THE UNIVERSITY OF HULL

The Role of Stress Echocardiography and Colour Doppler Myocardial Imaging in the Evaluation of Patients with Suspected Heart Failure.

Thesis submitted for the Degree of

Doctor of Medicine

To the

University of Hull

by

Dr Sudipta Chattopadhyay

MBBS (University of Calcutta)
MD (University of Calcutta)
MRCP (UK)

April 2009

Dedication

To
my dear wife and daughter
for
their patience and understanding

TABLE OF CONTENTS

APPENDIX

A. Addi tional figures.

Figure 1. The 16-segment model of the left ventricle.

Figure 2. The Bull's eye plot of the left ventricular segments with their respective arterial supply.

Figure 3. Typical myocardial and annular velocity pattern seen with cTDI.

Figure 4: Apico-basal gradient in velocity from annulus to apex.

Figure 5. Stress-induced impairment in early diastolic myocardial relaxation as measured at the septal annulus in a patient with HFNEF.

Figure 6. Appearance of LV Dyssynchrony with Stress in a patient HF with LVSD.

Figure 7. Uninterpretable cTDI curves in a patient with ventricular bigemminy due to ECG auto-calibration during acquisition.

Figure 8. Uninterpretable cTDI curves in a patient whose ECG electrodes got disconnected during acquisition.

B. Prese ntations and publications

Acknowledgements

I am most grateful to:

Professor John GF Cleland for conceptualising the project and acquiring the grant for it, his valuable guidance throughout the process of this research, his critical evaluation of the manuscripts and helping me with the publication of the results.

Dr M F Alamgir and Dr N P Nikitin for teaching me the art of dobutamine stress echocardiography.

Dr N P Nikitin for the teaching me the interpretation of tissue Doppler imaging.

Dr A L Clark for the assisting me in the arranging and analysing the data.

All the research and heart failure nurses who assisted me in evaluating the study patients.

My co-research fellows (Dr A Louise, Dr N Khan and Dr R DeSilva) for helping me organising the project.

The British Heart Foundation for giving us this project-grant.

And, above all, to all our participating patients who made this study possible.

Declaration

This thesis was written by myself and has not been submitted in support of an application for another degree or qualification. This thesis embodies work performed solely by myself, except as acknowledged above. All work relating to patients had received the approval of the Local Research and Ethic Committee of the Hull and East Yorkshire NHS Trust and was performed at the Hull Royal Infirmary. This research was funded by a project grant from the British Heart Foundation (Grant No. PG/2001/1088).

ABBREVIATIONS

A	Late diastolic mitral inflow velocity.
Aa	Late diastolic mitral annular velocity.
Am	Late diastolic myocardial velocity.
BMI	Body mass index.
BNP	Brain natriuretic peptide.
BSA	Body surface area.
CAD	Coronary artery disease.
CHF	Chronic heart failure.
CRT	Cardiac resynchronisation therapy.
cTDI	Colour tissue Doppler imaging.
DSE	Dobutamine stress echocardiography.
E	Early diastolic mitral inflow velocity.
Ea	Early diastolic mitral annular velocity.
ECG	Electrocardiography
EDT	E deceleration time.
Em	Early diastolic myocardial velocity.
ESE	Exercise stress echocardiography.
HDDSE	High-dose dobutamine stress echocardiography.
HFNEF	Heart failure with normal ejection fraction.
HFREF	Heart failure with reduced ejection fraction.
IVRT	Isovolumic relaxation time.
IVSDd	Interventricular septum dimension in diastole.
IVSDs	Interventricular septum dimension in systole.
LAD	Left atrial dimension.
LDDSE	Low-dose dobutamine stress echocardiography.
LV	Left ventricle.
LVEF	Left ventricular ejection fraction.
LVIDd	Left ventricular internal dimension in diastole.
LVIDs	Left ventricular internal dimension in systole.
LVOT	Left ventricular outflow tract.
LVPWd	Left ventricular posterior wall in diastole.
LVPWs	Left ventricular posterior wall in systole.
LVSD	Left ventricular systolic dysfunction.
NQRS	narrow QRS.
NT-proBNP	N-terminal pro-brain natriuretic peptide
NYHA	New York Heart Association.
pTDI	Pulsed wave tissue Doppler imaging.
QRSd	QRS duration.
RWMA	Regional wall motion abnormality
Sa	Systolic mitral annular velocity.
SBSE	Supine bicycle stress echocardiography.
Sm	Systolic myocardial velocity.
SPECT	Single photon emission computed tomography
Ts	Time from onset of QRS to peak ejection velocity
Tscor	Ts corrected for heart rate.
Tscordiff	Tsdiff corrected for heart rate.
Tsdiff	Difference between the maximum and minimum Ts
WMS	Wall motion score
WMSI	Wall motion score index
WQRS	Wide QRS.

Chapter 1: Introduction to heart failure

Defining heart failure

Heart failure has often been described as acute or chronic in terms of its clinical presentation, systolic or diastolic in relation to the timing of the cardiac dysfunction, right or left sided depending on whether the pulmonary or the systemic veins are congested etc. Heart failure is pathophysiologically defined as the inability of the heart to maintain an adequate cardiac output commensurate with the metabolic needs of the body while maintaining normal left ventricular filling (atrial) pressures. The Task Force for the diagnosis and treatment of chronic heart failure (CHF) of the European Society of Cardiology has defined CHF in clinical terms, as a syndrome where the patient has breathlessness and/or fatigue at rest and/or during exertion or ankle swelling and objective evidence of cardiac dysfunction at rest and, where doubt exists, some improvement in the symptoms and/or signs in response to treatment. (1)

Epidemiology of heart failure

Incidence

During the 1980s, the annual age-adjusted incidence of CHF among persons enrolled into Framingham Heart Study aged ≥45 years was 7.2 cases/1000 in men and 4.7 cases/1000 in women. The overall incidence for all ages was 2.3/1000 for men and 1.4/1000 for women. (2) The Rochester Study reported a lower incidence rate. (3) In Europe, the crude incidence of CHF (unadjusted for age) is 1-5/1000 population per annum. (4) A Finnish population-based surveillance study reported the age-adjusted annual incidence of 4/1000 for men and 1/1000 for women in the age group 45-75 years. (5) In general practice, the reported unadjusted annual incidence for all ages and both sexes was 3.3/1000 in Netherlands[1] and 2.3/1000 in the UK[2]. The Hillingdon study reported an annual crude incidence of 1.3/1000 for those aged ≥25 years. (6) The annual incidence increases with age. It increased from 0.02/1000 in those aged 25-34 years to 11.6 in those ≥85 years in the Hillingdon study (6) and from

[1] Van de Lisdonk EH, Van den Bosch WJHM, Huygen FJA, Lagro-Jansen ALM. Diseases in general practice. Utrecht, the Netherlands: Bunge, 1990

[2] Royal College of General Practitioners, Office of Population Census and Survey, and Department of Health and Social Security. Morbidity statistics from general practice: fourth national study. 1991-92. London: HMSO, 1995.

2.8/1000 in those aged 45-64 years to 43.5/1000 in those >75 years in a Dutch study.[1]

Prevalence

The prevalence of CHF was 24-25/1000 in subjects aged ≥ 45 years in the Framingham Heart Study (2) and 7.4-21.2/1000 in other US studies depending on the population studied, being higher in the elderly. (3;7-9) The Dutch studies[1,3] reported a prevalence of about 11/1000 while Swedish, (10) Italian (11) and Danish[2] studies have quoted much higher prevalence mainly because of the higher age of the patients studied. A survey of European secondary care reported that of the patients with a death or discharge diagnosis of heart failure, about 31% had left ventricular systolic dysfunction (LVSD) alone, 14% valve disease alone, 23% LVSD with valve disease (predominantly mitral regurgitation) and 32% heart failure with normal ejection fraction (HFNEF), although the diagnosis was questionable in a substantial proportion of the last group. (12) A survey of European primary care came to similar conclusions. (13) The prevalence in general practice in UK is 3.8-13/1000 across all ages.(14) The prevalence of CHF and LVSD in a heart failure clinic taking referrals from the general population was 23/1000 amongst patients aged ≥ 45 years. 19 The prevalence of CHF increases rapidly with age with 15% of over 85s suffering with it. (15) About 15% of non-institutionalised patients (aged >70 years) developed CHF over six years before they died and 24% of all deaths were preceded by CHF. (16) Extrapolating data from several studies, it is likely that the true prevalence of CHF and LVSD in Western Europe is about 1-2% of the whole population (i.e. about 1·5% of the population aged 25–75 years). In addition, about 1-2% has asymptomatic LVSD, 1% has HFNEF and about 2% has suspected CHF that is not confirmed by investigation. Thus the total burden, of heart failure and/or ventricular dysfunction in the community is about 5%. (15) The prevalence in men and women is roughly equal. Men are more likely to develop CHF at a younger age and due to ischaemic heart disease (IHD) and suffer with asymptomatic LVSD while women suffer more with HFNEF. (15)

---

[1] Lamberts H, Brouwer HJ, Mohrs J. Reason for encounter — and episode and process oriented standard output from the Transition Project. Part 1 & 2. Amsterdam: Dept. of General Practice, 1993

[2] Wendelboe O, Hansen JF. Prevalence of mild and severe congestive heart failure in the community. Heart Failure '95. International Meeting of the Working Group on Heart Failure of the European Society of Cardiology, 1995, Amsterdam

Epidemiology of LVSD

About half of patients with important LVSD are symptomatic but a substantial proportion of these develop HF symptoms subsequently. Men are more likely to be asymptomatic than women. Asymptomatic patients have a better prognosis than symptomatic ones. (17;18) The commonest presentation of asymptomatic LVSD is sudden death. (19)

LVSD is usually due to IHD most commonly myocardial infarction. About a third will have extensive coronary disease but no classical evidence of myocardial infarction. Less than 10% of LVSD is due to dilated cardiomyopathy, constituting a relatively high proportion of LVSD in people aged <50 years. (13;20)

The Epidemiology of HFNEF

The epidemiology of HFNEF is more complex. It is more common in older women and results from multiple pathologies. (13;20) It appears that conventional echocardiography is unreliable in the diagnosis of HFNEF as the Doppler criteria are controversial at best. NT-proBNP appears to be useful in identifying patients who are at increased risk of cardiovascular events and death and who respond to treatment. (21)

Epidemiological studies, mainly of hospital discharge populations, suggest that the prognosis of HFNEF is similar to or only slightly better than HF due to LVSD. (22;23) However, clinical trials suggest dramatically lower rates of hospitalisation with heart failure and death, compared to patients with LVSD. (21;24) This may reflect the effects of non-cardiac co-morbidity and mortality, as this constitute a higher proportion of events in these patients than for patients with LVSD. The prognosis of HFNEF patients included in clinical trials seems better than that suggested by epidemiology due to exclusion of patients with serious non-cardiac co-morbidity from clinical trial. It also suggests that many of the deaths observed in the epidemiological studies would not be prevented by trial interventions.

