D echo offers considerable promise as a rapid way to asses LV volumes and EF with better accuracy and reproducibility.[331] However, 3D echocardiography is currently only available in large tertiary hospitals and since many HF patients will be evaluated in smaller centres, 2D echocardiography will remain the mode of assessment for some time.

Assessment of diastolic function

Many echocardiographers now routinely assess diastolic filling grade, but in a sporadic way. Many accept the importance of filling pattern, but do not utilise preload manipulation to determine reversibility of patterns and there remains confusion about the significance of diastolic filling abnormalities in the setting of systolic impairment. Although tissue Doppler measurements are important diagnostic and prognostic indicators in HF their implementation may be slow. This also may be related to inadequate understanding of the clinical indication in various situations and the methods and normal values used. This is likely to be hampered even further by the widespread introduction of lower quality, cheaper echocardiography machines that do not have tissue Doppler technology. These machines will end up being used in general practice and by people who may be less than optimally skilled at performance and interpretation.

Handheld Echo

Handheld or portable echocardiography will change the way HF patients are managed both in the community and at the bedside in hospital. Handheld echocardiography is one of the most exciting recent ultrasound developments. These machines are small and inexpensive, allowing echocardiography to be applied in many situations and many people where it was previously not possible. However, both the imaging technology and storage capacity available on these machines is currently limited and as a result echocardiography examination will be abbreviated. As a result, some meaningful information will not be collected and despite all evidence to the contrary, physicians will assess LV function at repeated intervals for their own and their patients' reassurance. The challenge will be to ensure that all ultrasound practitioners are suitably experienced so that the information collected is meaningful.

Natriuretic hormones

The overlap of echocardiography and neurohormonal assessment will increase over the coming years. It is likely a two-tiered approach to HF diagnosis will evolve, where patients have a BNP assay performed prior to echocardiography. Those with clearly negative BNP levels will have HF ruled out as the diagnosis, those with elevated BNP will fall into two categories, both requiring echocardiography. Those patients with clearly elevated levels will require echocardiography to determine aetiology, whereas those with uncertain BNP levels will require an echocardiogram to diagnose or rule out HF. The precise role of BNP and echocardiography for prognosis and guiding treatment is unknown. It is possible that in multivariate analysis many of the echo parameters that predict adverse events will become less important when BNP is known. Monitoring of BNP may be beneficial for individual optimisation of pharmacotherapy in small number of HF patients but a similar role for echo has not clearly been established to date.

Left atrial volume

Left atrial volume is emerging as an important parameter in many different clinical situations, including patients with HF. The most likely discriminative effects will be in diastolic HF and

advanced systolic HF, where the range of EF is so small to be non-discriminative between individual patients.

Repeat Echocardiography

Current guidelines do not include repeat assessment of diastolic function in response to treatment. This reflects the limited availability of data regarding the efficacy of therapies for treatment of patients with preserved systolic function, so the effectiveness of treatment in these patients remains uncertain. However, any perceived or proven benefits would have to be weighed carefully against the cost of such assessments.

Summary

Echocardiography was established many decades ago and has become one of the most important and most commonly used diagnostic tools in cardiology. More recently, the move has been away from the identification of anatomy, pathology and function to providing surrogates of intra-cardiac pressure and to assess prognosis. All of which assists physician management of their patients. This thesis has explored ways to optimise contemporary echocardiographic methods in patients with HF and demonstrated that implementation of these methods may be beneficial for management of such patients. In summary, systolic function is best appreciated with the use of tissue harmonic imaging and diastolic assessment requires preload manipulation. Implementation of these contemporary and widely available methods in patients with HF will lead to enhanced diagnosis and prognosis. Although not conclusive, the results of these meta-analyses would suggest that it is important to assess diastolic filling regardless of underlying systolic function. Further, the meta-analysis in AMI patients, suggests that assessment of diastolic filling near to the acute coronary event is also prognostically useful, not only for predicting those patients who may not survive, but also for identifying those patients most likely to develop HF. Thus, a complete echocardiographic assessment in patients with HF or post AMI should include a quantitative assessment of systolic function using tissue harmonics imaging and diastolic filling assessment with preload manipulation and pulsed wave tissue Doppler assessment.

References

1. Cowie MR, Wood DA, Coats AJS, Thompson SG, Poole-Wilson PA, Suresh V, Sutton GC. Incidence and aetiology of heart failure; a population-based study. Eur Heart J 1999;20:421-28.
2. MacIntyre K, Capewell S, Stewart S, Chalmers JWT. Evidence of improving prognosis in heart failure: trends in case fatality in 66547 patients hospitalised between 1986 and 1995. Circulation 2000;102:1126-31.
3. Ho KKL, Anderson KM, Kannel WB, Grossman W, Levy D. Survival after the onset of congestive heart failure in Framingham Heart Study Subjects. Circulation 1993;88:107-15.
4. Doughty R, Yee T, Sharpe N, MacMahon S. Hospital admissions and deaths due to congestive heart failure in New Zealand, 1988-91. NZ Med J 1995;108:473-75.
5. Koelling TM, Chen RS, Lubwama RN, L'Italien GJ, Eagle KA. The expanding national burden of heart failure and the United States: The influence of heart failure and women. Am Heart J 2004;147:74-8.
6. Braunwald E. Heart Disease. A textbook of cardiovascular medicine. Third ed. WB Saunders, New York, 1988.
7. Cheesman M, Leech G, Chambers J, Monaghan M, Nihoyannopoulos P. Central role of echocardiography in the diagnosis and assessment of heart failure. Heart 1998;80:S1-S5.
8. Hunt SA, Baker DW, Chin MH, Cinquegrani MP, Feldman AM, Francis GS, Ganiats TG, Goldstein S, Gregoratos G, Jessup ML. ACC/AHA guidelines for the evaluation and management of chronic heart failure in the adult: executive summary: A report of the American College of Cardiology/American Heart Association task force on practice guidelines (committee to revise the 1995 guidelines for the evaluation and management of heart failure) developed in collaboration with the International Society for Heart and Lung Transplantation endorsed by the Heart Failure Society of America. J Am Coll Cardiol 2001;38:2101-13.
9. Remme WJ, Swedberg K. Comprehensive guidelines for the diagnosis and treatment of chronic heart failure: Task force for the diagnosis and treatment of chronic heart failure of the European Society of Cardiology. Eur J Heart Failure 2002;4:11-22.
10. Colquhoun MC, Waine C, Monaghan MJ, Struthers AD, Mills PG. Investigation in general practice of patients with suspected heart failure. Br Heart J 1995;74:335-36.
11. Schiller NB, Shah PM, Crawford M, DeMaria A, Devereux R, Feigenbaum H, Gutgesell H, Reichek N, Sahn D, Schittgner I, Silverman NH, Tajik AJ. American Society of Echocardiography Committee on Standards on Quantitation of Two-Dimensional Echocardiograms. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. J am Soc Echocardiogr 1989;2:358-67.
12. Devereux RB, Lutas EM, Casale PN, Kligfield P, Eisenberg RR, Hammond IW, Miller DH, Reis G, Alderman MH, Laragh JH. Standardization of M-mode echocardiographic left ventricular anatomic measurements. J Am Coll Cardiol 1984;4:1222-30.

13. Ohno M, Cheng C-P, Little W. Mechanism of altered patterns of left ventricular filling during the development of congestive heart failure. Circulation 1994;89:2241-50.
14. Lester SJ, Ryan EW, Schiller NB, Foster E. Best method in clinical practice and in research studies to determine left atrial size. Am J Cardiol 1999;84:829-32.
15. Gutman J, Wang Y, Wahr D, Schiller NB. Normal left atrial function determined by 2-dimensional echocardiography. Am J Cardiol 1983;51:336-40.
16. Appleton CP, Galloway JM, Gonzales MS, Gaball M, Basnight MA. Estimation of left ventricular filling pressures using two-dimensional and Doppler echocardiography in adult patients with cardiac disease. J Am Coll Cardiol 1993;22:1972-82.
17. Tsang TSM, Barnes ME, Gersh BJ, Bailey KR, Seward JB. Left atrial volume as a morphophysiologic expression of left ventricular diastolic dysfunction and relation to cardiovascular risk burden. Am J Cardiol 2002;90:1284-89.
18. Stefanadis C, Dernellis J, Toutouzas P. A clinical appraisal of left atrial function. Eur Heart J 2001;22:22-36.
19. Marwick TH. Techniques for comprehensive two dimensional echocardiographic assessment of left ventricular systolic function. Heart 2003;89:iii2-8.
20. Amico A, Lichtenberg G, Reisner S, CK S, Schwartz R, Meltzer R. Superiority of visual versus computerized echocardiographic estimation of radionuclide left ventricular ejection fraction. Am Heart J 1989;118:1259-65.
21. Silcocks P, Munro J, Steeds R, Channer K. Prognostic implications of qualitative assessment of left ventricular function compared to simple routine quantitative echocardiography. Heart 1997;78:237-42.
22. Bansal S, Vacek J, Ehler D. Consistency of echocardiographic ejection fraction: Variation and 'drift' by interpreter and practice site. Eur J Echocardiography 2002;3:44-6.
23. Cerqueira M, Weissman NJ, Dilsizian V, Jacobs A, Kaul S, Laskey W, Pennell DJ, Rumberger J, Ryan T, Vanni M. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart. A statement for healthcare professionals from the cardiac imaging committee on the council on clinical cardiology of the American Heart Association. Circulation 2002;105:539-42.
24. Galasko GI, Basu S, Lahiri A, Senior R. A prospective comparison of echocardiographic wall motion score index and radionuclide ejection fraction in predicting outcome following acute myocardial infarction. Heart 2001;86:271-6.
25. McGowan JH, Martin W, Burgess MI, McCurrach G, Ray SG, McDonagh TA, Cleland JG. Validation of an echocardiographic wall motion index in heart failure due to ischaemic heart disease. Eur J Heart Failure 2001;3:731-7.
26. Doughty RN, Whalley GA, Gamble GD, MacMahon S, Sharpe N. Effect of Carvedilol on left ventricualr regional wall motion in patients with heart failure caused by ischemic heart disease. J Cardiac Failure 2000;6:11-18.
27. McGowan J, Cleland J. The reliability of reporting left ventricular systolic function by echocardiography: A systematic review of three methods. Am Heart J 2003;146:388-97.