Morbidity and mortality

Heart failure remains an important cause of morbidity and mortality. A survey of heart failure in European primary care suggests that half of patients remained moderately or severely symptomatic on therapy with gross impairment of the quality of life after discharge, perhaps due to suboptimal treatment in most patients. (13) The mortality amongst newly diagnosed patients with heart failure may be as high as 20% during index admission. (25;26) The Bromley, (27) Hillingdon, (28) Framingham, (2) Rochester, (3) and Olmsted County (29) studies all suggest a 1-month survival of 80-85%, dropping to 57-68% at 18 months. The three-year mortality of patients with new onset heart failure is about 60%, with evidence of a small improvement over the last 15 years. (30;31) Mortality is biphasic, with a six month mortality of 35-40% presumably reflecting a rapid decline in cardiac dysfunction, a high-risk of cardiac arrhythmias and sudden death and serious co-morbidities. The mortality is subsequently about 7% per annum or, if rebased to those still alive at 6 months, 10-15% per annum. The calculated median survival of incident heart failure is 2-3 years and of those who survive the first year, about 5 years and few patients surviving >10 years. (30)

Most deaths in patients with LVSD are cardiovascular. Sudden death occurs in about 3% per year due to arrhythmias, acute vascular events or other causes. The lifetime risk of sudden death in an asymptomatic LVSD patient may be higher than that of symptomatic patients. (32)

Problem in interpreting epidemiology

Epidemiological studies often exclude young patients (e.g. <25 years) and have an upper age limit (e.g.75 years). The elderly populations with highest prevalence rates may thus be under-represented leading to an underestimation of prevalence. The incidence and prevalence averaged over all ages reported in a study population cannot be directly applied to the general population as the prevalence varies widely across age groups. (4) Prevalence of heart failure is often determined using data collected from medical records supplemented by direct questioning and/or examination of individuals within the general population, drug prescription data analysis, and general practitioner monitoring. Hospital discharge codes substantially underestimate hospital events related to HF (33)

Diagnosis of CHF is often difficult. Despite the definition, (1) there are considerable uncertainties in its diagnosis. Only about a third to half of the patients suspected of having CHF in primary care has the diagnosis confirmed in secondary care, (6;34;35) Uncertainties persist even after assessment of these patients in secondary care. A survey of US cardiologists indicated that they felt that they could diagnose only advanced heart failure with certainty by clinical means alone. (36) In the EuroHeart Failure survey programme, a diagnosis of heart failure could not made or excluded in 46% of patients seen in the hospital. (20) Whether heart failure was the cause of dyspnoea could be determined in only 50% of the patients with normal left ventricular ejection fraction (LVEF) who were assessed in a heart failure clinic in the UK.(37)

This uncertainty stems from several factors. First, the symptoms and signs of heart failure are non-specific. The positive predictive value of these symptoms is poor and the inter-observer agreement on the presence of symptoms and signs is low, especially amongst the non-specialists and in routine clinic setting. (38-42) Many patients with LVSD are asymptomatic. (15) The signs may disappear in well treated heart failure even when severe. The relationship between symptoms and cardiac dysfunction is poor (43) and symptoms are often similar across the different levels of ejection fraction. (44) The relation between heart size on chest x-ray and left ventricular function is poor (45) and upper lobe venous dilatation is a poor guide to the simultaneous pulmonary capillary wedge pressure. (46) Inter-observer agreement on the interpretation of pulmonary congestion on chest x-rays is only modest. (47)

Second, cardiac dysfunction is often inadequately quantified. The use of transthoracic echocardiography for the documentation of cardiac dysfunction and measurement of LVEF for diagnosis of heart failure is far from universal. The IMPROVEMENT of Heart Failure Programme reported large variations in the likelihood that a physician would request echocardiography for diagnosis of heart failure in primary care in Europe. On the whole only 45% of the family physicians surveyed would request an echocardiogram in a patient with suspected heart failure and almost 20% of patients enrolled did not have an echocardiogram. (13) This variation persists even in secondary care. The

EuroHeart Failure Survey reported that one third of the patients with known or suspected heart failure never had an echocardiogram. (20) The suggested assessment of cardiac function includes global and regional systolic and diastolic and valvular function. In clinical practice, however, the quantification of systolic LV function is often restricted to a single estimation of LVEF at rest. LVEF was reported in only 39% of the patients who had an echocardiogram in the IMPROVEMENT of Heart Failure Programme (13) and less than 2/3rd of the patients in the EuroHeart Failure Survey. (20)

Third, the modality by which LVEF is quantified is not standardised. Though echocardiography is the commonest and the recommended modality, contrast ventriculography, radionuclide ventriculography (RNVG) and cine magnetic resonance imaging (CMRI) are all used. The LVEF measured by these different modalities are not interchangeable or comparable. (48) Most (but not all) large clinical trials in heart failure and LVSD entered patients on the basis of LVEF measured by RNVG. However, LVEF in clinical practice is measured on echocardiography. Echocardiography tends to be overestimate LVEF compared to RNVG. (48) A proportion of patients whose LVEF is "normal" as measured by echocardiography would be diagnosed with LVSD using RNVG. Epidemiological studies also have commonly used echocardiography as the main method for estimating LVEF. (6;27;34;35;37) Prevalence of LVSD may be an underestimate compared to that measured on RVNG, a modality used to test benefits of treatments in clinical trials.

Fourth, the method used for estimating LVEF on echocardiography is often not robust. Most epidemiological studies measured LVEF from M-mode images. (6;27;34;35;37) M-mode echocardiography is acoustic window and operator dependent. It assumes an ellipsoid geometry of the LV that does not hold true when the LV undergoes progressive dilatation and becomes spherical and/or is dyssynchronous. (48) It also assumes that a single segment is representative of the entire LV and this is erroneous in patients with wall motion abnormalities. Inadequately defined endocardial borders, gain-dependent edge identification and variations in transducer position during imaging limit even the Simpson's method for measurement of LVEF. These methodological limitations introduce errors in estimates of the prevalence of LVSD. CMRI provides the most

accurate and reproducible measurements of LV volumes and thence the LVEF. LVEF by M-mode echocardiography is significantly different from that by CMRI with unacceptably wide Bland–Altman range of agreement. (48) Though the mean LVEF measured by CMRI and 2D echo using Simpson's rule were similar suggesting that 2D echo provides estimates of EF comparable to CMRI, the Bland–Altman range for these two modalities reveal wide limits of agreement. (48) Estimating LVEF in the presence of atrial fibrillation and bundle branch blocks is difficult by any method. Measurement of LVEF by Simpson's rule may be impossible in an about half of the acute myocardial infarction patients (49) and one third of elderly patients (50) due to poor image quality.

Fifth, heart failure may occur in the absence of significant abnormality of conventionally measured LVEF. A number of epidemiological studies have suggested that 30-50% of cases of HF have normal ejection fractions. (6;13;20;29;51-54) Amongst the patients enrolled in the Euroheart Failure Survey whose LVEF was recorded, an LVEF>40% was reported in 49% of the males and 72% of the females. But diastolic measurements were seldom reported. (20) Thus in these patients with suspected heart failure, normal ejection fractions either excluded the diagnosis of heart failure or generated significant uncertainty in this diagnosis. This reflects clinical practice where diastolic evaluation of ventricles in patients with suspected heart failure is seldom undertaken. This reluctance in diastolic evaluation arises from several factors. There is a general lack of appreciation of this condition. The IMPROVEMENT of Heart Failure Programme reported that almost a quarter of the primary care physicians in Europe are unaware of the concept of HFNEF and only a third of them differentiated heart failure with from without normal ejection fraction. (13) There are doubts surrounding the very existence of HFNEF. HF was deemed to be more often a misdiagnosis than a true entity in patients with normal ejection fraction as most of these patients have an alternative; often non-cardiological cause for their symptoms.(55) The lack of observed LVSD in these patients was deemed only to be "apparent" due to the transient and thus elusive nature of the LVSD resulting from ischaemia or arrhythmia induced regional wall motion abnormalities (56) or the remoteness of the measured LVEF from the episode of HF. (52) Studies have confirmed that though conventionally measured LVEF is normal in these patients, LV "systolic"

function is not. Selective impairment of long-axis systolic and diastolic dysfunction at rest that do not manifest as a major impairment of global LV systolic function occurs in the absence of depressed LVEF. (57-62) Despite these studies, the presence of "pure" diastolic dysfunction has been strongly argued for by some authors. Gandhi et al demonstrated a low prevalence of LVSD during an acute episode of heart failure and on subsequent follow-up in patients with hypertension and acute cardiogenic pulmonary oedema, suggesting that transient LV systolic dysfunction is not a common entity and transient new or exacerbation of pre-existing diastolic dysfunction may occur. (63) Zile et al suggested that diastolic LV dysfunction was so common amongst patients with normal LVEF that there was no need to measure diastolic function in these patients. (64) Other authors have suggested that stress-induced left ventricular outflow tract (LVOT) obstruction may result in symptoms of heart failure in these patients. (65) There is lack of universally accepted robust diagnostic criteria for diastolic heart failure (DHF). The diagnostic criteria for DHF published by The European Study Group on Diastolic Heart Failure in 1998 (66) was found to be of limited use (67) and thus did not gain widespread acceptance. Numerous studies using mitral valve blood flow Doppler showed a variable outcome in terms of predictive value for HFNEF. The criteria proposed by the European Study Group were fulfilled in only 43% of patients hospitalised for HFNEF.(68) The concordance between diagnosis of HFNEF based on conventional echocardiographic measure of LV diastolic dysfunction and that based on other diagnostic criteria is poor. (69;70) Both E/A ratio and IVRT poorly correlate to serum NT-proBNP in patients with HFNEF. (71;72) The assessment of LV diastolic function is technically challenging. The conventional echocardiographic parameters of diastolic dysfunction are dependent on left ventricular pre- and after- load, heart rate, PR interval and QRSd. The E/A is often "pseudonormalised" and thus underestimate the condition. About 50% of normal E/A are pseudonormal. Valsalva manoeuvre, that unmasks abnormal diastolic filling in patients with pseudonormalisation, is rarely undertaken. Valsalva is unobtainable in about 40% patients with pseudonormalisation due to inability to comprehend instructions or strain adequately. Deep inspiration may degrade image quality and limit E and A assessment at peak Valsalva. The change in the E/A with Valsalva, decrease with age. There are no cut-offs for the decrease in E or E/A ratio to reach a diagnostic threshold. The threshold

depends upon baseline values for E and A, the quality of Valsalva, degree of patient effort etc. The changes with Valsalva manoeuvre is less predictive of elevated LV filling pressure when EF is normal. Other measurements of diastolic dysfunction like pulmonary venous flow are difficult to obtain and accuracy of recordings is highly dependent on skill of the operator and body size of the patient. Artifacts from LA motion also affect these measurements.

Rationale for the thesis

The current guidelines recommend assessment of the LV function at rest for the diagnosis of heart failure (1) though symptoms of heart failure are often present only during exercise and are almost universally induced by it. Conventionally assessed resting LVEF may be normal or abnormal in patients with symptoms suggestive of heart failure. Resting echocardiography may be adequate in confirming the diagnosis if the LVEF is abnormal at rest. But this strategy would fail to explain the genesis of the exercise-induced symptoms of heart failure in patients with normal resting LVEF. Stress echocardiography may potentially unmask global, regional and long-axis systolic LV dysfunction that are absent at rest and are likely to be responsible for exercise-induced symptoms. It may also demonstrate changes in the severity of abnormalities present at rest and provide prognostic information.

Coronary artery disease (CAD) is widely prevalent amongst patients with heart failure and normal LVEF (52) and is thus expected to be so amongst patients with suspected heart failure. Patients with CAD with and without past myocardial infarctions have considerable volumes of myocardium served by stenotic coronary arteries. The resting LVEF is often normal in these patients. Severe brief ischaemia may cause prolonged but transient LVSD that persists after the ischaemic insult itself has resolved, a process termed exercise-induced "stunning". (73) Inducible ischaemia per se may present as breathlessness that could be misconstrued as a heart failure symptom. Exercise may also precipitate isolated diastolic dysfunction by inducing ischaemia, (74-81) systolic hypertension, (82-84) and tachycardia. (85) Exercise-induced increases in the LVOT gradient may also give rise to heart failure symptoms. (86;87) Even though exercise induced ischaemia could potentially provoke LV systolic and diastolic dysfunction extensive enough to

give rise to symptoms of heart failure in patients with normal ejection fraction, search for myocardial ischaemia has rarely been undertaken in these patients. Ischaemia was systematically evaluated in only 1(n=20) (88) of the 11 studies (n=763) reviewed by Choudhury et al (89) and was found to be absent. Studies that have reported low prevalence or even the absence of systolic dysfunction with or without diastolic impairment have not systematically excluded ischaemia as a cause for their symptoms. (63;90;91) Stress echocardiography could potentially identify ischaemia and clarify its possible role in the genesis of symptoms in these patients.