28. Caidahl K, Kazzam E, Lidberg J, Neumann Andersen G, Nordanstig J, Rantapaa Dahlqvist S, Waldenstrom A, Wikh R. New concept in echocardiography: harmonic imaging of tissue without use of contrast agent. Lancet 1998;352:1264-70.
29. Kornbluth M, Liang DH, Paloma A, Schnittger I. Native tissue harmonic imaging improves endocardial border definition and visualisation of cardiac structures. J Am Soc Echocardiogr 1998;11:693-701.
30. Mulvagh SL, Foley DA, Belohlavek M, Seward JB. Image enhancement by noncontrast harmonic echocardiography. Part 1. Qualitative assessment of endocardial visualization. Mayo Clin Proc 1998;73:1062-65.
31. Spencer K, Bednarz J, Rafter P, Korcarz C, Lang R. Use of harmonic imaging without echocardiographic contrast to improve two-dimensional image quality. Am J Cardiol 1998;82:794-99.
32. Skolnick DG, Sawada SG, Feigenbaum H, Segar DS. Enhanced endocardial visualisation with noncontrast harmonic imaging during stress echocardiography. J Am Soc Echocardiogr 1999;12:559-63.
33. Senior R, Soman P, Khattar RS, Lahiri A. Improved endocardial visualisation with second harmonic imaging compared with fundamental two-dimensional echocardiographic imaging. Am Heart J 1999;138:163-68.
34. Rubin DN, Yazbek N, Garcia MJ, Stewart WJ, Thomas JD. Qualitative and quantitative effects of harmonic echocardiographic imaging on endocardial edge definition and side-lobe artifacts. J Am Soc Echocardiogr 2000;13:1012-8.
35. Franke A, Hoffmann R, Kuhl HP, Lepper W, Breithardt OA, Schorman M, Hanrath P. Non-contrast second harmonic imaging improves interobserver agreement and accuracy of dobutamine stress echocardiography in patients with impaired image quality. Heart 2000;83:133-40.
36. Yu EH, Sloggett CE, Iwanochko RM, Rakowski H, Siu SC. Feasibility and accuracy of left ventricular volumes and ejection fraction determination by fundamental, tissue harmonic, and intravenous contrast imaging in difficult-to-image patients. J Am Soc Echocardiogr 2000;13:216-24.
37. Crouse LJ, Cherif J, Hanly DE, Kisslo JA, Labovitz AJ, Raichlen JS, Schutz RW, Shah PM, Smith MD. Opacification and border delineation improvement in patients with suboptimal endocardial border definition in routine echocardiography: Results of the phase III Albunex multicenter trial. J Am Coll Cardiol 1993;22:1494-500.
38. Schröder K, Agrawal R, Völler H, Schlief R, Schröder R. Improvement of endocardial border delineation in suboptimal stress-echocardiograms using the new left heart contrast agent SH U 508 A. Int J Cardiac Imaging 1994;10:45-51.
39. Hundley WG, Kizilbash AM, Afridi I, Franco F, Peshock RM, Grayburn PA. Effect of contrast enhancement on transthoracic echocardiographic assessment of left ventricular regional wall motion. Am J Cardiol 1999;84:1365-8, A8-9.
40. Weissman NJ, Cohen MC, Hack TC, Gillam LD, Cohen JL, Kitzman DW. Infusion versus bolus contrast echocardiography: A multicenter, open-label, crossover trial. Am Heart J 2000;139:399-404.

41. Feinstein SB, Cheirif J, Ten Cate FJ, Silverman PR, Heidenreich PA, Dick C, Desir RM, Armstrong WF, Quinones MA, Shah PM. Safety and efficacy of a new transpulmonary ultrasound contrast agent: initial multicenter clinical results. J Am Coll Cardiol 1990;16:316-24.
42. Cohen JL, Cheirif J, Segar DS, Gillam LD, Gottdiener JS, Hausnerova E, Bruns DE. Improved left ventricular endocardial border delineation and opacification with OPTISON (FS069), a new echocardiographic contrast agent. Results of a phase III Multicenter Trial. J Am Coll Cardiol 1998;32:746-52.
43. Grayburn PA, Weiss JL, Hack TC, Klodas E, Raichlen JS, Vannan MA, Klein AL, Kitzman DW, Chrysant SG, Cohen JL, Abrahamson D, Foster E, Perez JE, Aurigemma GP, Panza JA, Picard MH, Byrd BF, 3rd, Segar DS, Jacobson SA, Sahn DJ, DeMaria AN. Phase III multicenter trial comparing the efficacy of 2% dodecafluoropentane emulsion (EchoGen) and sonicated 5% human albumin (Albunex) as ultrasound contrast agents in patients with suboptimal echocardiograms. J Am Coll Cardiol 1998;32:230-6.
44. Kitzman D, Goldman D, Hack T, Gillam L, Fenster P, Segar D. Efficacy of DMP-115 contrast for left ventricular evaluation in patients with suboptimal baseline images: a multicentre, double blind, randomized, placebo controlled trial. J Am Soc Echocardiogr 1998;11:555.
45. Finkelhor R, Pajouh M, Kett A, Stefanski R, Bosich G, Youssefi M, Bahler R. Clinical impact of second harmonic imaging and left heart contrast in echocardiographic stress testing. Am J Cardiol 2000;85:740-43.
46. Hundley WG, Kizilbash AM, Afridi I, Franco F, Peshock RM, Grayburn PA. Administration of an intravenous perfluorocarbon contrast agent improves echocardiographic determination of left ventricular volumes and ejection fraction: comparison with cine magnetic resonance imaging. J Am Coll Cardiol 1998;32:1426-32.
47. Thomson HL, Basmadjian AJ, Rainbird AJ, Razavi M, Avierinos JF, Pellikka PA, Bailey KR, Breen JF, Enriquez-Sarano M. Contrast echocardiography improves the accuracy and reproducibility of left ventricular remodeling measurements: a prospective, randomly assigned, blinded study. J Am Coll Cardiol 2001;38:867-75.
48. Gandhok NK, Block R, Ostoic T, Rawal M, Ickle P, Devries S, Feinstien SB. Reduced forward output states affect the left ventricular opacification of intravenously administered Albunex. J Am Soc Echocardiogr 1997;10:25-30.
49. Feigenbaum H, Zaky A, Nasser W. Use of echocardiography to measure left ventricular stroke volume. Circulation 1967;38:1092-2099.
50. Pai RG, Bodenheimer MM, Pai SM, Koss JH, Adamick RD. Usefulness of systolic excursion of the mitral annulus as an index of left ventricular systolic function. Am J Cardiol 1991;67:222-24.
51. Willenheimer R, Israelsson B, Cline C, Rydberg E, Broms K, Erhardt L. Left atrioventricular plane displacement is related to both systolic and diastolic left ventricular performance in patients with chronic heart failure. Eur Heart J 1999;20:612-18.

52. Bruch C, Gradaus R, Gunia S, Breithardt G, Wichter T. Doppler tissue analysis of mitral annular velocities: Evidence for systolic abnormalities in patients with diastolic heart failure. J Am Soc Echocardiogr 2003;16:1031-6.
53. Lang RM, Vignon P, Weinert L, Bednarz J, Korcarz C, Sandelski RDMS J, Koch R, Prater D, Mor-Avi V. Echocardiographic quantification of regional left ventricular wall motion with color kinesis. Circulation 1996;93:1877-85.
54. Chan J, Wahi S, Marwick TH. Anatomical M-mode: a novel technique for the quantitative evaluation of regional wall motion analysis during stress echocardiography. In J Card Imaging 2002;16:247-55.
55. Gorscan J. Tissue Doppler echocardiography. Curr Opin Cardiol 2000;15:323-9.
56. Bargiggia G, C B, Recusani F, Raisaro A, de Servi S, Valdez-Cruz L, Sahn D, Tronconi L. A new method for estimating left ventricular dP/dT by continuous wave Doppler-echocardiography. Validation studies at cardiac catheterization. Circulation 1989;80:1287-92.
57. Chen C, Rodriguez L, Levine R, Weyman A, Thomas J. Noninvasive measurement of the time constant of left ventricular relaxation using the continuous-wave Doppler velocity profile of mitral regurgitation. Circulation 1992;86:271-8.
58. Armstrong W, Pellikka PA, Ryan T, Crouse L, Zoghbi WA. Stress echocardiography: Recommendations for performance and interpretation of stress echocardiography. J Am Soc Echocardiogr 1998;11:97-104.
59. Sawada S, Bapat a, Vaz D, Weksler J, Fineberg N, Greene A, Gradus-Pizlo I, Feigenbaum H. Incremental value of myocardial viability for prediction of long-term prognosis in surgically revascularised patients with left ventricular dysfunction. J Am Coll Cardiol 2003;42:2009-15.
60. Liao L, Cabell CH, Jollis JG, Velazquez EJ, Smith WT, Anstrom KJ, Pappas PA, Ryan T, Kisslo JA, Landolfo CK. Usefulness of myocardial viability or ischemia in predicting long-term survival of patients with severe left ventricular dysfunction undergoing revascularisation. Am J Cardiol 2004;93:1275-79.
61. Franchini M, Traversi E, Cannizzaro G, Cobelli F, Pozzoli M. Dobutamine Stress Echocardiography and Thallium-201 SPECT for Detecting Ischaemic Dilated Cardiomyopathy in Patients with Heart Failure. Eur J Echocardiogr 2000;1:109-15.
62. Ramahi TM, Longo MD, Cadariu AR, Rohlfs K, Slade M, Carolan S, Vallejo E, Wackers FJ. Dobutamine-induced augmentation of left ventricular ejection fraction predicts survival of heart failure patients with severe non-ischaemic cardiomyopathy. Eur Heart J. 2001;22:849-56.
63. Pratali L, Picano E, Otasevic P, Vigna C, Palinkas A, Cortigiani L, Dodi C, Bojic D, Varga A, Csanady M, Landi P. Prognostic significance of the dobutamine echocardiography test in idiopathic dilated cardiomyopathy. Am J Cardiol 2001;88:1374-78.
64. Scrutinio D, Napoli V, Passantino A, Ricci A, Lagioia R, Rizzon P. Low-dose dobutamine responsiveness in idiopathic dilated cardiomyopathy: relation to exercise capacity and clinical outcome. Eur Heart J 2000;21:927-34.

65. Naqvi TZ, Goel RK, Forrester JS, Siegel RJ. Myocardial contractile reserve on dobutamine echocardiography predicts late spontaneous improvement in cardiac function in patients with recent onset idiopathic dilated cardiomyopathy. J Am Coll Cardiol 1999;34:1537-44.
66. Pinamonti B, Perkan A, Di Lenarda A, Gregori D, Sinagra G. Dobutamine echocardiography in idiopathic dilated cardiomyopathy: clinical and prognostic implications. Eur J Heart Failure 2002;4:49-61.
67. Ommen SR, Nishimura RA. A clinical approach to the assessment of left ventricular diastolic function by Doppler echocardiography: update 2003. Heart 2003;89:iii18-23.
68. Nishimura R, Housmans PR, Hatle LK, Tajik AJ. Assessment of diastolic function of the heart: background and current applications of Doppler echocardiography, part1: physiologic and pathophysiologic features. Mayo Clinic Proc 1989;64:71-81.
69. Cohen GI, Pietrolungo JF, Thomas JD, Klein AL. A practical guide to assessment of ventricular diastolic function using Doppler echocardiography. J Am Coll Cardiol 1996;27:1753-60.
70. Nishimura RA, Tajik AJ. Evaluation of diastolic filling of left ventricle in health and disease: Doppler echocardiography is the clinician's Rosetta Stone. J Am Coll Cardiol 1997;30:8-18.
71. Oh JK, Appleton CP, Hatle LK, Nishimura RA, Seward JB, Tajik AJ. The noninvasive assessment of left ventricular diastolic function with two-dimensional and Doppler echocardiography. J Am Soc Echocardiogr 1997;10:246-70.
72. Nishimura RA, Abel MD, Hatle LK, Tajik AJ. Relation of pulmonary vein to mitral flow velocities by transesophageal Doppler echocardiography: effect of different loading conditions. Circulation 1990;81:1488-97.
73. Kuecherer HF, Kusumoto F, Muhiudeen IA, Cahalan MK, Schiller NB. Pulmonary venous flow patterns by transesophageal pulsed Doppler echocardiography: relation to parameters of left ventricular systolic and diastolic function. Am Heart J 1991;122:1683-93.
74. Yamamoto K, Nishimura RA, Chalki HP, Appleton CP, Holmes DR, Redfield MM. Determination of left ventricular filling pressure by Doppler echocardiography in patients with coronary artery disease: Critical role of left ventricular systolic function. J Am Coll Cardiol 1997;30:1819-26.
75. Poerner TC, Goebel B, Unglaub P, Süselbeck T, Kaden J, Borggrefe M, Haase KK. Non-invasive evaluation of left ventricular filling pressures in patients with abnormal relaxation. Clinical Science 2004;106:485-94.
76. Choong CY, Abascal VM, Thomas JD, Guerrero JL. Preload dependence of Doppler-derived indexes of left ventricular diastolic function in humans. J Am Coll Cardiol 1987;10:800-8.
77. Dumesnil JG, Gaudreault G, Honos GN, Kingma JG, Jr. Use of Valsalva maneuver to unmask left ventricular diastolic function abnormalities by Doppler echocardiography in patients with coronary artery disease or systemic hypertension. Am J Cardiol 1991;68:515-9.
78. Pozzoli M, Traversi E, Cioffi G, Stenner R, Sanarico M, Tavazzi L. Loading manipulations improve the prognostic value of Doppler evaluation of mitral flow in patients with chronic heart failure. Circulation 1997;95:1222-30.

79. Brunner-LaRocca HP, Rickli H, Jost CHA, Jenni R. Left ventricular end-diastolic pressure can be estimated by either changes in transmitral inflow pattern during Valsalva maneuver or analysis of pulmonary venous flow. J Am Soc Echocardiogr 2000;13:599-607.
80. Schwammenthal E, Popescu BA, Popescu AC, Di Segni E, Guetta V, Rath S, Eldar M, Feinberg MS. Association of left ventricular filling parameters assessed by pulsed wave Doppler and colour M-mode Doppler echocardiography with left ventricular pathology, pulmonary congestion, and left ventricular end-diastolic pressure. Am J Cardiol 2004;94:488-91.
81. Firstenberg M, Levine B, Garcia MJ, Greenberg N, Cardon LA, Morehead AJ, Zuckerman J, Thomas JD. Relationship of echocardiographic indices to pulmonary capillary wedge pressures in healthy volunteers. J Am Coll Cardiol 2000;36:1664-9.
82. Moller JE, Sondergaard E, Poulsen SH, Seward JB, Appleton CP, Egstrup K. Color M-mode and pulsed wave tissue Doppler echocardiography: powerful predictors of cardiac events after first myocardial infarction. J Am Soc Echocardiogr 2001;14:757-63.
83. Nagueh S, Middleton K, Koplen H. Doppler tissue imaging: a non-invasive technique for evaluation of left ventricular relaxation and estimation of left ventricular filling pressures. J Am Coll Cardiol 1997;30:1527-33.
84. Ommen SR, Nishimura RA, Appleton CP, Miller FA, Oh JK, Redfield MM, Tajik AJ. Clinical utility of Doppler echocardiography and tissue Doppler imaging in the estimation of left ventricular filling pressures. A comparative simultaneous Doppler-catheterisation study. Circulation 2000;102:1788-94.
85. Nagueh SF, Mikati I, Kopelen HA, Middleton KJ, Quinones MA, Zoghbi WA. Doppler estimation of left ventricular filling pressure in sinus tachycardia. A new application of tissue Doppler imaging. Circulation. 1998;98:1644-50.
86. Appleton CP, Jensen JL, Hatle LK, Oh JK. Doppler evaluation of left and right ventricular diastolic function: A technical guide for obtaining flow velocity recordings. J Am Soc Echocardiogr 1997;10:271-91.
87. Hofmann T, Keck A, van Ingen G, Simic O, Ostermeyer J, Meinertz T. Simultaneous measurement of pulmonary venous flow by intravenous catheter Doppler velocimetry and transesophageal Doppler echocardiography: Relation to left atrial pressure and left atrial and left ventricular function. J Am Coll Cardiol 1995;26:239-49.
88. Nishimura RA, Appleton CP, Redfield MM, Ilstrup DM, Holmes DR, Jr., Tajik AJ. Noninvasive Doppler echocardiographic evaluation of left ventricular filling pressures in patients with cardiomyopathies: a simultaneous Doppler echocardiographic and cardiac catheterization study. J Am Coll Cardiol 1996;28:1226-33.
89. Kuecherer H, Muhiudeen I, Kusumoto F, Lee E, Moulinier L, Cahalan M, Schiller NB. Estimation of mean left atrial pressure from transesophageal pulsed wave Doppler echocardiography of pulmonary venous flow. Circulation 1990;82:1127-39.
90. Pozzoli M, Capomolla S, Pinna G, Cobelli F, Tavazzi L. Doppler echocardiography reliably predicts pulmonary artery wedge pressure in patients with chronic heart failure with and without mitral regurgitation. J Am Coll Cardiol 1996;27:883-93.

91. Nagueh SF, Kopelen H, Quinones M. Assessment of left ventricular filling pressures by Doppler in the presence of atrial fibrillation. Circulation 1996;94:2138-45.
92. Chirrillo F, Brunazzi M, Barbiero M, Giavarina D, Pasqualini M, Franceschini-Grisola E, Cotogoni A, Cavarzerani A, Rigatelli G, Stritoni P, Longhini C. Estimating mean pulmonary wedge pressure in patients with chronic atrial fibrillation from transthoracic Doppler indices of mitral and pulmonary venous flow velocity. J Am Coll Cardiol 1997;30:19-26.
93. Temporelli P, Scapellato F, Corrà U, Eleuteri E, Imparato A, Giannuzzi P. Estimation of pulmonary wedge pressure by transmitral Doppler in patients with chronic heart failure and atrial fibrillation. Am J Cardiol 1999;83:724-7.
94. Garcia M, Smedira N, Greenberg N, Main ML, Firstenberg M, Odabashian J, Thomas J. Color M-mode Doppler flow propagation velocity is a preload insensitive index of left ventricular relaxation: animals and human validation. J Am Coll Cardiol 2000;35:201-8.
95. Traversi E, Cobelli F, Pozzoli M. Doppler echocardiography reliably predicts pulmonary artery wedge pressure in patients with chronic heart failure even when atrial fibrillation is present. Eur J Heart Failure 2001;3:173-81.
96. Yamamoto T, Oki T, Yamada H, Tanaka H, Ishimoto T, Wakatsuki T, Tabata T, Ito S. Prognostic value of the atrial systolic mitral annular motion velocity in patients with left ventricular systolic dysfunction. J Am Soc Echocardiogr 2003;16:333-9.
97. Dokainish H, Zoghbi WA, Lakkis N, Al-Bakshy F, M D, MA Q, Nagueh SF. Optimal noninvasive assessment of left ventricular filling pressures. A comparison of tissue Doppler echocardiography and B-type natriuretic peptide in patients with pulmonary artery catheters,. Circulation 2004;109:2432-9.
98. Little W, Ohno M, Kitzman D, Thomas J, Cheng C. Determination of left ventricular chamber stiffness from the time for deceleration of early left ventricular filling. Circulation 1995;92:1933-9.
99. Margulies KB, Jaffer S, Pollack PS, Ennis KJ. Physiological significance of early deleceration time prolongation in asymptomatic elderly subjects. J Cardiac Fail 1999;5:92-99.
100. Rossvoll O, Hatle LK. Pulmonary venous flow velocities recorded by transthoracic Doppler ultrasound: relation to left ventricular diastolic pressures. J Am Coll Cardiol 1993;21:1687-96.
101. Gheorghiade M, Bonow RO. Chronic heart failure in the United States: A manifestation of coronary artery disease. Circulation 1998;97:282-89.
102. Masoudi FA, Havranek EP, Smith G, Fish RH, Steiner JF, Ordin DL, Krumholz HM. Gender, age, and heart failure with preserved left ventricular systolic function. J Am Coll Cardiol 2003;41:217-23.
103. Remme WJ, Swedberg K. Guidelines for the diagnosis and treatment of chronic heart failure. Eur Heart J 2001;22:1527-60.
104. The European Study Group on Diastolic Heart Failure. How to diagnose diastolic heart failure. Eur Heart J 1998;19:990-1003.

105. Khunti K, Hearnshaw H, Baker R, Grimshaw G. Heart failure in primary care: qualitative study of current management and perceived obstacles to evidence-based diagnosis and management by general practitioners. Eur J Heart Failure 2002;4:771-77.
106. Rutten FH, Grob.bee DE, Hoes AW. Diagnosis and management of heart failure:a questionnaire general practitioners and cardiologists. Eur J Heart Failure 2003;5:345-48.
107. Senni M, Rodeheffer RJ, Tribouilloy CM, Evans JM, Jacobsen SJ, Bailey KR, Redfield MM. Use of echocardiography in the management of congestive heart failure in the community. J Am Coll Cardiol 1999;33:164-70.
108. Khunti K. Systematic review of open access echocardiography for primary care. Eur J Heart Failure 2004;6:79-83.
109. Varadarajan P, Pai R. Prognosis of congestive heart failure in patients with normal versus reduced ejection fractions: Results from a cohort of 2,258 hospitalised patients. J Cardiac Failure 2003;9:107-12.
110. Stewart S, MacIntyre K, Hole DJ, Capewell S, McMurray JJV. More 'malignant' than cancer? Five-year survival following a first admission for heart failure. Euro J Heart Failure 2001;3:315-22.
111. Gradman A, Deedwania P, Cody R, Massie B, Packer M, Pitt B, Goldstein S. Predictors of total mortality and sudden death in mild to moderate heart failure. Captopril-Digoxin Study Group. J Am College Cardiol 1989;14:564-70.
112. Cohn JN, Rector TS. Prognosis of congestive heart failure and predictors of mortality. Am J Cardiol 1988;62:25A-30A.
113. van den Broek SA, van Veldheisen DJ, de Graeff PA, Landsman ML, Hillege H, Lie KI. Comparison between New York Heart Association classification in the assessment of functional status and prognosis in patients with mild to moderate chronic congestive heart failure secondary to either ischaemic or idiopathic cardiomyopathy. Am J Cardiol 1992;70:359-63.
114. White H, Norris R, Brown M, Brandt P, Whitlock R, Wild C. Left ventricular end-systolic volume as the major determinant of survival after recovery from myocardial infarction. Circulation 1987;76:44-51.
115. Curtis J, Sokol S, Wang Y, Rathore S, Ko D, Jadbabaie F, Portney E, Marshalko S, Radford M, Krumholz H. The association of left ventricular ejection fraction, mortality, and cause of death in stable outpatients with heart failure. J Am Coll Cardiol 2003;42:736-42.
116. Wong M, Staszewsky L, Latini R, Barlera S, Glazer R, Aknay N, Hester A, Anand I, Cohn JN. Severity of left ventricular remodeling defines outcomes and response to therapy in heart failure. Valsartan Heart Failure Trial (Val-HeFT) Echocardiographic Data. J Am Coll Cardiol 2004;43:2022-7.
117. Dries DL, Exner DV, Domanski MJ, Greenberg B, Stevenson LW. The prognostic implications of moderate renal insufficiency in asymptomatic patients with left ventricular systolic dysfunction. J Am Coll Cardiol 2000;35:681-9.