CAD with and without associated myocardial infarction is common in patients with heart failure with reduced LVEF. (92) Stress echocardiography is also likely to be helpful in the assessment of the burden of myocardium that is dysfunctional but viable (hibernating) and/or is reversibly ischaemic in patients with LVSD.

Another potential mechanism for the exercise induced deterioration of LV systolic function in patients with heart failure and LVSD is intra-ventricular dyssynchrony that is induced or exacerbated with stress. LV dyssynchrony at rest is seen in patients with heart failure and LVSD irrespective of the QRSd. (93-96) Studies investigating the effects of exercise or pharmacological stress on ventricular dyssynchrony have yielded conflicting results. (97-100) Indices of dyssynchrony did not change in subjects without heart disease in these studies whether the stressor was exercise or dobutamine. In patients with heart failure, changes in the dyssynchrony indices in response to stress were either absent (97;99) or unreported.(98;100) Stress echocardiography could identify these changes

The heart could be stressed during echocardiography using exercise (treadmill and upright or supine bicycle ergometry), pharmacology (inotropes like dobutamine, arbutamine or enoximone and vasodilators like dipyridamole or adenosine) or electricity (pacing). Dobutamine stress echocardiography was used for this thesis. Though most physiological, exercise stress echocardiography has several disadvantages. Imaging the heart during any form of exercise is difficult. Movement and increased rate and depth of

respiration may render the image quality suboptimal. It is well recognised that only 40% of patients tested for CAD, can perform a truly diagnostic exercise test (101;102) This proportion is likely to be even lower in the elderly patients, with musculoskeletal or neuromotor problems, general frailty and breathlessness. Treadmill exercise, the available form of exercise stress in our setting, has additional limitations. The heart cannot be continuously imaged. Thus the time of onset of ischaemia and changes in the cardiac function at each level of exercise cannot be precisely identified. Myocardial viability, a prognostically important component of left ventricular evaluation in patients with heart failure, cannot be assessed with exercise stress echocardiography (ESE). British Society of Echocardiography Policy Committee does not recommend exercise echocardiography for assessment of viability in dysfunctional myocardial segments. (103) The end-points of the test are non-echocardiographic i.e. attainment of target heart rate, ST-segment changes, development of symptoms etc. These changes with exercise occur later in the ischaemic cascade than the wall motion changes. (104) Thus ischaemia is detected later. And lastly, because ischaemia induced wall motion abnormalities may resolve quickly, imaging needs to be completed quickly after the completion of exercise. It is recommended that post-exercise imaging be accomplished within 60–90 seconds of termination of exercise. But even under "study" conditions, this was barely achievable and information gained at peak exercise was lost in significant proportion of patients with post-exercise imaging. About 34% of new RWMA that develop at peak exercise resolve by the time images were acquired after exercise and 29% patients would have been missed had imaging been performed after exercise alone. (105) More precisely, new RWMA at peak exercise resolved at post-exercise imaging obtained within 80 seconds of exercise termination in 31% of patients with positive exercise echocardiography. There was a significant decrease in heart rate between peak exercise and the image acquisition. (106) No new RWMA was however missed when images where acquired within the recommended time in another study. (107) These problems could be overcome with supine bicycle stress testing. This was not available in our setting. Both exercise and dobutamine have a similar accuracy for the detection of coronary disease. (107-109)

As an adjunct to 2-D grey-scale stress echocardiography, colour tissue Doppler imaging (cTDI) was used to quantitatively assess global, especially long-axis, and regional myocardial function. cTDI is a useful technique that provides an objective and reproducible measure of global, regional and longitudinal systolic and diastolic function at rest and different levels of stress. This technique has been extensively used in cardiovascular research and its usefulness in the assessment of the LV function has been confirmed both at rest and during stress. The application of this technique is discussed in detail later.

Aims of the thesis

The principle aim of this thesis is to assess the application of conventional DSE supplemented by cTDI in the evaluation of patients with suspected heart failure. The reasons for patients declining or being excluded from DSE would be recorded to assess the applicability of this imaging technique to a general population of patients with heart failure. In particular, the prevalence, both at rest and during pharmacological stress, of the global and regional systolic and diastolic abnormalities of cardiac function that could cause or contribute to the symptoms of CHF in an unselected population of subjects suspected of having heart failure would be determined.

Hypotheses

- DSE supplemented with cTDI is likely to be applicable only to a highly selected group of patients with suspected heart failure.
- Quantitative echocardiography using cTDI would supplement conventional DSE in further unmasking abnormalities not otherwise detected.
- In subjects who undergo DSE, it would clarify the prevalence of stress induced changes in global, regional or long axis systolic or diastolic function in patients with symptoms of heart failure with reduced or normal ejection fraction.
- In patients with HFNEF, DSE would detect changes in global, regional or long axis systolic or diastolic function that would explain the genesis of symptoms in these patients.
- In patients with heart failure and LVSD, DSE would detect changes in intraventricular dyssynchrony.

Chapter 2: Stress echocardiography

Introduction

Wann et al first introduced echocardiography during stress in 1979. (110) It is based on the principle proposed by Gallagher et al (111) and then by Ross et al (112) that during stress-induced ischaemia, the decrement in myocardial contractile function is directly related to the decrease in regional subendocardial blood flow. 2-dimensional echocardiography, by virtue of its ability to assess regional and global contractile function, is an excellent tool for obtaining valuable information on cardiac function when combined with any stress-producing modality. It is widely available, rapidly performed, and safe without radiation and highly versatile test that can be used in variety of environments and for a variety of indications.

Methodology

Modalities of stress

The heart can be stressed during echocardiography using exercise (treadmill and upright or supine bicycle ergometry), pharmacological agents (vasodilators like dipyridamole or adenosine and inotropes like dobutamine, arbutamine or enoximone) or electricity (pacing). Exercise and dobutamine are the commonest stressors used in clinical practice. Both exercise and dobutamine have a similar accuracy for the detection of coronary disease. (107-109) Although both exercise and dobutamine induce ischaemia through increasing cardiac work, the haemodynamic responses to the two are different. Despite increasing contractility, systolic blood pressure does not increase to a major degree because dobutamine reduces peripheral vascular resistance. Although both stressors can achieve the same heart rate, both systolic blood pressure and the rate-pressure product at peak stress are significantly greater with exercise than with dobutamine. Dobutamine stress was used for this study.

Vasodilator stress work by the induction of coronary steal with minimal haemodynamic effects in the setting of severe or extensive coronary disease. British Society of Echocardiography Policy Committee recommends that vasodilator stress echocardiography should only be considered when physical stress is not possible and there are contraindications to dobutamine (103) because its sensitivity to assess mild to moderate CAD is low, it is unable to

assess myocardial viability and it is contraindicated in asthma and untreated conduction abnormalities.

Imaging techniques

Native 2-dimensional transthoracic echocardiography with harmonic imaging is routinely used. Parasternal long and short axis and apical 4-chamber, 2-chamber and 3-chamber views, optimised for image quality, are recorded. The images are acquired in suspended respiration (at end-expiration if possible to avoid Valsalva manoeuvre, which can degrade image quality) to minimize translational motion. Minimizing depth and using the narrowest sector angle attain maximum frame rates. The recommended frame rates are at least 25 frames per second to be increased to 30 when heart rates >140 beats is reached. Gains are adjusted and highest possible transducer frequency is used to maximise image resolution. Steep lateral decubitus position minimises apical foreshortening. Acquisition and storage of digital loops is standard. Digital imaging allows split or "quad-screen" side-by-side displays for comparison of regional function at rest and stress and real-time reviews of changes in contractility on a frame-by-frame basis. Simultaneous side-by-side display of previously acquired loops facilitates acquisition of new images in a comparable plane. At least two cardiac cycles is acquired when the patient is in sinus rhythm and five in atrial fibrillation. Loops are edited to exclude atrial or ventricular premature complexes.

If resting native images are sub-optimal in quality, echocardiographic contrast may be used. Left ventricular contrast is used for enhancement of the endocardial border. Myocardial contrast is used to directly assess myocardial motion, thickening and perfusion. When ultrasound contrast agents are used contrast specific imaging modalities is employed (reducing the mechanical index to minimise bubble destruction). The best images are recorded several cardiac cycles after the appearance of contrast in the LV. When less than 80% of the endocardial border is adequately visualised, the use of contrast agents for endocardial border delineation is strongly recommended. (113)

Study protocol

During echocardiography dobutamine is injected intravenously via a syringe

pump using standardised protocol depending on the indication of the test. (103) For assessment myocardial ischaemia, dobutamine is infused starting at 10 mcg/kg/min, with increment of 10 mcg/kg/min every three minutes to a maximum of 40 mcg/kg/min. Some studies have used a maximum dose of 50 mcg/kg/min. If the heart rate response is "inadequate", atropine is administered in 0.3 mg increments every 60 seconds until the target heart rate or a maximum dose of 1.2 mg is reached. Atropine may also be administered early if heart rate has not increased after the 20 mcg/kg/min of dobutamine. Atropine should be used to increase the sensitivity of the test in patients whose beta-blocker cannot be stopped. It is contraindicated in patients with glaucoma and history of urinary retention. For assessment of myocardial viability, dobutamine is infused starting at 5 mcg/kg/min followed every five minutes by 10 mcg/kg/min and 20 mcg/kg/min stages. Further stages at 30 and 40 mcg/kg/min may be used to assess a "biphasic" response. The sensitivity of the test for detection of ischaemia is reduced in patients on blockers due to its negative inotropic effect. (114) Thus, as recommended, beta-blockers were stopped 48 hours before the test.

Images are recorded at rest and in the final 60 seconds of every stage of the protocol and sometimes during recovery. The British Society of Echocardiography Policy Committee recommends acquisition, for detection of ischaemia, at baseline, low stress (10% increase in heart rate), intermediate stress (70% of the age predicted heart rate), peak stress (85% of the age predicted heart rate) and sometimes during recovery. Continuous echocardiographic monitoring of ventricular function and out flow tract gradient is informative.

Blood pressure and 12-lead ECG monitoring is continued throughout the test. Heart rate and rhythm, blood pressure, symptoms and wall motion abnormalities are recorded at the end of each stage, during any symptoms and at test termination. The persons present at the test include one skilled in acquisition and interpretation of the echocardiographic images and one trained in haemodynamic and ECG monitoring. All personnel should be trained in basic life support. Someone with training in advanced life support should be immediately available if needed even if not present during the test. If contrast

agents are used, patient should be monitored for hypersensitivity reactions.