118. Shen W, Tribouilloy CM, Rey J, Baudhuin J, Boey S, Dugfosse H, Lesbre J. Prognostic significance of Doppler-derived left ventricular diastolic filling variables in dilated cardiomyopathy. Am Heart J 1992;124:1524-33.
119. Ortiz J, Matsumoto AY, Gheffer CGM, Silva CES, Durazzo AE, Baretto ACP, Nanda NC. Prognosis in dilated myocardial disease: influence of diastolic dysfunction and anatomical changes. Echocardiography. 1993;10:247-54.
120. Pinamonti B, Di Lenarda A, Sinagra G, Camerini F. Restrictive left ventricular filling pattern in dilated cardiomyopathy assessed by Doppler echocardiography: Clinical, echocardiographic and hemodynamic correlations and prognostic implications. J Am Coll Cardiol 1993;22:808-15.
121. Xie GY, Berk MR, Smith MD, Gurley JC, DeMaria AN. Prognostic value of Doppler transmitral flow patterns in patients with congestive heart failure. J Am Coll Cardiol 1994;24:132-39.
122. Werner GS, Schaefer C, Dirks R, Figulla HR, Kreuzer H. Prognostic value of Doppler echocardiographic assessment of left ventricular filling in idiopathic dilated cardiomyopathy. Am J Cardiol 1994;73:792-8.
123. Rihal CS, Nishimura RA, Hatle LK, Bailey KR, A.J. T. Congestive heart failure/LV hypertrophy: Systolic and diastolic dysfunction in patients with clinical diagnosis of dilated cardiomyopathy: Relation to symptoms and prognosis. Circulation 1994;90:2772-9.
124. Belardinelli R, Georgiou D, Cianci G, Berman N, Ginzton L, Purcaro A. Exercise training improves left ventricular diastolic filling in patients with dilated cardiomyopathy. Circulation 1995;91:2775-84.
125. Giannuzzi P, Temporelli PL, Bosmini E, Silva P, Imparato A, Corra U, Galli M, Giordano A. Independent and incremental prognostic value of Doppler-derived mitral deceleration time of early filling in both symptomatic and asymptomatic patients with left ventricular dysfunction. J Am Coll Cardiol 1996;28:383-90.
126. Piszczek I, Cieslinski A. Prognostic significance of Doppler-derived and left ventricular diastolic filling variables in patients with dilated cardiomyopathy. Pol Arch Med Wewn 1996;96:552-60.
127. Pinamonti B, Zecchin M, Di Lenarda A, Gregori D, Sinagra G, Camerini F. Persistence of restrictive left ventricular filling pattern in dilated cardiomyopathy: An ominous prognostic sign. J Am Coll Cardiol 1997;29:604-12.
128. Sun JP, James K, Yang X, Solankhi N, Shah M, Arheart K, Thomas J, Stewart W. Comparison of mortality rates and progression of left ventricular dysfunction in patients with idiopathic dilated cardiomyopathy and dilated versus non-dilated right ventricular cavities. Am J Cardiol 1997;80:1583-7.
129. Hurrell D, Oh J, Mahoney D, Miller F, Seward J. Short deceleration time of mitral inflow E velocity: Prognostic implication with atrial fibrillation. J Am Soc Echocardiogr 1998;11:450-7.
130. Temporelli PL, Corra U, Imparato A, Bosimini E, Scapellato F, Giannuzzi P. Reversible restrictive left ventricular diastolic filling with optimized oral therapy predicts a more favorable prognosis in patients with chronic heart failure. J Am Coll Cardiol 1998;31:1591-7.

131. Fruhwald FM, Fahrleitner A, Watzinger N, Fruhwald S, Dobnig H, Schumacher M, Maier R, Zweiker R, Klein WW. Natriuretic peptides in patients with diastolic dysfunction due to idiopathic dilated cardiomyopathy. Eur Heart J 1999;20:1415-23.
132. Rich M, Stitziel N, Kovacs S. Prognostic value of diastolic filling parameters derived using a novel image processing technique in patients ≥ 70 years of age with congestive heart failure. Am J Cardiol 1999;84:82-6.
133. Yu HC, Sanderson JE. Different prognostic significance of right and left ventricular diastolic dysfunction in heart failure. Clin Cardiology 1999;22:504-12.
134. Bettencourt P, Ferreira A, Dias P, Pimenta J, Fries F, Martins L, Cerqueira-Gomes M. Predictors of prognosis in patients with stable mild to moderate heart failure. J Cardiac Fail 2000;6:306-13.
135. Akioka K, Takeuchi K, Yanagi S, Hirota K, Sakamoto K, Yoshimura T, Toda I, Yoshikawa J. Prognostic value of Doppler transmittal flow patterns and cardiac natriuretic peptides in patients with chronic congestive heart failure admitted for episodes of acute decompensation. Heart Vessels. 2000;15:53-60.
136. Tabet JY, Logeart D, Geyer C, Guiti C, Ennezat PV, Dahan M, Cohen-Solal A. Comparison of the prognostic value of left ventricular filling and peak oxygen uptake in patients with systolic heart failure. Eur Heart J 2000;21:1864-71.
137. Dini FL, Michelassi C, Micheli G, Rovai D. Prognostic value of pulmonary venous flow Doppler signal in left ventricular dysfunction. J Am Coll Cardiol 2000;36:1295-302.
138. Florea V, Henein M, Cicoira M, Anker S, Doehner W, Ponikowski P, Francis D, Gibson D, Coats AJ. Echocardiographic determinants of mortality in patients > 67 years of age with chronic heart failure. Am J Cardiol 2000;86:158-61.
139. Hansen A, Haass M, Zugck C, Krueger C, Unnebrink K, Zimmermann R, Kuebler W, Kuecherer H. Prognostic value of Doppler echocardiographic mitral inflow patterns: Implications for risk stratification in patients with congestive heart failure. J Am Coll Cardiol 2001;37:1049-55.
140. Yong Y, Nagueh SF, Shimoni S, Shan K, He ZX, Reardon MJ, Letsou GV, Howell JF, Verani MS, Quinones MA, Zoghbi WA. Deceleration time in ischemic cardiomyopathy. Relation to echocardiographic and scintigraphic indices of myocardial viability and functional recovery after revascularisation. Circulation 2001;103:1232-37.
141. Morales FJ, Asencio MC, Oneto J, Lozano J, Otero E, Maestre M, Iraavedra M, Martinez P. Deceleration time of early filling in patients with left ventricular systolic dysfunction: functional and prognostic independent value. Am Heart J 2002;143:1101-6.
142. Faris R, Coats A, Henein M. Echocardiography-derived variables predict outcome in patients with non-ischemic dilated cardiomyopathy with or without a restrictive filling pattern. Am Heart J 2002;144:343-50.
143. Wang M, Yip G, Wang A, Zhang Y, Ho P, Tse M, Lam P, Sanderson JE. Peak early diastolic mitral annulus velocity by tissue Doppler imaging adds independent and incremental prognostic value. J Am Coll Cardiol 2003;41:820-6.

144. Liu J, Tanaka N, Murata K, Ueda K, Wada Y, Oyama R, Matsuzaki M. Prognostic value of pseudonormal and restrictive filling patterns on left ventricular remodeling and cardiac events after coronary artery bypass grafting. Am J Cardiol 2003;91:550-4.
145. Sabharwal N, Cemin R, Rajan K, Hickman M, Lahiri A, Senior R. Usefulness of left atrial volume as a predictor of mortality in patients with ischemic cardiomyopathy. Am J Cardiol 2004;94:760-63.
146. Hillis G, Møller JE, Pellikka PA, Gersh BJ, Wright R, Ommen S, Reeder G, Oh J. Noninvasive estimation of left ventricular filling pressure by E/e' is a powerful predictor of survival after acute myocardial infarction. J Am Coll Cardiol 2004;43:360-7.
147. Zheng Z, Meissner A, Hausmann H, Alexander H, Simon R. Prognostic value of Doppler transmitral filling patterns in patients with chronic heart failure. Chinese Med J 2004;117:176-82.
148. Cowburn PJ, Cleland JGF, Coats AJS, Komajda M. Risk stratification in chronic heart failure. Eur Heart J 1998;19:696-710.
149. Vasan RS, Larson MG, Benjamin EJ, Evans JC, Reiss CK, Levy D. Congestive heart failure in subjects with normal versus reduced left ventricular ejection fraction: prevalence and mortality in a population-based cohort. J Am Coll Cardiol 1999;33:1948-55.
150. Smith GL, Masoudi FA, Vaccarino V, Radford MJ, Krumholz HM. Outcomes in heart failure patients with preserved ejection fraction: Mortality, readmission, and functional decline. J Am Coll Cardiol 2003;41:1510-18.
151. Tsutsui H, Tsuchihashi M, Takeshita A. Mortality and readmission of hospitalized patients with congestive heart failure and preserved versus depressed systolic function. Am J Cardiol 2001;88:530-33.
152. Willenheimer R, Cline C, Erhardt L, Israelsson B. Left ventricular atrioventricular plane displacement: an echocardiographic technique for rapid assessment of prognosis in heart failure. Heart 1997;7:230-6.
153. Rydberg E, Erhardt L, Brand B, Willenheimer R. Left atrioventricular plane displacement determined by echocardiography: a clinically useful, independent predictor of mortality in patients with stable coronary artery disease. J Intern Med 2003;254:479-85.
154. Pozzoli M, Capomolla S, Sanarico M, Pinna G, Cobelli F, Tavazzi L. Doppler evaluations of left ventricular diastolic filling and pulmonary wedge pressure provide similar prognostic information in patients with systolic impairment. Am Heart J 1995;129:716-25.
155. Nijland F, Kamp O, Karreman AJ, van Eenige MJ, Visser CA. Prognostic implications of restrictive left ventricular filling in acute myocardial infarction: a serial Doppler echocardiographic study. J Am Coll Cardiol 1997;30:1618-24.
156. Møller JE, Søndergaard E, Poulsen SH, Egstrup K. Pseudonormal and restrictive filling patterns predict left ventricular dilatation and cardiac death after a first myocardial infarction: A serial color m-mode Doppler echocardiographic study. J Am Coll Cardiol 2000;36:1841-6.
157. Møller JE, Hillis GS, Oh JK, Seward JB, Reeder GS, Wright RS, Park SW, Bailey KR, Pellikka PA. Left Atrial Volume: A Powerful Predictor of Survival After Acute Myocardial Infarction. Circulation 2003;107:2207-12.