The end-points for test termination include attainment of target heart rate (THR) {85% of (220-age in years)}, decrease in systolic blood pressure >20 mmHg below the level recorded at the previous level of test, increase in the systolic blood pressure to ≥240/120 mmHg, new or worsening wall motion or thickening abnormalities in at least two adjacent segments, new or worsening wall motion or thickening abnormalities with or without ventricular dilatation, intolerable symptoms of chest pain or severe breathlessness, >2mm flat or down-sloping ST depression or >1mm ST elevation in any lead, recurrent ventricular couplets or triplets, single run of non-sustained ventricular tachycardia (defined at >5 consecutive ventricular ectopics), sustained ventricular tachycardia or new atrial fibrillation and finally global reduction in the systolic function

Study analysis and interpretation.
Normal myocardium contracts at rest and increases its contractility and thickening during stress. Detection of myocardial ischaemia by DSE is based on the principle that motion and thickening of the left ventricular wall decreases with stress-induced relative reduction in myocardial blood flow. Myocardial viability is diagnosed on the basis that dobutamine at low-dose increases contractility in dysfunctional and viable myocardium by activating contractile reserve but not in dysfunctional and non-viable myocardium.(115)

During DSE, changes in regional wall motion and thickening and global left ventricular volumes, shape and ejection fraction are visually estimated at each level of stress by comparing acquired loops side-by-side. Analysis of thickening is better than analysis of motion in estimating contractile function as the later may be influenced by translation and tethering For systematic description of regional contractile function the left ventricular wall has been divided into standardised segments. In 1989, the American Society of Echocardiography recommended a 16-segment model for LV segmentation. (116) This model consists of basal and midventricular segments of the anteroseptal, inferoseptal, inferior, posterior, lateral and anterior walls and 4 segments at the apex: inferoseptal, inferior, lateral and anterior segments. In 2002, the apical cap, a segment beyond the end of the LV cavity was added by the American Heart

Association Writing Group on Myocardial Segmentation and Registration for Cardiac Imaging, as the 17th segment in an attempt to establish segmentation standards applicable to all types of imaging and not only echocardiography. (117) However, the ASE recommends using the 16-segment model of for studies assessing wall-motion abnormalities, as the tip of the normal apex (segment 17) does not move. (118) This model was used for this thesis. For analysis of regional contractile function, each of the 16 segments of the left ventricular wall is designated a semi-quantitative score at each level of stress: normal=1, hypokinesia=2, akinesia=3, dyskinesia=4, and aneurysmal (diastolically deformed)=5. (116) Wall motion score index (WMSI) is calculated by dividing the sum of the scores in each segment by the number of segments analysed. WMSI of 1 is normal; higher score indicates wall motion abnormalities. WMSI and LVEF are linearly correlated. (119;120)

The response of the myocardium to dobutamine varies according to its contractile state. "Normal" myocardium contracts at rest and increases its contractility and thickening at peak stress. Mild hypokinesia is considered normal. "Ischaemic" myocardium contracts normally at rest but is hypokinetic, akinetic or dyskinetic at peak stress. Dysfunctional but "viable" non-ischaemic myocardium (stunned myocardium) is hypokinetic or akinetic at rest, improves with low dose of dobutamine and sustains that improvement at high dose. Dysfunctional and "viable" but ischaemic myocardium (hibernating myocardium) demonstrates a "biphasic" response to dobutamine (the hypokinetic or akinetic myocardium improves in contractility with low dose dobutamine stress but then worsens with higher dose). This indicates myocardial dysfunction due to ischaemia and strongly predicts its recovery following revascularisation. Dysfunctional and non-viable myocardium ("scar") is akinetic or dyskinetic at rest and does not change with dobutamine stimulation. Whether the development of dyskinesia in an akinetic segment represents ischaemia is still a matter of debate. It has been suggested that these changes result from increase in the wall stress rather than induced ischaemia. The absence of a hyperdynamic response at higher doses of dobutamine is also difficult to interpret.

Myocardial substrate for ischaemia heart failure

Ischaemia affects several aspects of LV function. Foremost of these is impairment of systolic contraction of the myocardium. When the balance between the normo-contractile and hypo-contractile myocardium is tipped unfavourably, the long-axis followed by the global systolic function of the LV is impaired. The systolic dysfunction of the myocardium due to ischaemia results from such pathophysiological processes as hibernation, stunning, repetitive stunning and varying degrees of myocardial scarring and fibrosis. All these processes may co-exist in the same ventricle and even within the same region of the ventricle. These pathophysiological states of the myocardium respond distinctly to dobutamine stimulation.

Myocardial hibernation

Diamond et al, in 1978, were the first to use the word "hibernation" in the introduction to an experimental study that demonstrated that post-extrasystolic potentiation markedly restored systolic shortening of acutely dysfunctional ischaemic myocardium suggesting a preservation of contractile reserve within it up to shortly after complete arterial occlusion. This responsiveness was lost with time as the myocardium reached a point of non-viability. (121) After reviewing the literature suggesting that akinetic LV segments that were previously assumed to be fibrotic and non-viable recovered systolic function after revascularisation, Rahimtoola et al (122) proposed the concept of "myocardial hibernation". It refers to a prolonged sub-acute or chronic stage of myocardial ischaemia in which myocardial contractility and metabolism and consequently ventricular function are reduced to match the reduced blood supply to achieve a new state of equilibrium whereby myocardial necrosis is prevented and the myocardium is capable of returning to normal or near normal function on restoration of adequate blood supply. (123) This is a state of "perfusion-contraction match" where cellular viability is maintained at the expense of normal contractile function in the face of chronically reduced oxygen supply leading to overall LV dysfunction. (124;125) Reduced contractility reduces oxygen demand thus maintaining viability despite poor perfusion.

Hibernating myocardium is physiologically characterised by hypo-contractility with persistent inotropic reserve, reduced resting perfusion (126) (though some studies have claimed the contrary) (127-129) and metabolic activity and

severely impaired vasodilatory coronary flow reserve. During recruitment of inotropic reserve with intravenous dobutamine oxidative metabolism and glucose utilisation increases as does the perfusion (129;130) but prolonged stimulation may lead to myonecrosis. Restoration of blood flow to chronically underperfused myocardium leads to the functional recovery of hibernating myocardium.

Myocardial Stunning

Heyndrickx et al, in 1975, described the phenomenon where regional mechanical function remained impaired for prolonged periods after short episodes of coronary occlusion in conscious dogs. (131) Myocardial stunning, a term coined in 1982, (132) is a state of reversible contractile dysfunction that results from a short period of interruption of blood flow and persists after restoration of normal or near-normal perfusion despite the absence of irreversible damage. (133) This was subsequently noted after selective subendocardial (134) and exercise-induced ischaemia (135) It may result from single or multiple completely reversible ischaemic episode or a single, partly irreversible ischaemic episode and exercise, in presence or absence of coronary stenosis. Exercise-induced increase in myocardial oxygen demands in the face of limited supply (flow-limiting stenosis) is likely to be a common clinical scenario in patients with CAD with symptoms of heart failure. This may provoke myocardial ischaemia and contractile abnormalities that persist after cessation of exercise when demand returns to the resting state. (135;136) Stunning has been demonstrated after exercise, particularly in patients with multi-vessel disease. (137;138) Exercise can induce both ischaemic myocardial dysfunction and post-ischaemic myocardial stunning in hypertrophied ventricles in the absence of any coronary stenosis. (139)

Stunning is a state of "perfusion-contraction mismatch" where the contraction is impaired even though the perfusion is intact. Stunned myocardium has persistent inotropic reserve, normal resting perfusion and decreased coronary flow reserve. Dobutamine challenge recruits the inotropic reserve without deterioration of metabolism and does not produce necrosis even on prolonged stimulation.

Repetitive Stunning

One of the key differences between stunning and chronic hibernation is that resting perfusion is intact in stunning but reduced in hibernation. However some studies have reported normal resting perfusion in dysfunctional myocardium thought to be "hibernating". (127-129;140) An inverse relationship has also been demonstrated between the degree of contractile dysfunction and coronary reserve. (140) These facts have prompted investigators to postulate that some patients thought to suffer with chronic hibernation are actually suffering from "repetitive stunning". This is a state of persistent myocardial dysfunction resulting from cumulative effect of repetitive brief episodes of ischaemia in myocardium (with normal resting perfusion but severely reduced coronary flow reserve) that is not capable of increasing its blood flow sufficiently to meet its metabolic demands leading to repetitive stunning. Repetitive bouts of myocardial stunning can produce a prolonged, reversible depression of contractility that mimics myocardial "hibernation". (141)

In ischaemic cardiomyopathy, dysfunctional segments with severely reduced (hibernating) and near normal (stunned) resting perfusion may co-exist in the same ventricle in humans.(142) Some myocardial regions that are hibernating at rest may develop ischaemia during exercise with a subsequent process of post-ischaemic stunning superimposed on the baseline hibernating state. This phenomenon has been shown in animals. (141) It appears that there is a temporal progression from stunning, characterized by (nearly) normal flow (with reduced flow reserve), to hibernation, with reduced resting flow. Revascularisation of myocardium with adequate perfusion at rest but with recurrent ischaemic episodes during stress may successfully reverse persistent contractile dysfunction caused by repetitive stunning. (143) The timing of functional recovery after revascularisation appears to differ between stunned and hibernating myocardium. Stunned myocardium recovery appears to be early after revascularisation and more complete, while recovery of hibernating myocardium is late and often incomplete.(144)

Myocardial necrosis and scarring

Myocardial necrosis and scarring occur as sequelae of single or recurrent myocardial infarctions, with loss of functioning myocytes, development of

fibrosis and subsequent left ventricular dysfunction and remodelling. Atkinson et al in 1989, described heart failure due to severe CAD without MI in 26% of consecutive necropsies with ischaemic cardiomyopathy.(145) This suggested that LVSD is related to progression of CAD and does not require a distinct coronary event, such as MI with enzymatic elevation. (92) Superimposed on the ventricles with irreversibly damaged myocardium is chronic hibernation. The balance between perfusion and tissue viability is so precarious in this state that this cannot be maintained indefinitely and that myocardial necrosis and associated fibrosis will ultimately occur if blood flow is not increased. (146-148) Loss of cardiomyocytes by apoptosis, de-differentiation of myocytes, loss of contractile components within the remaining myocytes, increased glycogen deposit and interstitial fibrosis characterises chronic hibernation. (149) This suggests that adaptive changes to chronic hypo-perfusion are incomplete. (147) The severity of these changes does not correlate with the degree of hypoperfusion and wall motion abnormality. Activation of neurohormonal systems in patients with heart failure and CAD lead to direct stimulation of interstitial fibrosis that contributes to the pathophysiology of heart failure. (150) The extent of fibrosis is the major determinant of postoperative functional recovery, (147;151) indicating that there may be a progressive diminution of the chance for complete structural and functional recovery after restoration of blood flow with time.

Pathophysiology of myocardial response to dobutamine

In the early 1970s, it was documented using contrast ventriculography that resting wall motion abnormalities may improve with use of inotropic agents (epinephrine, isoproterenol, and post-extrasystolic potentiation). (152) This improvement was predictive of subsequent improvement with coronary bypass surgery. (153-155) Since then several imaging techniques have been used to identify ventricles with dysfunctional and viable myocardium and predict recovery with revascularisation. Of these, DSE is widely used and has been used in this study.

Dysfunctional segments that are hypoperfused or normally perfused exhibit contractile reserve with dobutamine (142) though this improvement of contractile function is not sustained in the former in keeping with the reduced

coronary flow reserve. (143) Dobutamine elicits a contractile response in hypoperfused dysfunctional segments without precipitating ischaemia by concomitant increase in myocardial blood flow. The percentage of increase in blood flow during dobutamine infusion in the dysfunctional myocardium approached that of normal myocardial regions. (129;156) However, prolonged stimulation by dobutamine of a dysfunctional myocardium is known to precipitate ischaemia and even myocardial infarction. (157) Another potential mechanism whereby the contractile response may be elicited during dobutamine, despite reduced resting myocardial flow, is through the peripheral vasodilator effect of dobutamine, which causes reduction in LV size and end systolic wall stress by reducing afterload, thus increasing systolic wall thickening for the same myocardial blood flow. (158) Low-dose DSE identifies this contractile reserve while high-dose DSE identifies inducible myocardial ischaemia by direct visualisation of the consequential regional and global contractile dysfunction.