158. Temporelli PL, Giannuzzi P, Nicolosi GL, Latini R, Franzosi MG, Gentile F, Tavazzi L, Maggioni AP. Doppler-derived mitral deceleration time as a strong prognostic marker of left ventricular remodeling and survival after acute myocardial infarction: Results of the GISSI-3 Echo substudy. J Am Coll Cardiol 2004;43:1646-53.
159. Garcia-Rubira J, Molano F, Espina A, Calvo R, Gonzalez-Valday M, Garcia-Martinez J, Cruz J. Abnormal filling pattern of the left ventricle and outcome in acute myocardial infarction. Int J Cardiol 1997;61:143-9.
160. Sakata K, Kashiro S, Hirata S, Yanagisawa A, Ishikawa K. Prognostic value of Doppler transmitral flow velocity patterns in acute myocardial infarction. Am J Cardiol 1997;79:1165-9.
161. Poulsen SH, Jensen SE, Egstrup K. Longitudinal changes and prognostic implications of left ventricular diastolic function in first acute myocardial infarction. Am Heart J 1999;137:910-8.
162. Tsai WC, Tsai LM, Teng JK, Li YH, Lin LJ, J.H. C. Prognostic value of Doppler-derived mitral deceleration time in postinfarction patients with left ventricular ejection fractions of 35% or more. J Form Med Assoc 1999;98:70-2.
163. Burgess M, Atkinson P, Ray S. Restrictive left ventricular filling pattern after myocardial infarction: significance of concomitant preserved systolic function. Echocardiography. 2000;17:659-64.
164. Cerisano G, L. B, Buonamici P, Valenti R, Carrabba N, Dovellini V, Pucci PD, Santoro GM, Antoniucci D. Prognostic implications of restrictive left ventricular filling in reperfused anterior acute myocardial infarction. J Am Coll Cardiol 2001;37:793-9.
165. Otasevic P, Neskovic AN, Popovic Z, Vlahovic A, Bojic D, Popovic AD. Short early filling deceleration time on day 1 after acute myocardial infarction is associated with short and long-term left ventricular remodelling. Heart 2001;85:527-32.
166. Moller JE, Sondergaard E, Poulsen SH, Seward JB, Appleton CP, Egstrup K. Color M-mode and pulsed wave tissue Doppler echocardiography: powerful predictors of cardiac events after first myocardial infarction. J Am Soc Echocardiogr 2001;14:757-167.
167. Moller JE, Egstrup K, Kober L, Poulsen SH, Nyvad O, Torp-Pedersen C. Prognostic importance of systolic and diastolic function after acute myocardial infarction. Am Heart J 2003;145:147-53.
168. Szymanski P, Rezler J, Stec S, Bundaj A. Long-term prognostic value of an index of myocardial performance in patients with myocardial infarction. Clin Cardiol 2002;25:378-83.
169. Kinova E. Left ventricular function in acute coronary syndromes - clinical and echocardiographic assessment (Phd Thesis), Sophia University 2003.
170. Moller JE, Dahlstrom U, Gotzsche O, Lahiri A, Skagen K, Andersen GS, Egstrup K. Effects of losartan and captopril on left ventricular systolic and diastolic function after acute myocardial infarction: Results of the Optimal Trial in Myocardial Infarction (OPTIMAAL) echocardiographic substudy. Am Heart J 2004;147:494-501.
171. Beinart R, Boyko V, Schwammenthal E, Kuperstein R, Sagie A, Hod H, Matetzky S, Behar S, Eldar M, Feinberg MS. Long-term prognostic significance of left atrial volume in acute myocardial infarction. J Am Coll Cardiol 2004;44:327-34.

172. Quintana M, Edner M, Kahan T, Hjemdahl P, Sollevi A, Rehnqvist N, for the ATTACC investigators. Is left ventricular diastolic function an independent marker of prognosis after acute myocardial infarction? Int J Cardiol 2004;96:183-9.
173. Kinova E, Kozhuharov H. Left ventricular diastolic filling patterns as predictors of heart failure after myocardial infarction:a colour M-mode Doppler study. Hellenic J Cardiol 2004;45:23-31.
174. Karvounis HI, Nouskaaaas IG, Farmakis TM, Vrogistinos KM, Papadopoulos CE, Zaglavara TA, Parharidis GE, Louridas GE. Evaluation of a Doppler-derived index combining systolic and diastolic left ventricular function in acute myocardial infarction. Angiology. 2004;55:21-8.
175. Capomolla S, Pinna G, Febo O, Caporotondi A, Guazzotti G, La Rovere M, Gnemmi M, Mortara A, Maestri R, Cobelli F. Echo-Doppler mitral flow monitoring: An operative tool to evaluate day-to-day tolerance to and effectiveness of beta-adrenergic blocking agent therapy in patients with chronic heart failure. J Am Coll Cardiol 2001;38:1675-84.
176. Davies SW, Fussell AL, Jordan SL, Poole-Wilson PA, Lipkin DP. Abnormal diastolic filling patterns in chronic heart failure - relationship to exercise capacity. Eur Heart J 1992;13:749-57.
177. Peltier M, Slama M, Garbi S, Enriquez-Sarano M, Goissen T, Tribouilloy CM. Prognostic Value of Doppler-derived myocardial performance index in patients with left ventricular systolic dysfunction. Am J Cardiol 2002;90:1261-3.
178. Redfield MM, Jacobsen S, Burnett JC, Mahoney DW, Bailey K, Rodeheffer RJ. Burden of systolic and diastolic ventricular dysfunction in the community. JAMA 2003;289:194-202.
179. Gavazzi A, Berzuini C, Campana C, Inserra C, Ponzetta M, Sebastiani R, Ghio S, Recusani F. Value of right ventricular ejection fraction in predicting short-term prognosis of patients with severe chronic heart failure. J Heart Lung Transpl 1997;16:774-85.
180. Karatasakis GT, Karagounis LA, Kalyvas PA, Manginas A, Athanassopoulos GD, Aggelakas SA, Cokkinos DV. Prognostic significance of echocardiographically estimated right ventricular shortening in advanced heart failure. Am J Cardiol 1998;82:329-34.
181. Ghio S, Gavazzi A, Campana C, Inserra C, Klersy C, Sebastiani R, Arbustini E, Recusani F, Tavazzi L. Independent and additive prognostic value of right ventricular systolic function and pulmonary artery pressure in patients with chronic heart failure. J Am Coll Cardiol 2001;37:183-8.
182. Ghio S, Recusani F, Klersy C, Sebastiani R, Laudisa ML, Campana C, Gavazzi A, Tavazzi L. Prognostic usefulness of the tricuspid annular plane systolic excursion in patients with congestive heart failure secondary to idiopathic or ischemic dilated cardiomyopathy. Am J Cardiol 2000;85.
183. Koelling TM, Aaronson KD, Cody RJ, Bach DS, Armstrong WF. Prognostic significance of mitral regurgitation and tricuspid regurgitation in patients with left ventricular systolic failure. Am Heart J 2002;144:524-9.
184. Trichon BH, Felker M, Shaw LK, Cabell CH, O'Connor CM. Relation of frequency and severity of mitral regurgitation to survival among patients with left ventricular systolic dysfunction and heart failure. Am J Cardiol 2003;91:538-43.

185. Cabell CH, Trichon BH, Velazquez EJ, Dumesnil JG, Anstrom KJ, Ryan T, Miller AB, Belkin RN, Cropp AB, O'Connor CM, Jollis JG. Importance of echocardiography in patients with severe non-ischemic heart failure: The Second Prospective Randomised Amlodopine Survival Evaluation (PRAISE-2) Echocardiographic Study. Am Heart J 2004;147:151-7.
186. The SOLVD Investigators. Effect of enalapril in patients with reduced left ventricular ejection fractions and congestive heart failure. N Engl J Med 1991;325:293-302.
187. The CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). N Eng J Med 1987;316:1429-35.
188. The, SOLVD, Investigators. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. N Eng J Med 1992;327:685-91.
189. Yusuf S, Pepine CJ, Garces C, Pouleur H, Salem D, Kostis J, Benedict C, Rousseau M, Bourassa M, Pitt B. Effect of enalapril on myocardial infarction and unstable angina in patients with low ejection fractions. Lancet. 1992;340:1173-8.
190. Pfeffer MA, Braunwald E, Moye LA, Basta L, Brown EJ, Cuddy TE, Davis BR, Geltman EM, Goldman S, Flaker GC, Klein M, Lamas GA, Packer M, Rouleau J, Rutherford J, Wertheimer JH, Hawkins CM, Investigators. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the Survival and Ventricular Enlargement Trial. N Eng J Med 1992;327:669-77.
191. Kober L, Torp-Pedersen C, Carlsen JE, Bagger H, Eliasen P, Lyngborg K, Videbaek J, Cole DS, Auclert L, Pauly NC. A clinical trial of the angiotensin-converting-enzyme inhibitor trandolapril in patients with left ventricular dysfunction after myocardial infarction. Trandolapril Cardiac Evaluation (TRACE) Study Group. N Eng J Med 1995;333:1670-6.
192. Australia, New, Zealand. Heart Failure Research Collaborative Group. Effects of carvedilol in patients with congestive heart failure due to ischaemic heart disease: final results from the Australia-New Zealand Heart Failure Research Collaborative Group trial. Lancet 1997;349:375-80.
193. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, Palensky J, Wittes J. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study. N Engl J Med 1999;341:709-17.
194. The HOPE Investigators. Effects of an angiotensin-converting-enzyme inhibitor on cardiovascular events in high-risk patients. N Eng J Med 2000;342:145-53.
195. Arnold J, Yusuf S, Young J, Mathew J, Johnstone D, Avezum A, Lonn E, Pogue J, Bosch J, Investigators obotH. Prevention of heart failure in patients in the Heart Outcomes Prevention Evaluation (HOPE) study. Circulation 2003;107:1284-90.
196. Gottdiener JS, McClelland RL, Marshall R, Shemanski L, Furberg CD, Kitzman DW, Cushman M, Polak J, Gardin JM, Gersh BJ, Aurigemma GP, Manolio TA. Outcome of Congestive Heart Failure in Elderly Persons: Influence of Left Ventricular Systolic Function: The Cardiovascular Health Study. Ann Intern Med 2002;137:631-39.

197. Yusuf S, Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJV, Michelson EL, Olofsson B, Ostergren J. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. Lancet 2003;362:777-81.
198. Moss A, Zareba W, Hall W, Klein H, Wilber D, Cannom D, Daubert J, Higgins S, Brown M, Andrews M, Investigators for the Multicentre Automatic Defibrillator Implantation Trial II Investigators. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. N Engl J Med 2002;346:877-83.
199. Buxton A, Lee K, Fisher J, Josephson M, Prystowsky E, Hafley G. A randomized study of the prevention of sudden death in patients with coronary artery disease. N Eng J Med 1999;341:1882-90.
200. Bristow MR, Saxon LA, Boehmer J, Krueger S, Kass DA, De Marco T, Carson P, DiCarlo L, DeMets D, White BG, DeVries DW, Feldman AM, Comparison of medical therapy, pacing and defibrillation in heart failure (COMPANION) Investigators. Cardiac resynchronisation therapy with or without implantable defibrillator in advanced heart failure. N Eng J Med 2004;350:2140-50.
201. Yu C-M, Chau E, Sanderson JE, Fan K, Tang M-O, Fung W-H, Lin H, Kong S-L, Lam Y-M, Hill MRS, Lau C-P. Tissue Doppler Echocardiographic Evidence of Reverse Remodeling and Improved Synchronicity by Simultaneously Delaying Regional Contraction After Biventricular Pacing Therapy in Heart Failure. Circulation 2002;105:438-45.
202. Sogaard P, Egeblad H, Pedersen AK, Kim WY, Kristensen BO, Hansen PS, Mortensen PT. Sequential Versus Simultaneous Biventricular Resynchronization for Severe Heart Failure: Evaluation by Tissue Doppler Imaging. Circulation 2002;106:2078-84.
203. Bordacher P, Garrigue S, Lafitte S, Reuter S, Jais P, Haissaguerre M, Clementy J. Interventricular and intra-ventricular electromechnical delays in right ventricular paced patients with heart failure: implications for upgrading to biventricular stimulation. Heart 2003;89:1401-5.
204. Bader H, Garrique S, Lafitte S, Reuter S, Jais P, Haissaguerre M, Bonnet J, Clementy J, Roudaut R. Intra-left ventricular electromechanical asynchrony.A new independent predictor of severe cardiac events and heart failure patients in. J Am Coll Cardiol 2004;1143:248-56.
205. Oguz E, Dagdeviren B, Bilsel T, Akdemir O, Erdinler I, Akyol A, Ulufer T, Tezel T, Gurkan K. Echocardiographic prediction of long-term response to biventricular pacemaker in severe heart failure. Eur J Heart Failure 2002;4:83-90.
206. Sharpe N, Murphy J, Smith H, Hannan S. Treatment of patients with symptomless left ventricular dysfunction after myocardial infarction. Lancet 1988:255-59.
207. Doughty RN, Whalley GA, Gamble G, MacMahon S, Sharpe N. Left ventricular remodeling with carvedilol in patients with congestive heart failure due to ischemic heart disease. Australia-New Zealand Heart Failure Research Collaborative Group. J Am Coll Cardiol 1997;29:1060-6.
208. Cohn J, Ferrari R, Sharpe N, Remodeling. Cardiac remodeling - concepts and clinical implications: a consensus paper from an international forum on cardiac remodeling. J Am Coll Cardiol 2000;35:569-82.
209. St. John Sutton M, Sharpe N. Left ventricular remodelling after myocardial infarction. Circulation 2000;101:2981-88.