Possible clinical role of DSE in suspected heart failure

CAD is common in patients with heart failure. More than 70% of the patients with heart failure symptoms and LVSD have underlying CAD. (2;92) Most patients will have had a myocardial infarction but perhaps a third will have extensive coronary disease but no classical evidence of myocardial infarction. (13;20) In a review of 31 studies of HFNEF published between January 1970 and March 1995, Vasan et al reported that the prevalence of coronary disease varied from 5-67%. Studies including patients with a mean age of 55-71 years reported a prevalence of 14-67%. (52) CAD is thus likely to be highly prevalent amongst patients with suspected HF and play a significant role in the genesis of their symptoms. Angina could present as breathlessness. Myocardium subtended by critically stenosed arteries is likely to suffer persistent contractile dysfunction due to either hibernation or repetitive stunning. (127;140) Both dysfunctional and normal segments may suffer with ischaemia.

Detection and quantification of coronary artery disease

DSE has been extensively used to diagnose CAD. After a review of 28 studies, Geleijnse et al reported mean sensitivity, specificity and accuracy of DSE for a total of 2,246 patients as 80%, 84% and 81% respectively. Mean sensitivity

increased significantly from 74% for single-vessel disease to 86% for double-vessel disease and to 92% for triple-vessel disease. (159)

Several studies have shown ESE and DSE to have a similar accuracy for the detection of coronary disease. (107-109) Studies directly comparing ESE and DSE, reported a sensitivity of 76-85% and 72-86%, specificity 77-94% and 81-97% and accuracy of 82-87% and 80-87% for ESE and DSE respectively. (108;160-162) The sensitivities of detecting patients with 3 and multi-vessel CAD were also similar (100% and 90% for ESE compared to 100% and 95% for DSE). (108) Peak exercise imaging has higher sensitivity and similar specificity to post-exercise imaging for detection of CAD. (106)

DSE also fares favourably when compared to single photon emission computed tomography (SPECT) in its ability to detect CAD. DSE had similar sensitivity (90% vs 96%) but higher specificity (90 vs 71%) compared to SPECT for detection of CAD. Diagnostic accuracy of dobutamine and exercise SPECT was also similar (90 vs 89%). (163)

Several factors affect sensitivity, specificity and accuracy with which DSE detects CAD. False negative tests result from sub-maximal stress, on-going beta-blocker therapy, female sex, single vessel disease, intermediate coronary stenosis and poor image quality. There are indications that segments visually reported to be non-ischaemic on DSE but are subtended by stenosed arteries (a false negative result) may fail to develop ischaemia because afterload reduction during DSE leads to lower myocardial oxygen consumption. These segments thus truly lack induced ischaemia, rather than having unrecognized wall-motion abnormalities. (164) False positive tests result from interpreter bias towards over interpretation, cardiomyopathies and hypertensive response to stress. Wall motion abnormalities in the left circumflex territory tend to be underestimated while those in the basal inferior wall and septum (in the presence of LBBB and post-cardiac surgery) are overestimated.

DSE in patients with both concentric remodelling has a lower sensitivity than observed in other groups. (165) There is a close inverse relation between systolic wall stress and systolic function at rest (166) and peak stress. (167) The

lower metabolic requirements of myocardium exposed to lower systolic wall stress at rest and peak stress protects it from developing ischaemia severe enough to induce wall motion abnormalities. Thus, patients with low systolic wall stress at peak dobutamine have a hyperdynamic response during DSE. In this situation, the detection of a new wall motion abnormality may be difficult because of tethering effects from adjacent hyperdynamic segments and LV cavity obliteration.

Accuracy of DSE when compared to angiographically demonstrated coronary stenosis is often affected by the limitations of an angiographic cutoff for significant disease, including the variation of the physiologic effect of a stenosis based on site, length, and vessel size, as well as over- and under-estimation of coronary lesion severity. DSE is a more sensitive marker of ischaemia in lesions involving larger (>2.6 mm diameter) vessels than smaller vessels. The quantitative angiography parameters associated with ischaemia are a minimum lumen diameter of <1 mm diameter, per cent diameter stenosis of >52%, and per cent area stenosis of >75%. The minimal lumen diameter is most predictive of an abnormal dobutamine stress test. Although the sensitivity for identifying multi-vessel disease is high, it is not uncommon to understate the number of diseased vessels. This phenomenon occurs when the most critical lesion gives rise to test end-points and the test is stopped leaving the less severe lesions undetected. Sensitivity analysis is affected by the cut-offs used to define "significant" stenosis that has varied between studies. Sensitivity is greatest when significant stenosis is defined as a threshold of >70% diameter narrowing and falls when significant stenosis is defined as >50% diameter narrowing. The presence of cardiomyopathy, microvascular disease, an acute hypertensive response to stress, and significant concentric remodelling all affect accuracy increasing the likelihood of a false-negative result. The ability to precisely identify an obstruction in the LAD exceeds that for the posterior circulation due to 1) the greater ease with which the LAD territory is visualised compared to the posterior endocardium, 2) the greater amount of myocardium perfused by the anterior circulation and 3) because of the overlap between the right coronary artery and circumflex coronary artery territories, precise separation of these territories has been problematic. Suboptimal stress reduces the accuracy with which CAD is detected.

Detection of viability of dysfunctional myocardium

It has long been observed that revascularisation improves systolic function of akinetic segments that were presumed to be non-viable.(123) This is only likely if the akinetic segments are pre-operatively viable. Improvement of the contractile function of a dysfunctional myocardial segment with restoration of perfusion is the only absolute proof of its viability. It is therapeutically useful to determine if and how much of a left ventricle consists of dysfunctional and viable (hibernating or stunned) as opposed to dysfunctional and non-viable (scar) myocardium. This identifies patients with LVSD that are most likely to benefit from revascularisation especially surgical as the risks of performing surgical revascularisation in patients with severe LVSD vary between 11% and 16%. (168) Observational studies have suggested that revascularisation offers a prognostic advantage in patients with high volumes of hibernating myocardium over medical therapy whereas revascularising non-viable myocardium may be harmful. (169-176)

In a meta-analysis of 28 studies (925 patients) using low-dose DSE (LDDSE) to detect functional recovery of hypo-contractile segments after revascularisation, Bax et al (177) calculated a weighted mean sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of LDDSE in predicting functional recovery as 82%, 79%, 78% and 83% respectively. The same for all 32 studies (using low-dose and high-dose DSE) taken together were 81%, 80%, 77% and 85% respectively. From analysis of 18 studies involving 563 patients that directly compared DSE with nuclear techniques, the sensitivity, specificity, PPV and NPV were 88%, 53%, 63% and 83% for the nuclear techniques compared to 76%, 81%, 79% and 79% for the DSE, respectively. When the analysis was restricted to 11 studies comparing LDDSE and nuclear techniques without stress (thus excluding studies that assessed viability and ischaemia) the weighted mean sensitivities of DSE and nuclear imaging were 74% and 90%, specificities were 57% and 80%, PPV were 84% and 75% and NPV were 69% and 80% respectively. Thus LDDSE has lower sensitivity and NPV and higher specificity and PPV compared to the nuclear modalities of imaging.

The difference in the specificity and sensitivity of LDDSE compared to the nuclear techniques results partly from the difference in the physiological mechanism by which each of the modalities detect myocardial viability. LDDSE tests for myocardial contractility, a function that requires the integrity of multiple cellular processes. In contrast, nuclear techniques identify viability in the myocardium if there is cellular uptake of a tracer. This requires adequate perfusion and intact cell membrane function. Positron emission tomography (PET), in addition, requires integrity of the biochemical processes that generate the high-energy phosphates. When faced with chronic ischaemia, contractility, because of the complexity of the process, is likely to be in jeopardy earlier than cell membrane function. Thus myocardial segments with systolic dysfunction will manifest thallium uptake due to intact cell membrane and adequate perfusion but lack inotropic reserve during DSE. Studies comparing DSE and PET, have reported dysfunctional segments with preserved metabolic activity but no contractile reserve. (178) Thus nuclear modalities are likely to identify more myocardium with intact cell membrane as "viable" though the contractile apparatus within these cells are in disarray. Restoration of blood supply to this "viable" myocardium is unlikely to restore its contractile function. Thus these methods are more likely to pronounce viability in dysfunctional segments that do not recover with revascularisation.

Several factors contribute to the inaccuracies of DSE in detecting viability. Evaluation of the changes in myocardial function before and after revascularisation may be suboptimal due to inadequate images. False-positive prediction of improvement in function of the hypo- and akinetic segments with revascularisation result from the following: 1) The tethering effect of systolic contraction of normal segments on non-contractile segments may be interpreted falsely as inotropic reserve in these segments 2) Subendocardial infarction gives rise to hypokinesia as myocardial thickening occurs mainly a the subendocardium. Increased contraction of the normal mid and epicardial regions adjacent to these areas may predict functional improvement in these segments with revascularisation though that does not occur. 3) Reassessment of function after revascularisation may be undertaken too early as recovery may occur up to 12 to 14 months after revascularisation. 4) Ischaemia (or necrosis)

before, during, or after revascularisation may render a segment initially deemed viable, non-viable thus resulting in failure of improvement. 5) The balance between resting perfusion and the physiological demand of the myocardium may be so precarious in long-hibernating segments that they may be viable at the time of initial assessment but may have undergone enough morphological changes between the initial assessment and revascularisation to render them non-viable. 6) Incomplete revascularisation as a result of diffuse atherosclerotic disease may prevent improvement. 7) A repeat angiogram is rarely undertaken before wall motion is assessed after revascularisation. Graft occlusion shortly after complete revascularisation may prevent a segment that was predicted to improve from improving. 8) Contractile function of stunned myocardium, like hibernating myocardium, improves with LDDSE thus suggesting improvement with revascularisation. The improvement of function after revascularisation is routinely tested at rest. Stunned myocardium, contrary to hibernating myocardium, already has near normal perfusion at rest. Revascularisation thus is unlikely to improve their resting function. Function of these segments, however, may show improvement if tested under stress. False-negative prediction results when a viable segment is deemed non-viable 1) due to inadequate inotropic stimulation 2) MBF and coronary flow reserve may have been reduced to such a marked degree that inotropic stimulation even a low dose induced ischaemia with consequent deterioration rather than improvement in function 3) structural changes in the hibernations myocardium is far too progressed to allow for an adequate immediate response that could be visually observed and 4) resting tachycardia will sometimes render the myocardium ischaemic and dobutamine stimulation will only augment ischaemia.

Other factors as different cut-offs for uptake of tracers to define viability, inconsistency in the modality used before revascularisation to detect viability and after to detect functional improvement, whether the segment in question is hypokinetic or akinetic and the duration after which functional recovery is tested also affect the sensitivity and specificity of these tests.

Predicting improvement in LVEF with revascularisation

The LVEF is a very powerful predictor of prognosis. Consequently, improvement in global LVEF with restoration of perfusion may be prognostically

more important than improvement in regional function. Observational studies have consistently showed that LVEF increases after revascularisation in patients with contractile reserve demonstrated on LDDSE but not in those without. This improvement is seen only in ventricles with significant volume of dysfunctional and viable myocardium with contractile reserve. (176;179) The precise proportions of viable segments needed to result in improvement in the LVEF differ among the studies. It is currently unclear how much viability is needed to result in improvement in the LVEF after revascularization. The available evidence suggests that 20-30% of the LV needs to be dysfunctional but viable to allow improvement in the LVEF. Few studies have emphasised that the extent of viability (i.e. the number of viable segments) determines the degree of improvement of LVEF after revascularisation. (179;180)

Challenges in the interpretation of systolic function with DSE

DSE has several limitations. Though quality of the images has improved with harmonic imaging and contrast echocardiography, this still remains the main obstacle in accurate interpretation of DSE. Analysis of cardiac wall motion and thickening becomes inaccurate if delineation of the endocardial border is inadequate, the same segments are not visualised on multiple views and the segments are not seen in the same imaging plane at different levels of stress. This may not be possible due to poor acoustic windows. Digitisation and simultaneous display of previously acquired loops when acquiring new ones have partly solved some of these problems. Interpretation of RWMA is more difficult in small LV cavities because of the smaller endocardial circumference over which the abnormality can be detected. (165)

The interpretation of DSE is based on a subjective visual analysis of grey-scale images. There is a learning curve before an observer can independently interpret the images. This means that even proficient echocardiographers require special training in order to become expert in stress echocardiography. (181) Interpretation is more congruent amongst experienced observers. However, there is wide variability in the interpretation of the images even among experts in different institutions. (182) This is partly due to institutional standards and conventions of interpretation that are not uniform. There is substantial regional variation in wall thickening of the normal left ventricle in

response to dobutamine. This heterogeneity is magnified by dobutamine infusion, making differentiation of this normal variation from the variation due to coronary artery disease difficult. Lack of uniformity in interpretation of worsening wall motion abnormalities in areas with resting abnormalities makes recognition of ischaemia in these areas difficult. Each interpreter may have a different threshold for identifying wall motion as abnormal, and therefore read with various degrees of 'aggressiveness'. Whether a segment that is mildly hypokinetic is considered a normal variant or abnormal is observer dependent. Mild hypokinesia at rest that becomes severe but not akinesia at peak stress is difficult to interpret. Similarly, interpretation of stress-induced dyskinesia in akinetic segments at rest is also not clear. These later changes are more likely to denote changes in wall stress rather than ischaemia. Detecting inducible wall motion abnormalities in some segments e.g. the inferobasal segment is particularly difficult. Diagnosis of triple vessel disease can be difficult if new or worsening wall motion is taken as an end-point for the test as the most severe lesion gives rise to the end-point leaving the other less severe lesions undetected. Difficulty in interpretation also arises when the extent of ischaemia is small (e.g. mild single-vessel stenosis with collaterals or mild stenosis in the presence of a stenosis elsewhere causing limiting symptoms).

Assessment of heart failure with normal ejection fraction

The cause of exercise intolerance in patients with HFNEF is unclear. Most studies on HFNEF have focused LV function at rest though the symptoms are often absent at rest and almost universally induced with exercise. Very little is known on the effect of stress on LV function in HFNEF. Exercise may induce myocardial ischaemia, transient but extensive enough to impair global EF, long-axis systolic and/or diastolic function. One other mechanism suggested is an impairment of LV diastolic relaxation during exercise. Kitzman et al demonstrated a smaller LV end-diastolic volume, a higher LV end-diastolic pressure and a rise in the left atrial pressure with exercise in 7 patients with HFNEF. The lack of increase in the end-diastolic LV volume with a marked increase in LV filling pressures during exercise in these patients suggested impaired diastolic relaxation. (183) Similar changes have been reported in normotensive patients with normal LVEF without inducible myocardial

ischaemia and exaggerated SBP response to exercise (83) and in about a third of patients with conventional indications for cardiac catheterisation. (184)

Impairment of myocardial relaxation during exercise may result form stress induced ischaemia, tachycardia and hypertension superimposed on primary myocardial defect of diastolic relaxation. Myocardial ischaemia impairs both regional (185;186) and global left ventricular diastolic relaxation (74-81) and this occurs earlier than the impairment of systolic contraction. (187) In patients with coronary artery disease, ischaemia induced by dobutamine (76;80) and exercise,(75) results in a transmitral flow pattern consistent with delayed relaxation. Even transient, reversible episodes of ischaemia can impair LV relaxation and elevate LV filling pressures.(74) Regional impairment of myocardial relaxation of ischaemic segments even when systolic contraction is preserved has been seen at rest,(79) after dobutamine stress (188) and coronary occlusion. (81) The lengthening rate in LV segments associated with a stenosed artery is reduced with stress. (185) Despite the foregoing data, studies evaluating the effect of ischaemia in patients with HFNEF are lacking.

Stress-induced tachycardia may worsen ischaemic diastolic relaxation by increasing myocardial oxygen demand and decreasing coronary perfusion time so that ischaemic diastolic dysfunction might occur even in the absence of coronary disease, especially in hypertrophic hearts. This also shortens diastole allowing less time for relaxation. This is exaggerated in hypertrophied and fibrosed myocardium that is unable to generate a higher rate of diastolic relaxation. This prevents relaxation from being complete between beats causing the diastolic pressures to increase.(85;189) This may occur at lower heart rates in failing hearts, which contrary to normal hearts, may exhibit a flat or even negative relaxation velocity versus heart rate relationship. So, as heart rate increases, relaxation rate does not increase or even decreases. (189)

Slower LV relaxation during exercise results from increased LV after-load due exaggerated systolic blood pressure response and increased circulating angiotensin II that impairs LV relaxation. (82) In hypertensives, a rapid increase in SBP at rest (63) or following exercise (183) results in deterioration of LV

diastolic function without worsening systolic function. Similar changes in response to stress have been demonstrated in patients with HFNEF. (84)

DSE has the potential to explore the mechanisms of diastolic dysfunction. Though not in routine use, assessment of diastolic echocardiographic indices during stress is feasible. (190-194) The mitral inflow indices are often difficult to assess and interpret at high heart rates during stress. The fusion of the E and the A waves is a major limitation. (191) In addition, factors that change during stress e.g. heart rate, preload, after load, QRS duration and PR interval affect these parameters considerably making interpretation difficult. As a result, direct measurement of myocardial relaxation velocity and the non-invasive measure of left atrial pressure using tissue Doppler imaging has largely superseded the conventional assessment of the LV diastolic function. These later parameters are relatively independent of loading conditions are now in routine use.

Assessment of patients with dyssynchrony

Application of DSE or ESE in the assessment of LV dyssynchrony has been tested in a small number of studies. In heart failure patients, exercise can alter the magnitude of ventricular dyssynchrony. Assessment of LV dyssynchrony under exercise (97;195) or dobutamine stress (99;100) is feasible. Lafitte et al demonstrated that the mean LV dyssynchrony in patients with normal LVEF was not modified with stress. Exercise variably affected LV dyssynchrony. It increased, remained stable and decreased in about 34%, 37% and 29% patients respectively. These changes varied considerably from patient to patient. Patients manifesting changes with exercise most commonly had ischaemic cardiomyopathy. (97) Valzania et al tested the effect of dobutamine stress on CRT responders with QRSd ≥ 130 ms. The dyssynchrony indices did not change from rest to stress irrespective of whether the CRT was "on" or "off". The measured timings were not corrected for heart rate and the heart rates achieved at stress were low. (99)

The other role of DSE in patients with dyssynchrony may its ability to assess the burden of dysfunctional but viable myocardium. This may determine response to CRT. Hummel et al demonstrated that in patients with ischaemic cardiomyopathy the extent of myocardial viability, assessed by myocardial

contrast echocardiography, predicts acute and long-term improvement in LV performance, exercise tolerance, and reduction in LV end-diastolic dimension with CRT. (98) Da Costa et al showed that presence of contractile reserve independently predicted long-term haemodynamic prognosis and recovery of mechanical function in patients who benefit from CRT.(100)

Conclusion

DSE is a versatile tool that has been extensively used for the assessment of left ventricular global, regional and long-axis systolic and diastolic function. It would potentially be a useful tool in the assessment of patients with suspected heart failure.

Chapter 3: Tissue Doppler imaging

Introduction

Since it was first described by McDicken et al in 1992, tissue Doppler imaging (TDI) or tissue velocity imaging (TVI) has developed as an echocardiographic technique to quantitatively assess the motion of cardiac structures, mainly the myocardium. In this thesis this technique was applied at rest and as adjunct to DSE to interrogate the myocardium of patients with suspected heart failure. What follows is a comprehensive review of literature on the use of TDI in patients with heart failure.

Physical principles and Technical considerations

TDI is based on the principle of Doppler shift or Doppler effect. Christian Doppler first described this phenomenon in 1842 in relation to light waves as a change in frequency and wavelength of the wave for an observer moving relative to a source of the wave. In 1845, the Dutch scientist CHDB Ballot tested this hypothesis for sound waves. He confirmed that the observed frequency of sound waves is higher than the emitted frequency when the source and the observer approach and lower when the two recede relative to each other. For waves that propagate in a medium, such as sound waves, the velocities of the observer and of the source are relative to the medium in which the waves are transmitted. The total Doppler effect may therefore result from motion of the source, motion of the observer, or motion of the medium.

In Doppler echocardiography the velocities of structures of or within the heart are derived from the Doppler shift observed when they (the source of reflected ultrasound) move towards or away from a static transducer (the observer). In conventional blood pool Doppler echocardiography, the moving objects are erythrocytes that reflect low amplitude and high frequency ultrasound. In contrast, the ultrasound reflected from the moving cardiac structures (valve leaflets, valve annuli, papillary muscles, ventricular and atrial walls etc) is of high amplitude (about 40dB higher than that from the erythrocytes) and low frequency. For conventional Doppler echocardiography, a high-pass filter eliminates the later signals leaving those from the erythrocytes for display. For tissue Doppler echocardiography the signals derived from cardiac tissue motion are input directly into the autocorrelator without passing through the high-pass

filter. In addition, lower gain amplification is used to improve the ability to measure low velocities. Velocities of 0.1 to 0.2 cm/s (a level associated with cardiac tissue motion) can then be detected. This technique is used to measure velocity and timing of motion of cardiac structures, their displacement in relation to the transducer and their deformation.

The cardiac structures can be interrogated using spectral pulsed Doppler (pTDI) or colour-coded Doppler mapping (cTDI). Pulsed Doppler measures velocities in one sample volume at a time by spectral analysis. The pTDI is simple to acquire, provides high quality records of Doppler profiles and the analysis of velocities, acceleration and deceleration of structures is straightforward. However, analysis can only be done on-line and only one structure can be interrogated at a time. This takes considerable time limiting its use in evaluating regional myocardial function during stress echocardiography. Moreover, the inability to interrogate all the cardiac structures in the same cardiac cycle makes comparison of the measurements difficult. Use of pTDI in differentiating subepicardial and subendocardial myocardial velocities is constrained by its low spatial resolution. In cTDI each pixel of the Doppler spectrum is colour coded according to the velocity of the structure and the direction of its motion. Brighter hues correspond to higher velocities (up to the Nyquist limit). Any motion towards the transducer is coded red and that away from the transducer is coded blue. cTDI samples the velocities of all the pixels in a sector nearly simultaneously and display the average velocity by autocorrelation. cTDI offers rapid visual estimation of movement of structures, good spatial resolution and the ability to measure velocity of multiple structures in the same cardiac cycle. Off-line analysis of recoded loops is possible allowing sufficient time for regional assessment. Velocities measured by pTDI is about 20-25% higher than that with cTDI as pTDI measures peak velocities while the cTDI measures modal velocities of all pixels within the sector. cTDI and pTDI correlate well at rest and stress, but pTDI are greater than cTDI velocities at rest and stress. (196) Temporal resolution of the images can be enhanced by increasing the frame rates. Frame rates well over 150 Hz can be obtained by minimizing the depth and sector angle and increasing the pulse repetition frequency during acquisition. cTDI acquired at high frame rates is thus particularly suited for use with stress echocardiography.