210. Harjai KJ, Nunez E, Turgut T, Shah MP, Humphrey S, Newman J, Cherif J, Smart FW, Ventura HO. The independent effects of left ventricular ejection fraction on short-term outcomes and resource utilization following hospitalization for heart failure. Clin Cardiol 1999;22:184-90.
211. Cintron G, Johnson G, Francis G, Cobb F, Cohn JN. for the V-HeFT VA Cooperative Studies Group. Prognostic significance of serial changes in left ventricular ejection fraction in patients with congestive heart failure. Circulation 1993;87(suppl VI):VI-17-VI-23.
212. Parameshwar J, Shackell MM, Richardson A, Poole-Wilson PA, Sutton GC. Prevalence of heart failure in three general practices in north west London. Br J Gen Pract 1992;42:287-89.
213. Korup E, Kober L, Torp-Pedersen C, Toft E. Prognostic usefulness of repeated echocardiographic evaluation after acute myocardial infarction. TRACE Study Group. Trandolapril Cardiac Evaluation. Am J Cardiol 1999;83:1559-62, A7.
214. Kober L, Torp-Pedersen C, Jorgensen S, Eliasen P, Camm AJ. Changes in absolute and relative importance in the prognostic value of left ventricular systolic function and congestive heart failure after acute myocardial infarction. TRACE Study Group. Trandolapril Cardiac Evaluation. Am J Cardiol 1998;81:1292-7.
215. Badano L, Stoian J, Cervesato E, Bosimini E, Gentile F, Giannuzzi P, Heyman J, Lucci D, Maggioni AP, Piazza R, Nicolosi GL. Reproducibility of wall motion score and its correlation with left ventricular ejection fraction in patients with acute myocardial infarction. Am J Cardiol 1996;78:855-8.
216. Darasz KH, Underwood SR, Bayliss J, Forbat SM, Keegan J, Poole-Wilson PA, Sutton GC. Measurement of left ventricular volume after anterior myocardial infarction: comparison of magnetic resonance imaging, echocardiography, and radionuclide ventriculography. Int J Cardiovasc Imaging 2002;18:135-42.
217. Kornbluth M, Liang DH, Brown P, Gessford E, Schnittger I. Contrast echocardiography is superior to tissue harmonics for assessment of left ventricular function in mechanically ventilated patients. Am Heart J 2000;140:291-6.
218. Sharpe N, Smith H, Murphy J, Greaves S, Hart H, Gamble G. Early prevention of left ventricular dysfunction after myocardial infarction with angiotensin-converting-enzyme inhibition. Lancet 1991;337:872-76.
219. Peffer M, Lamas G, Vaughan D, Parisi A, Braunwald E. Effect of captopril on progressive ventricular dilatation after anterior myocardial infarction. N Engl J Med 1988;319:80-86.
220. Gilbert EM, Anderson JL, Deitchman D, Yanowitz FG, O'Connell JB, Renlund DG, Bartholomew M, Mealey PC, Larrabee P, Bristow MR. Long-term beta-blocker vasodilator therapy improves cardiac function in idiopathic dilated cardiomyopathy: a double-blind, randomised study of bucindolol versus placebo. Am J Med 1990;88:223-29.
221. Bristow M, Gilbert E, Abraham WT, Adams K, Fowler M, Hershberger RE. Carvedilol produces dose-related improvements in left ventricular function and survival in patients with chronic heart failure. Circulation 1996;94:2807-16.

222. MERIT-HF, Study, Group. Effect of metoprolol CR/XL in chronic heart failure: metoprolol CR/XL randomised intervention trial in congestive heart failure (MERIT-HF). Lancet 1999;353:2001-07.
223. Doughty RN, Whalley GA, Walsh HJ, Gamble GD, Lopez-Sendon J, Sharpe N. Effects of Carvedilol on left ventricular remodeling after acute myocardial infarction. The CAPRICORN Echo Substudy. Circulation 2004;109:201-6.
224. Hole T, Otterstad JE, St.John Sutton M, Froland G, Holme I, Skjaerpe T. Differences between echocardiographic measurements of left ventricular dimensions and function by local investigators and a core laboratory in a 2-year follow-up study of patients with an acute myocardial infarction. Eur J Echocardiography 2002;3:263-70.
225. Kitzman DW, Goldman ME, Gillam LD, Cohen JL, Aurigemma GP, Gottdiener JS. Efficacy and safety of the novel ultrasound contrast agent *Perflutren* (Definity) in patients with suboptimal baseline left ventricular echocardiographic images. Am J Cardiol 2000;86:669-74.
226. Belohlavek M, Tanabe K, Mulvagh SL, Foley DA, Greenleaf JF, Seward JB. Image enhancement by noncontrast harmonic echocardiography. Part II. Quantitative assessment with use of contrast-to-speckle ratio. Mayo Clin Proc 1998;**73**:1066-1070.
227. Kasprzak JD, Paelinck B, Ten Cate FJ, Vletter WB, de Jong N, Poldermans D, Elhendy A, Bouakaz A, Roelandt JR. Comparison of native and contrast-enhanced harmonic echocardiography for visualization of left ventricular endocardial border. Am J Cardiol 1999;83:211-7.
228. Main ML, Asher CR, Rubin DN, Odabashian JA, Cardon LA, Thomas JD, Klein AL. Comparison of tissue harmonic imaging with contrast (sonicated albumin) echocardiography and Doppler myocardial imaging for enhancing endocardial border resolution. Am J Cardiol 1999;83:218-22.
229. Reilly JP, Tunick PA, Timmermans RJ, Stein B, Rosenzweig BP, Kronzon I. Contrast echocardiography clarifies uninterpretable wall motion in intensive care unit patients. J Am Coll Cardiol 2000;35:485-90.
230. Nguyen TT, Dhond MR, Sabapathy R, Bommer WJ. Contrast microbubbles improve diagnostic yield in ICU patients with poor echocardiographic windows. Chest. 2001;120:1287-92.
231. Yong Y, Wu D, Fernandes V, Kopelen HA, Shimoni S, Nagueh SF, Callahan JD, Bruns DE, Shaw LJ, Quinones MA, Zoghbi WA. Diagnostic accuracy and cost-effectiveness of contrast echocardiography on evaluation of cardiac function in technically very difficult patients in the intensive care unit. Am J Cardiol 2002;89:711-8.
232. Sapin PM, Schroder KM, Gopal AS, Smith MD, DeMaria AN, King DL. Comparison of two- and three-dimensional echocardiography with cineventriculography for measurement of left ventricular volume in patients. J Am Coll Cardiol 1994;24:1054-63.
233. Lafitte S, Dos Santos P, Kerouani A, Robhan T, Roudaut R. Improved reliability for echocardiographic measurement of left ventricular volume using harmonic power imaging mode combined with contrast agent. Am J Cardiol 2000;85:1234-8.

234. Chuang ML, Hibberd MG, Salton CJ, Beaudin RA, Riley MF, Parker RA, Douglas PS, Manning WJ. Importance of imaging method over imaging modality in noninvasive determination of left ventricular volumes and ejection fraction: assessment by two- and three-dimensional echocardiography and magnetic resonance imaging. J Am Coll Cardiol 2000;35:477-84.
235. Nahar T, Croft L, Shapiro R, Fruchtman S, Diamond J, Henzlova M, Machac J, Buckley S, Goldman ME. Comparison of four echocardiographic techniques for measuring left ventricular ejection fraction. Am J Cardiol 2000;86:1358-62.
236. Van Camp G, Franken RR, Schoors D, Hagers Y, Koole M, Demoor D, Melis P, Block P. Impact of second harmonic imaging on the determination of the global and regional left ventricular function by 2D echocardiography: a comparison with MIBI gated SPECT. Eur J Echocardiography 2000;1:122-9.
237. Himelman RB, Cassidy MM, Landzberg JS, Schiller NB. Reproducibility of quantitative two-dimensional echocardiography. Am Heart J 1988;115:425-31.
238. Senior R, Sridhara BS, Basu S, Henley M, Handler CE, Raftery EB, Lahiri A. Comparison of radionuclide ventriculography and 2D echocardiography for the measurement of left ventricular ejection fraction following acute myocardial infarction. Eur Heart J 1994;15:1235-9.
239. Otterstad JE, Froeland G, St. John Sutton M, Holme I. Accuracy and reproducibility of biplane two-dimensional echocardiographic measurements of left ventricular dimensions and function. Eur Heart J 1997;18:507-13.
240. Uchimoto R, Niwa K, Tsuda N, Miyazawa T, Bräutigam M. Comparison of the efficacy of two air-based contrast agents in dogs. Euro J Ultrasound 2000;11:127-33.
241. Hurrell DG, Nishimura RA, Ilstrup DM, Appleton CP. Utility of preload alteration in assessment of left ventricular filling pressure by Doppler echocardiography: a simultaneous catheterization and Doppler echocardiographic study. J Am Coll Cardiol 1997;30:459-67.
242. Castello R, Pearson AC, Lenzen P, A.J. L. Evaluation of pulmonary venous flow by transesophageal echocardiography in subjects with a normal heart: comparison with transthoracic echocardiography. J Am Coll Cardiol 1991;18:65-71.
243. Tabata T, Thomas JD, Klein AL. Pulmonary venous flow by Doppler echocardiography: Revisited 12 years later. J Am Coll Cardiol 2003;41:1243-50.
244. Williams MJA, McClements BM, Picard MH. Improvement of transthoracic pulmonary venous flow Doppler signal with intravenous injection of sonicated albumin. J Am Coll Cardiol 1995;26:1741-6.
245. Dini FL, Traversi E, Franchini M, Micheli G, Cobelli F, Pozzoli M. Contrast-enhanced Doppler hemodynamics for noninvasive assessment fo patients with chronic heart failure and left ventricular systolic dysfunction. J Am Soc Echocard 2003;16:124-31.
246. Palazzuoli A, Carrera A, Calabria P, Puccetti L, Pastrorelli M, Pasqui AL, Auteri A, Bruni F. Effects of carvedilol therapy on restrictive diastolic filling pattern in chronic heart failure. Am Heart J 2004;147:73-79.