The basic data obtained by TDI is velocity. Displacement of the interrogated tissue can be derived by temporal integration of velocities. Strain represents the degree of relative deformation of the interrogated myocardium and strain rate, the rate of that deformation. Strain rate reflects how fast regional myocardial shortening or lengthening occurs. It is calculated from myocardial Doppler velocities measured at two locations separated by a given distance. Strain rate equals the instantaneous spatial velocity gradient and has units of $second^{-1}$. When the two velocities being measured are different, there is deformation of the tissue in-between. Strain is calculated as the time integral of strain rate and is a dimensionless quantity. In the long axis it represents shortening fraction, and in the short axis, thickening fraction. Deformation imaging is sensitive to misalignment between the cardiac axis and the ultrasound beam. Measurements also become inaccurate at low frame rates due to inadequate resolution of the different peaks of the velocity profile. Thus, the smallest possible sector should be used at minimum depth to attain highest possible frame rates. This may be best achieved by interrogating a single wall at a time. Strain and strain rate are relatively homogeneous throughout the myocardium and, compared to tissue velocity imaging, are less influenced by cardiac motion. However, the strain and strain rate signals generally show more background noise. Myocardial function can be more accurately assessed with strain and strain rate imaging. As only velocity imaging was used for this thesis, deformation imaging will not be discussed further.

TDI effectively complements conventional echocardiography. The measurements are quantitative, relatively independent of perfect image quality, are obtainable with minimal disruption/incremental time to standard imaging and can be interpreted quickly and objectively. The normal ranges have been defined for most groups of patients. Good reproducibility has been reported for off-line measurements even by inexperienced observers. (197) The integration of simple TDI data improves the accuracy of DSE interpretation by novice readers and experienced echocardiographers not formally trained in stress echocardiography but not that of expert stress echocardiographers.(198)

Physiological considerations

LVEF is the most frequently used index of cardiac function. Stroke output results from systolic reduction in the LV volumes due to myocardial contraction both in the long and short axes. Long axis contraction of the of the ventricle is made possible by the orientation of the myocardial fibre bundles that are arranged in three layers. The mid-wall myocardial fibres that predominate are arranged circumferentially while the subendocardial and subepicardial muscle bundles are aligned longitudinally with slight spiral arrangement. The later connect the cardiac apex, which is fixed in relation to the chest wall, to the base (i.e. atrio-ventricular annulus) that moves towards and away from the apex in systole and diastole respectively. The reduction of the systolic volume in the minor axis is mediated by radial contraction of the mid-wall myocardial fibres (bellow action). The reduction of the systolic volume in the major axis is mediated by shortening of the longitudinal fibres (piston action). This systolic shortening is associated with a concomitant transverse thickening which then also contributes to the reduction in the minor axis volume. The long axis normally shortens by 10% to 12% with ejection at the same time as the minor axis falls by 25%. (199)

The mitral annular velocity (MAV) and myocardial Doppler velocity (MDV) in the long-axis are best measured when scanning from the apical approach as the atrio-ventricular ring and the myocardial segments move towards and away from the relatively fixed apex in systole and diastole respectively parallel or almost parallel to the ultrasound beam. Longitudinal motion has higher amplitude and is less affected by rotational and translational cardiac activity. These two factors make the measurements at the annulus and the non-apical segments from the apical approach, less prone to error and more reproducible. (200) Velocities of radial contraction can also be obtained if myocardial segments are interrogated in the short-axis views. But these are more difficult to interpret as they are more affected by rotational and translational movements of the heart. Radial velocities have not measured in this thesis and thus this will not be discussed further.

The velocity profile obtained with TDI consists two positive systolic peaks (S_1 during isovolumic contraction and S_2 during ejection phase), a negative early diastolic (E) and a negative late diastolic wave (A). The E wave corresponds to

the early rapid filling phase and the A wave to the late rapid filling phase or the atrial contraction. The suffix "m" is used to denote MDV and "a" for MAV. A post-systolic velocity in early diastole (PS) is often seen in ischaemic heart disease and chronic heart failure. Though the genesis of this wave is uncertain, it may reflect the presence of dysfunctional but viable (stunned or hibernating) myocardium. The diastolic MAV can be measured almost universally, easily and quickly and has lowest interobserver variability compared to other diastolic indices. (201) Ea is an index of LV relaxation. Tau, the time constant of isovolumic LV pressure decline correlates inversely with peak Ea velocity. (202) This correlation is stronger in patients with abnormal versus normal systolic function. (192) Aa reflects annular motion away from the apex secondary to atrial contraction. There is no correlation between E and A velocities from the mitral inflow and the Ea and Aa velocities from the mitral annulus in normal subjects. However, the E/A ratio correlates well with Ea/Aa ratio. (203) Another index of diastolic function that is routinely derived is the E/Ea ratio (ratio of the early diastolic velocity from the mitral inflow and the early diastolic MAV) that estimates the LV filling pressure. The correlation between E/Ea and PCWP has been well established in various cardiac conditions in sinus rhythm, sinus tachycardia and cardiac transplant .(192;193;204;205)

As opposed to the blood flow velocities during diastole as measured from the mitral inflow Doppler, the diastolic MAV are relatively independent of left ventricular loading conditions. Garcia et al showed a lack of correlation between the peak Ea and peak E velocity, suggesting the relative preload independence of peak Ea. (206) Sohn et al confirmed the independence of the septal Ea (Ea_{sep}) from the loading conditions in patients with relaxation abnormalities. Saline loading and nitroglycerine infusion did not affect Ea_{sep} velocity and Ea_{sep}/Aa_{sep} ratio in contrast to the E velocity. The Ea_{sep} and Ea_{sep}/Aa_{sep} ratio inversely correlated with tau. (202) Ea partially corrects the influence of relaxation on the transmitral E velocity. (204) Firstenberg et al tested the dependence of diastolic MAV on loading conditions in normal subjects. Preload altering manoeuvres (lower body negative pressure and saline loading) had no significant effect on lateral Ea (Ea_{lat}), whereas Ea_{sep} was affected in parallel to the E wave. The E/A, E/Ea_{lat} or E/Ea_{sep} did not change. The PCWP correlated strongly with E and Ea_{sep} but weakly with Ea_{lat} and not with E/Ea_{sep} or E/Ea_{lat}

ratio suggesting that Ea_{sep} is preload dependent when relaxation is normal. However, this preload dependence decreases with worsening tau. This suggests that while Easep is preload dependent when relaxation normal, but minimally so when it is impaired. (207) Agmon et al came to similar conclusion in patients undergoing haemodialysis. The Ea_{sep} and Ea_{lat} decreased with volume depletion in parallel to that in the E velocity. However, the percent change in E velocities was higher than the percent change in Ea_{lat} but not Ea_{sep}. The E/Ea_{lat} decreased but not the E/Ea_{sep}. The Aa at either site remained unchanged. (208) In patients with chronic stable angina and LVSD maneuvers like Trendelenberg, reverse Trendelenberg and amyl nitrate did not affect the Ea. (209)

The Sa, Ea and Aa are positively and non-linearly correlated across a wide range of LVEFs. (61;62;210) This relation results from the inter-dependence of the systole and diastole. The normal LV contracts to a volume less than its equilibrium volume during systole due to the longitudinal shortening and "twisting" motion of the LV. This compresses the elastic cardiac elements generating potential energy that is stored within the coiled fibres of the myocardium. This creates early diastole-restorative forces that produce a `suction' effect that lowers LV pressure and increases early filling. Thus the strength and coordination of the previous systole determines early diastolic filling velocity. As myocyte contractile function decline, recoil declines as well resulting in parallel decrease in the Sa and Ea. Other mechanisms e.g. uncoordinated systolic contraction, changes in the extracellular matrix also act to impair diastolic function. The Aa is also dependent on ventricular systole. (210) The excursion of the mitral annular ring towards the apex during ventricular systole stretches the pectinate muscles of the atria. This creates a stored potential energy within these muscles and increases the atrial volume, creating a suction effect, which draws blood from the pulmonary veins. The potential energy generated by this stretch, the amount of movement of the annulus away from the apex during early diastole and finally the effect of atrial systole to draw the mitral valve ring away from the apex all determine the late diastolic velocity.

There is a considerable degree of heterogeneity of velocities within the myocardium. There is a graded reduction in all MDVs from the annulus to the apex. This does not represent a graded reduction in contractility from apex to base as this gradient is not seen when strain rate is measured. (211) The longitudinal motion of the apex relative to the transducer is small resulting in very low amplitude velocities making these measurements unreliable. Thus, like most investigators, these segments were excluded from the analysis. The MDVs measured at the free-walls of the LV (lateral, anterior and posterior) are greater than that of the para-septal walls (septum, inferior or anteroseptal) due to the predominance of longitudinal myocardial fibres in these walls. (212;213) Consequently, in the absence of prominent RWMA the most suitable site for the assessment of longitudinal LV systolic function are the free LV wall and the lateral end of the mitral annulus. The MDVs at the interventricular septum are also affected by the activity of the right ventricle and rotational movements probably due to the predominance of circular myocardial fibers in this wall. In the parasternal view, velocities are lower in the anteroseptal wall than in the posterior wall. The translational motion of the heart within the chest during the cardiac cycle is anteriorly directed in systole and posteriorly directed in diastole. Velocities related to these motions are superimposed on the intrinsic wall velocities, increasing them at the posterior wall, and decreasing them in the septum during systole and vice-versa during diastole. These variations of regional velocity in the normal heart mandate the use of site-specific normal ranges for diagnostic purposes. (214)

Myocardial velocities are age dependent, with higher Sa, Ea and Aa in younger patients. (212;215) Mitral annular motion decreases by up to 20% whereas the short axis increases by up to 18%, with increasing age in normal adults independent of systolic blood pressure, LV wall thickness, heart rate or sex. (216) Yip et al reported 18% and 30% decrease in systolic mitral annular displacement and Sa respectively with age (210) though this inverse correlation may be weak. (217) This relation persists at peak dose dobutamine, in both men and women. (218) Studies have consistently reported an inverse relation between age and Ea and a direct one between age and Aa both in health and cardiac disease. (210;217;219-222) In healthy subjects, age is the most important variable affecting Ea, Aa and the E/Ea. (221) Yip et al reported 49%

and 56% decrease in early diastolic mitral annular displacement and Ea respectively, with advancing age. The Aa increased by 25-30%. (210) The correlation between age and Ea is stronger than that between age and Sa. (217) E/Ea is directly correlated to age. (221) Similar changes are seen in hypertensives with LVH though the E/Ea values are slightly higher for each age category compared with normal patients. (222) Heart rate affects regional MDV (218) but not the MAV. (210)

Global LV function in HFNEF

Sa is reduced in patients with HFNEF compared to healthy controls. (57-62) There is a decremental continuum of Sa from normal to HFNEF to HF with reduced ejection fraction (HFREF) so that Sa in patients with HFNEF is lower than normal but higher than in HFREF. (58;59;61;223;224) However, Kasner et al reported similar values of Sa_{sep} and Sa_{lat} amongst patients with invasively confirmed diastolic dysfunction compared to controls. (225) Subnormal Sa and reduced AV plane displacement are reported in 38% and 21-33% of patients with HFNEF respectively in two separate studies. (58;60) Using pTDI, Sa <7.95 cm/s separated the HFNEF patients from control subjects with a sensitivity of 83% and a specificity of 83% in one study. (61) Using pTDI, Sa <5.8 cm/s identified HFNEF with a sensitivity of 82%, specificity of 73% and a negative predictive value of 98.7%. (223)

Ea velocity in the HFNEF patients is lower than controls. (57;58;61;223) The site at which the velocities are measured may influence whether it is reduced in HFNEF patients. Kasner et al reported lower Ea_{lat} but not Ea_{sep} in HFNEF compared to controls. (225) Patients with pseudonormal filling, defined as the combination of normal mitral inflow variables and prolonged tau (≥50 ms), could be separated from patients with normal filling patterns by an Ea velocity <8.5 cm/s and a Ea/Aa ratio <1 with a sensitivity of 88% and specificity of 67%. (202) In comparison to controls, the Ea is reduced to a greater extent than Sa in the HFNEF patients. (58;61)

In a large cohort of patients with HFREF, conventionally diagnosed DHF, asymptomatic diastolic dysfunction (DD) and normal subjects, Yu et al reported lower regional systolic and diastolic velocities in DHF patients than in controls.