247. Traversi E, Pozzoli M, Cioffi G, Capomolla S, Forni G, Sanarico M, Tavazzi L. Mitral flow velocity changes after 6 months of optimized therapy provide important hemodynamic and prognostic information in patients with chronic heart failure. Am Heart J 1996;132:809-19.
248. Gardin JM, Dabestani A, Takenaka K, Rohan MK, Knoll M, Russell D, Henry WL. Effect of imaging view and sample volume location on evaluation of mitral flow velocity by pulsed Doppler echocardiography. Am J Cardiol 1986;57:1335-9.
249. Wijbenga AA, Mosterd A, Kasprzak JD, Ligthart JM, Vletter WB, Balk AH, Roelandt JR. Potentials and limitations of the Valsalva maneuver as a method of differentiating between normal and pseudonormal left ventricular filling patterns. Am J Cardiol 1999;84:76-81.
250. Schwammenthal E, Popescu BA, Popescu AC, Di Segni E, Kaplinsky E, Rabinowitz B, Guetta V, Rath S, Feinberg MS. Noninvasive assessment of left ventricular end-diastolic pressure by the response of the transmitral a-wave velocity to a standardized Valsalva maneuver. Am J Cardiol 2000;86:169-74.
251. Cheitlin MD, Armstrong WF, Aurigemma GP, Beller GA, Bierman FZ, Davis JL, Douglas PS, Faxon DP, Gillam LD, Kimball TR. ACC/AHA/ASE 2003 guideline update for the clinical application of echocardiography: summary article: a report of the American college of cardiology/American heart association task force on practice guidelines (ACC/AHA/ASE committee to update the 1997 guidelines for the clinical application of echocardiography). J Am Coll Cardiol 2003;42:954-70.
252. Farias CA, Rodriguez L, Garcia MJ, Sun JP, Klein AL, Thomas JDITJD. Assessment of diastolic function by tissue Doppler echocardiography: comparison with standard transmitral and pulmonary venous flow. J Am Soc Echocardiogr 1999;12:609-17.
253. Bruch C, Schmermund A, Bartel T, Schaar J, Erbel R. Tissue Doppler imaging: a new technique for assessment of pseudonormalization of the mitral inflow pattern. Echocardiography. 2000;17:539-46.
254. Poerner TC, Goebel B, Unglaub P, Sueselbeck T, Strotmann JM, Pfleger S, Borggrefe M, Haase KK. Detection of a pseudonormal mitral inflow pattern: an echocardiographic and tissue Doppler study. Echocardiography. 2003;20:345-56.
255. Boccalandro F, Loghin C, Darwood S, Seung-Ho K, Barasch E. Restrictive left ventricular filling pattern with preserved systolic function assessed by Doppler echocardiography: Clinical. echocardiographic and prognostic implications. Cardiology 2002;98:148-53.
256. Dini FL, Dell'Anna R, Micheli A, Michaelassi C, Rovai D. Impact of blunted pulmonary venous flow on the outcome of patients with left ventricular systolic dysfunction secondary to either ischaemic or idiopathic dilated cardiomyopathy. Am J Cardiol 2000;85:1455-60.
257. Yong Y, Nagueh SF, Shimoni S, Shan K, He ZX, Reardon MJ, Letsou GV, Howell JF, Verani MS, Quinones MA, Zoghbi WA. Deceleration time in ischemic cardiomyopathy. Relation to echocardiographic and scintigraphic indices of myocardial viability and functional recovery after revascularisation. Circulation 2001;103:1232-37.

258. Kuperstein R, Feinberg MS, Rosenblat S, Beker B, Eldar M, Schwammenthal E. Prevalence, etiology, and outcome of patients with restrictive left ventricular filling and relatively preserved systolic function. Am J Cardiol 2003;91:1517-9.
259. Dini FL, Cortigiani L, Baldini U, Boni A, Nuti R, Barsotti L, Micheli G. Prognostic value of left atrial enlargement in patients with idiopathic dilated cardiomyopathy and ischemic cardiomyopathy. Am J Cardiol 2002;89:518-23.
260. Rossi A, Cicoira M, Zanolla L, Sandrini R, Golia G, Zardini P, Enriquez-Sarano M. Determinants and prognostic value of left atrial volume in patients with dilated cardiomyopathy. J Am Coll Cardiol 2002;40:1425-30.
261. Alameda M, Moya JL, Garcia Lledo JA, Recarte MA, Guzman G, Vaticon C, Balaguer J, Asin E. Prognostic evaluation of patients with systolic dysfunction: functional and echocardiographic evaluation. Rev Esp Cardiol. 2002;55:372-82.
262. Rossi A, Ciciora M, Golia G, Zanolla L, Franceschini L, Marino P, Graziani M, Zardini P. Amino-terminal propeptide of type III procollagen is associated with restrictive mitral filling pattern in patients with dilated cardiomyopathy: a possible link between diastolic dysfunction and prognosis. Heart 2003;90:650-4.
263. Gackowski A, Isnard R, Golmard J, Pousset F, Carayon A, Montalescot G, Hulot J, Thomas D, Piwowarska W, Komajda M. Comparison of echocardiography and plasma B-type natriuretic peptide for monitoring the response to treatment in acute heart failure. Eur Heart J 2004;25:1788-96.
264. Cerisano G, Bolognese L, Carrabba N, Buonamici P, Santoro GM, Antoniucci D, Santini A, Moschi G, Fazzini PF. Doppler-derived mitral deceleration time. An early strong predictor of left ventricular remodelling after reperfused anterior acute myocardial infarction. Circulation 1999;99:230-6.
265. Poulsen SH, Jensen SE, Gøtzsche O, Egstrup K. Evaluation and prognostic significance of left ventricular diastolic function assessed by Doppler echocardiography in the early phase of a first acute myocardial infarction. Eur Heart J 1997;18:1882-89.
266. Oh JK, Ding ZP, Gersh BJ, Bailey KR, Tajik AJ. Restrictive left ventricular diastolic filling identifies patients with heart failure after acute myocardial infarction. J Am Soc Echocardiogr 1992;5:497-503.
267. Doughty RN, Wright SP, Pearl A, Walsh HJ, Muncaster S, Whalley GA, Gamble GD, Sharpe N. Randomized, controlled trial of integrated heart failure management. The Auckland Heart Failure Management Study. Eur Heart J 2002;23:139-46.
268. Xie GY, Berk MR, Smith MD, DeMaria AN. Relation of Doppler transmitral flow patterns to functional status in congestive heart failure. Am Heart J 1996;131:766-71.
269. Shen WF, Feng YY, Pan JL, Wang GD, Wang MH, Gong LS, Tribouilloy C, Lesbre JP. Prognostic importance of left ventricular diastolic filling velocity profiles in dilated cardiomyopathy. Chinese Med J 1993;106:266-71.

270. Werner GS, Fuchs JB, Schulz R. Doppler echocardiographic analysis of diastolic function in dilatative cardiomyopathy for the evaluation of its progression and prognosis. Deutsche Medizinische Wochenschrift 1995;120:507-14.
271. Fuchs JB, Werner GS, Schilz R, Kreuzer H. Prognostic value of changes in left ventricular diastolic function in patients with idiopathic dilated cardiomyopathy. Zeitschrift fur Kardiologie 1995;84:712-23.
272. Dujardin K, Tei C, Yeo TC, Hodge DO, Rossi A, Seward JB. Prognostic value of a Doppler index combining systolic and diastolic performance in idiopathic dilated cardiomyopathy. Am J Cardiol 1998;82:1071-6.
273. Boni A. Echocardiographic evaluation of left ventricular diastolic function in patients with dilated cardiomyopathy: Correlation among Doppler, hemodynamic and clinical findings. Giornale Italiano di Cardiologia. 1998;28:1120-7.
274. Lapu-Bula R, Robert A, De Kock M, D'Hondt A, Detry JM, Melin JA, Vanoverschelde JL. Risk stratification in patients with dilated cardiomyopathy: contribution of Doppler-derived left ventricular filling. Am J Cardiol 1998;82:779-85.
275. Yamamuro A, Yoshida K, Akasaka T, Hozumi T, Takagi T, Honda Y, Okura H, Yoshikawa J. Prognostic value of serial Doppler echocardiographic follow-up of transmitral flow patterns in patients with congestive heart failure who presented with pulmonary edema. Jap J Cardiology 1996;27:321-7.
276. Lipsitz LA, Byrnes N, Hossain M, Douglas P, Waksmonski CA. Restrictive left ventricular filling patterns in very old patients with congestive heart failure: clinical correlates and prognostic significance. J Am Geriatrics Soc 1996;44:634-7.
277. Werner GS, Fuchs JB, Schulz R, Figulla HR, Kreuzer H. Changes in left ventricular filling during follow-up study in survivors and nonsurvivors of idiopathic dilated cardiomyopathy. J Cardiac Failure 1996;2:5-14.
278. Garcia-Rubira J, Garcia-Martinez J, Hidalgo R, Gomez-Barrado J, Rodriguez Revuelta M, Rodriguez Banos J, Cruz J. Doppler transmitral flow pattern is an independent prognostic factor in acute myocardial infarction. Cardiology 1997;88:203-6.
279. Moller JE, Sondergaard E, Seward JB, Appleton CP, Egstrup K. Ratio of left ventricular peak E-wave velocity to flow propagation velocity assessed by color m-mode Doppler echocardiography in first myocardial infarction. J Am Coll Cardiol 2000;35:363-70.
280. Poulsen SH, Jensen SE, Nielsen JC, Moller JE, Egstrup K. Serial changes and prognostic implications of a Doppler-derived index of combined left ventricular systolic and diastolic myocardial performance in acute myocardial infarction. Am J Cardiol 2000;85:19-25.
281. Poulsen SH, Moller JE, Norager B, Egstrup K. Prognostic implications of left ventricular diastolic dysfunction with preserved systolic function following acute myocardial infarction. Cardiology 2001;95:190-7.
282. Poulsen SH, Jensen SE, Moller JE, Egstrup K. Prognostic value of left ventricular diastolic function and association with heart rate variability after the first acute myocardial infarction. Heart 2001;86:376-80.

283. Hole T, Vegsundvag JA, Morstol TH, Skjaerpe T. Early changes in left ventricular volume and function are predictors for long-term remodelling in patients with acute transmural myocardial infarction and preserved systolic function. J Am Soc Echocard 2003;16:630-7.
284. Schwammenthal E, Adler Y, Amichai K, Sagie A, Behar S, Hod H, Feinberg MS. Prognostic value of global myocardial performance indices in acute myocardial infarction. Chest 2003;124:1645-51.
285. Moller JE, Poulsen SH, Sondergaard E, Seward JB, Appleton CP, Egstrup K. Impact of early changes in left ventricular filling pattern on long-term outcome after acute myocardial infarction. Int J Cardiology 2003;89:207-15.
286. Vaskelyte J, Stoskute N, Kinduris S, Ereminiene E. Coronary bypass grafting in patients with severe left ventricular dysfunction: predictive significance of left ventricular diastolic filling pattern. Eur J Echocardiogr 2001;2:62-7.
287. Aurigemma GP, Gottdiener JS, Shemanski L, Gardin J, Kitzman D. Predictive value of systolic and diastolic function for incident congestive heart failure in the elderly: The Cardiovascular Health Study. J Am Coll Cardiol 2001;37:1042-48.
288. Troughton RW, Frampton CM, Yandle TG, Espiner EA, Nicholls MG, Richards AM. Treatment of heart failure guided by plasma aminoterminal brain natriuretic peptide (NT-proBNP) concentrations. Lancet 2000;355:1126-30.
289. Hellerman JP, Jacobsen SJ, Gersch BJ, Rodeheffer RJ, Reeder GS, Roger VL. Heart failure after myocardial infarction: A review. Am J Med 2002;113:324-30.
290. Spencer FA, Meyer TE, Gore JM, Goldberg RJ. Heterogeneity in the management and outcomes of patients with acute myocardial infarction complicated by heart failure. The national registry of myocardial infarction. Circulation 2002;105:2605-10.
291. Hasdai D, Topol EJ, Kilaru R, Battler A, Harrington RA, Vahanian A, Ohman EM, Granger CB, Van de Werf F, Simoons ML. Frequency, patient characteristics, and outcomes of mild-to-moderate heart failure complicating ST-segment elevation acute myocardial infarction: Lessons from 4 international fibrinolytic therapy trials. Am Heart J 2003;145:73-79.
292. Steg PG, Dabbous O, Feldman LJ, Cohen Solal A, Aumont M, Lopez-Sendon J, Budaj A, Goldberg RJ, Klein W, Anderson FA, the GRACE Investigators. Determinants and prognostic impact of heart failure complicating acute coronary syndromes. Observations from the Global Registry of Acute Coronary Events (GRACE). Circulation 2004;109:494-9.
293. Hellerman JP, Jacobsen SB, Redfield MM, Reeder G, Weston SA, Roger VL. Heart failure after myocardial infarction: clinical presentation and survival. Euro J Heart Failure 2005;7:119-25.
294. Rott D, Behar S, Hod H, Feinberg MS, Boyko V, Mandelzweig L, Kaplinsky E, Gottlieb S. Improved survival of patients with acute myocardial infarction with significant left ventricular dysfunction undergoing invasive coronary procedures. Am Heart J 2001;141:267-76.
295. Bonow RO, Bacharach SL, Green KM, Rosing DR, Lipson LC, Leon MB, Epstein SE. Impaired left ventricular diastolic filling in patients with coronary artery disease: assessment with radionuclide angiography. Circulation 1981;64:315-23.

296. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB for the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) Group. Meta-analysis of observational studies in epidemiology. A proposal for reporting. JAMA 1996;283:15.
297. Gerber IL, Stewart RAH, French JK, Legget ME, Greaves SC, West TM, Kerr AJ, Richards AM, White HD. Associations between plasma natriuretic peptide levels, symptoms, and left ventricular function in patients with chronic aortic regurgitation. Am J Cardiol 2003;92:755-58.
298. Gerber IL, Stewart RAH, Legget ME, West TM, French RL, Sutton TM, Yandle TG, French JK, Richards AM, White HD. Increased plasma natriuretic peptide levels reflect symptom onset in aortic stenosis. Circulation 2003;107:1884-90.
299. Sutton TM, Stewart RAH, Gerber IL, West TM, Richards AM, Yandle TG, Kerr AJ. Plasma natriuretic peptide levels increase with symptoms and severity of mitral regurgitation. J Am Coll Cardiol 2003;41:2280-87.
300. Kucher N, Printzen G, Goldhaber S. Prognostic role of brain natriuretic peptide in acute pulmonary embolism. Circulation 2003;107:2545-7.
301. Kruger S, Graf J, Merx M, Koch K, Kunz D, Hanrath P, Janssens U. Brain natriuretic peptide predicts right heart failure in patients with acute pulmonary embolism. Am Heart J 2004;147:60-5.
302. Hunt PJ, Richards AM, Nicholls MG, Yandle TG, Doughty RN, Espiner EA. Immunoreactive amino-terminal pro-brain natriuretic peptide (NT-proBNP): a new marker of cardiac impairment. Clin Endocrinol 1997;47:287-96.
303. Richards AM, Nicholls G, Yandle TG, Frampton C, Espiner EA, Turner JG, Buttimore RC, Lainchbury JG, Elliott JM, Ikram H, Crozier IG, Smyth DW. Plasma N-terminal pro-brain natriuretic peptide and adrenomedullin: new neurohormonal predictors of left ventricular function and prognosis after myocardial infarction. Circulation 1998;97:1921-29.
304. Troughton RW, Prior DL, Pereira JJ, Martin M, Fogarty A, Morehead A, Yandle TG, Richards AM, Starling RC, Young J, Thomas JD, Klein AL. Plasma B-type natriuretic peptide levels in systolic heart failure: importance of left ventricular diastolic function and right ventricular systolic function. J Am Coll Cardiol 2004;43:416-22.
305. Catuzzo B, Ciancamerla F, Bobbio M, Longo M, Trevi G. In patients with severe systolic dysfunction, only brain natriuretic peptide is related to diastolic restrictive pattern. J Cardiac Failure. 2003;9:303-10.
306. Kazanegra R, Cheng V, Garcia A, Krishnaswamy P, Gardetto N, Clopton P, Maisel A. A rapid test for B-type natriuretic peptide correlates with falling wedge pressures in patients treated for decompensated heart failure: a pilot study. J Cardiac Failure 2001;7:21-29.
307. Redfield MM, Rodenheffer RJ, Jacobsen SJ, Mahoney DW, Bailey KB, Burnett JC. Plasma brain natriuretic peptide concentration: impact of age and gender. J Am Coll Cardiol 2002;40:976-82.

308. Wang TJ, Larson MG, Levy D, Leip EP, Benjamin EJ, Wilson PWF, Sutherland P, Omland T, Ramachandran SV. Impact of age and sex on plasma natriuretic peptide levels in healthy adults. Am J Cardiol 2002;90:254-8.
309. Wallen T, Landahl S, Hedner K, Nakao K, Saito Y. Brain natriuretic peptide predicts mortality in the elderly. Heart 1997;77:264-67.
310. Cataliotti A, Malatino LS, Jougasaki M, Zoccali C, Castellino P, Giacone G, Bellanuova I, Tripepi G, Seminara G, Parlongo S, Stancanelli B, Bonanno G, Fatuzzo P, Rapisarda F, Belluardo P, Signorelli SS, Heublein DM, Lainchbury JG, Leskinen HK, Bailey KB, Redfield MM, Burnett JC. Circulating natriuretic peptide concentrations in patients with end-stage renal disease: role of brain natiuretic peptide as a biomarker for ventricular remodeling. Mayo Clin Proc 2001;76:1111-19.
311. Mark DB, Felker GM. B-type natriuretic peptide- a biomarker for all seasons. N Eng J Med 2004;350:718-20.
312. Davis M, Espiner E, Richards G, Billings J, Town I, Neill A, Drennan C, Richards M, Turner J, Yandle T. Plasma brain natriuretic peptide in assessment of acute dyspnoea. Lancet 1994;343:440-44.
313. Mueller C, Scholer A, Laule-Kilian K, Martina B, Schindler C, Buser P, Pfisterer M, Perruchoud AP. Use of B-type natriuretic peptide in the evaluation and management of acute dyspnoea. N Eng J Med 2004;350:647-54.
314. Bayes-Genis A, Santalo-Bel M, Zapico-Muniz E, Lopez L, Cotes C, Bellido J, Leta R, Casan P, Ordonez-Llanos J. N-terminal probrain natriuretic peptide (NT-proBNP) in the emergency diagnosis and in-hospital monitoring of patients with dyspnoea and ventricular dysfunction. Eur J Heart Failure 2004;6:301-8.
315. Lainchbury JG, Campbell E, Frampton C, Yandle TG, Nicholls MG, Richards AM. Brain natriuretic pepetide and N-terminal brain natriuretic peptide in the diagnosis of heart failure in patients with acute shortness of breath. J Am Coll Cardiol 2003;42:728-35.
316. Maisel AS, Krishnaswarmy P, Nowak RM, McCord J, Hollander JE, Duc P, Omland T, Storrow AB, Abraham WT, Wu AHB, Clopton P, Steg PG, Westheim WT, Knudsen CW, Perez A, Kazanegra R, Herrman HC, McCullough P. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. New Engl J Med 2002;347:161-7.
317. Logeart D, Saudubray C, Beyne P, Thabut G, Ennezat P-V, Chavelas C, Zanker C, Bouvier E, Cohen Solal A. Comparative value of Doppler echocardiography and B-type natriuretic peptide assay in the etiologic diagnosis of acute dyspnea. J Am Coll Cardiol 2002;40:1794-800.
318. Cowie MR, Struthers AD, Wood DA, Coats AJ, Thompson SG, Poole-Wilson PA, Sutton GC. Value of natriuretic peptides in assessment of patients with possible new heart failure in primary care. Lancet 1997;350:1347-51.
319. Nielsen LS, Svanegaard J, Klitgaard NA, Egeblad H. N-terminal pro-brain natriuretic peptide for discriminating between cardiac and non-cardiac dyspnoea. Eur J Heart Failure 2004;6:63-70.

320. McDonagh TA, Holmer S, Raymond I, Luchner A, Hildebrant P, Dargie HJ. NT-proBNP and the diagnosis of heart failure: a pooled analysis of three European epidemiological studies. Eur J Heart Failure 2004;6:269-73.
321. Wright SP, Doughty RN, Pearl A, Gamble GD, Whalley GA, Walsh HJ, Gordon G, Bagg W, Oxenham H, Yandle T. Plasma amino-terminal pro-brain natriuretic peptide and accuracy of heart-failure diagnosis in primary care: A randomized, controlled trial. J Am Coll Cardiol 2003;42:1793-800.
322. Fisher C, Berry C, Blue L, Morton JJ, McMurray JJV. N-terminal pro B type natriuretic peptide, but not the new putative cardiac hormone relaxin, predicts prognosis in patients with heart failure. Heart 2003;89:897-81.
323. Isnard R, Pousset F, Chafirovskaia O, Carayon A, Hulot JS, Thomas D, Komajda M. Combination of B-type natriuretic peptide and peak oxygen consumption improves risk stratification in outpatients with chronic heart failure. Am Heart J 2003;146:729-35.
324. Anand IS, Fisher LD, Chian Y-T, Latini R, Masson S, Maggioni AP, Glazer RD, Tognoni G, Cohn JN. Changes in brain natriuretic peptide and norepinephrine over time and mortality and morbidity in the Valsartan Heart Failure Trial (Val-HeFT). Circulation 2003;107:1278-83.
325. Gwechenberger M, Hulsmann M, Berger R, Graf S, Springer C, Stanek B, Pacher R. Interleukin-6 and B-type natriuretic peptide are independent predictors for worsening of heart failure in patients with progressive congestive heart failure. J Heart Lung Transplant 2004;23:839-44.
326. Latini R, Masson S, Anand IS, Salio M, Hester A, Judd D, Barlera S, Maggioni AP, Tognoni with heart failure enrolled in Val-HeFT. Euro Heart J 2004;25:292-9.
327. de Groote P, Dagorn J, Soudan B, Lamblin N, McFadden E, Bauters C. B-type natriuretic peptide and peak oxygen consumption provide independant information for risk stratification in patients with stable congestive heart failure. J Am Coll Cardiol 2004;43:1584-9.
328. Logeart D, Thabut G, Jourdain P, Chavelas C, Beyne P, Beauvais F, Bouvier E, Cohen Solal A. Predischarge B-type natriuretic peptide assay for identifying patients at high risk of re-admission after decompensated heart failure. J Am Coll Cardiol 2004;43:635-41.
329. The Taskforce on Heart Failure of the European Society of Cardiology. Guidelines for the diagnosis of heart failure. Euro Heart J 1995;16:741-51.
330. Devereux RB, Roman MJ, Liu JE, Welty TK, Lee ET, Rodeheffer R, Fabsitz RR, Howard BV. Congestive heart failure despite normal left ventricular systolic function in a population-based sample: The strong heart study. Am J Cardiol 2000;86:1090-96.
331. Jenkins C, Bricknell K, Henekom L, Marwick T. Reproducibility and accuracy of echocardiographic measurements of left ventricular parameters using real-time three-dimensional echocardiography. J Am Coll Cardiol 2004;44:878-86.