The systolic velocity (both regional and the average of the 6 basal segments) in the 4 groups was related as follows: HFREF<DHF<DD<controls. The Em (both regional and the average of the 6 basal segments) was related as follows: HFREF=DHF<DD<controls.(59)

Nikitin et al reported higher E/Ea ratio and similar Ea/Aa ratio in patients with HFNEF compared to controls. (57) Kasner et al also reported higher E/Ea_{lat} in HFNEF compared to control subjects. An E/Ea ratio >8 was found in 86% of HFNEF patients, who showed a significant increase in all diastolic indexes compared with control subjects. The E/Ea_{lat} correlated best with LVEDP. (225)

Assessment of LV filling pressure

E/Ea and invasively determined LVEDP are positively and linearly correlated. In patients undergoing cardiac catheterisation for angina or HF, the correlation between mean LVDP and Ea_{sep} is consistently equivalent or better than the Ea_{lat} or the two together. The correlation is better in patients with impaired than in those with normal LVEF. The E/Ea_{sep} had the highest predictive accuracy for the mean LVDP when all patients were considered. E/Ea (pTDI) >15 had 86% specificity (64% positive predictive value) for mean LVDP >15 mm Hg (97% negative predictive value for E/Ea <8). (191) In patients who have had heart transplants, E/E_{lat} (pTDI) correlated strongly with the mean PCWP. An E/Ea ≥8 identified a mean PCWP >15 mm Hg with a sensitivity of 87% and a specificity of 81%. Changes in the mean PCWP were closely reflected in the changes in E/Ea_{lat}. A change in E/Ea >2.5 detected a change in PCWP ≥5 mm Hg, with a sensitivity of 77% and a specificity of 75%. There was no relation between changes in Ea and corresponding changes in PCWP, suggesting that the changes observed in Ea in the patients with transplants reflected the state of myocardial relaxation. (205)

Nikitin et al reported a higher 6-site averaged E/Ea (cTDI) in patients with HFNEF compared to controls. (57) Ea_{lat} was lower in patients with asymptomatic impaired relaxation and symptomatic HF with pseudonormalisation, compared to the normals. E/Ea_{lat} was elevated in the pseudonormal group compared with the other two groups. The mean PCWP correlated significantly with E/Ea_{lat} but not with Ea_{lat}. An E/Ea ratio >10

predicted mean PCWP >12 mmHg with sensitivity of 91% and specificity of 81% and mean PCWP >15 mm Hg, with a sensitivity of 97% and a specificity of 78%. (204) Nagueh et al divided patients with several cardiac conditions in sinus tachycardia into 3 groups according to the mitral inflow patterns a) fused E and A (sub-grouped as A1 if velocity peaked in the first half of the diastolic filling period and A2 if it did so in the second half), b) E<A and c) E>A. PCWP related weakly to Ea and Aa and strongly with E/Ea_{lat} irrespective of the inflow pattern and LVEF. PCWP >12 mmHg was predicted by E/Ealat >10 with sensitivity of 78% and specificity of 95%, >8 with sensitivity of 87% and specificity of 70% and >12 sensitivity of 68% and specificity of 96%. If patients with and without tachycardia are taken into account, PCWP >15 mmHg was best predicted by E/Ea >10 (sensitivity, 92%; specificity, 80%). (193) In patients with hypertrophic cardiomyopathy, the preA LVEDP correlated strongly to E/Ea. The changes in LVEDP matched changes in E/Ea. E/Ea ≥10 had the best combination of sensitivity (92%) and specificity (85%) for preA pressure >15 mmHg. (226) Amongst patients with atrial fibrillation, Ea correlated with tau and the E/Eá ratio correlated with LVDP. The E/Ea ≥11 predicted LVDP ≥15 mmHg (sensitivity 75%; specificity 93%). (227) In patients undergoing clinically indicated cardiac catheterisation E/E_{sep} correlated best with pre–A LVDP irrespective of the LVEF and the mitral inflow pattern. E/Ea_{sep} ≥9 best discriminated pre-A LVDP >12 mmHg from normal pre-A pressure (sensitivity, 81%; specificity, 80%). (228) In patients with normal or reduced LVEF undergoing right heart catheterisation, Rivas-Gotz et al showed that different cutoffs for E/Ea were needed to predict mean PCWP >15 mmHg depending on whether the LVEF was <50% or ≥50%. Best sensitivity and specificity were obtained when Ea (pTDI) was measured at the lateral annulus. E/Ea_{lat} >11 had a sensitivity and specificity of 85% and 82% respectively in patients with LVEF<50%. In subjects with LVEF ≥50% E/Ea >10 had a sensitivity and specificity of 79% and 80% respectively. In patients with wall motion abnormalities, a stronger correlation between the LVEDP and the E/Ea was obtained if the Ea was averaged over 2 or 3 periannular sites.(229) In patients with HFREF and HFNEF, PCWP correlated with E/Ea_{sep} irrespective of the LVEF. LVEDP >15 mmHg was identified by E/Ea_{sep} >11 in the HFNEF group (sensitivity, 94%; specificity, 90%; PPV, 94%; NPV, 91%) and by >14 mmHg in patients HFREF (sensitivity, 71%; specificity,100%; PPV, 100%; NPV, 39%). (230) Ea is reduced in comparison to normals and the E/Ea relates to

pre-A LVDP and to LVEDP in patients with aortic stenosis. E/Ea ≥13 identified an LVEDP >15 mmHg (sensitivity, 93%; specificity, 88%) (231) Amongst patients with a wide range of LVEF undergoing clinically indicated cardiac catheterisation, Hadano et al reported a poor correlation between E/Ea and LVEDP and a modest one between E/Ea and PCWP irrespective of the LVEF. E/Ea ≤14 predicted mean PCWP≤12 mmHg with 100% sensitivity and 85% specificity.(232)

The effect of exercise on E/Ea has been investigated. In healthy subjects all the mitral inflow velocities and the MAV increase proportionately with exercise thus leaving the E/A, E/Ea and Ea/Aa unchanged.(194) In patients with HFNEF, the E, Ea and the E/Ea increased with exercise. E/Ea ≤15 predicted normal PCWP (<20 mmHg) with a sensitivity of 89%. Conversely, in all cases where the E/Ea was >15, the PCWP was elevated. An E/Ea >15 during exercise was associated with PCWP >20 mm Hg.(233) Dyspnoeic patients with normal LVEF and no ischaemia underwent ESE. E/Ea increased with exercise in 35% of the patients with resting E/Ea <10 but did not increase in the rest of these patients or any patient with E/Ea >10. There was no significant difference in changes of mitral inflow indices (E, A, E/A, deceleration time) between groups. Exercise duration was significantly shorter in patients whose E/Ea increased with exercise and ones with resting E/Ea>10 compared to the one with E/Ea<10 both at rest and stress.(234) Using invasive measures as standard Burgess et al validated exercise induced changes in the E/Ea ratio in subjects with normal LVEF. Patients with a normal mean LVDP both at rest and exercise had the lowest E/Ea at rest with no change with exercise. Patients with an elevated mean LVDP only during exercise had a significant increase in E/Ea from rest to exercise. Patients with an elevated mean LVDP at rest had a high resting E/Ea with no significant change with exercise. E/Ea correlated with mean LVDP at rest and during exercise. An exercise E/Ea >13 had a sensitivity of 73% and a specificity of 96% for identification of an exercise mean LVDP >15. Ea and E/Ea had a better correlation with exercise capacity. Exercise E/Ea >10 had a sensitivity of 71% and a specificity of 69% for prediction of a reduced exercise capacity (<8 METS).(183)

Several studies show that the E/Ea ratio is related to the exercise capacity. In patients with HFREF the average of Ea measured at the septal and lateral annuli (Ea_{av}) and the E/Ea_{av} correlated with peak VO_2. (235) In patients with AF, E/Ea is an independent predictor of exercise capacity. Patients achieving ≤7 METs had higher E, higher E/Ea ratio and lower Ea than those patients showing a peak of >7 METs. (236) In patients with HFREF peak oxygen consumption correlates with Ea_{lat} and E/Ea_{lat} but not with conventional Doppler indexes. E/Ea_{lat} >11.3 predicts severe exercise intolerance with sensitivity of 88% and specificity 86%.(237) In patients with CAD and normal LVEF MAV increased and E/Ea decreased with increasing VO_2max. VO_2max independently predicted by Sm and E/E_{av}. Patients in the lowest VO_2max category had higher E and lower Ea velocities resulting in higher E/Ea values. Patients with lower MAV reached lower VO_2max. (238) Skaluba et al found that TDI was effective in predicting exercise capacity in patients irrespective of the LVEF. Resting Ea, Ea/Aa and E/Ea correlated with exercise tolerance. The best individual correlate of exercise performance was E/Ea_{sep} and only E/Ea_{sep} ≥10 was an independent predictor of reduced exercise tolerance in the multivariate analysis. E/Ea_{sep} ≥10.6 had a sensitivity and specificity of 85% and 88% respectively in predicting exercise capacity of <7 METS. Patients with E/Ea_{sep} <10 performed better on the treadmill than the patients with E/Ea ≥10. Exercise capacity was similar in patients with a normal mitral inflow pattern and those with a slow relaxation pattern when E/Ea was <10. In contrast, the subjects with slow relaxation and E/Ea_{sep} ≥10 performed nearly as poorly as did the groups with pseudonormal/restrictive LV filling patterns. (239)

In patients assessed for suspected HF, E/Ea >15 had 83% sensitivity and 82% specificity for confirming the diagnosis in the overall population. E/Ea >15 predicted presence of HF with 79% sensitivity and 93% specificity in patients with normal ejection fraction and 92% sensitivity and 72% specificity in patients with reduced ejection fraction. Overall, BNP and E/Ea have similar diagnostic accuracy for CHF in this patient population.(240) In patients with suspected HF and normal LVEF, E/Ea_{av} of 11.5 (sensitivity, 80%; specificity, 94.3%) E/Ea_{lat} of 9.8 (83.3% and 88.9%) and E/Ea_{sep} of 12.7 (76.7% and 91.4%) predicted HF. E/Ea ratios and BNP provided similar accuracy for predicting decompensated HF. E/Ea_{av} yielded independent additional information to a model based on the

clinical judgment and BNP level.(241) In patients with new onset acute dyspnoea, indeterminate BNP, normal LVEF and no radiological pulmonary oedema, average E/Ea >10 was a powerful predictor of congestive HF (sensitivity 100% and specificity 78.6%).(242) In chronic hypertensive patients with acute dyspnea and normal LVEF the E/Ea >11 precisely predicted the diagnosis of HF (sensitivity 77.8%, specificity 100%, and accuracy 89.5%).(243)

Some caution is to be exercised when interpreting estimates of PCWP or LVEDP from the TDI. cTDI and pTDI measurements are not interchangeable. Though the systolic and diastolic velocities quantified by the two methods correlate very well, those measured with cTDI are lower than pTDI. Consequently, E/Ea by cTDI is higher than by pTD1.(244) The site of the measurement (septal versus lateral) and the LVEF influence Ea and consequently the E/Ea ratio. E/Ea is unreliable for predicting LV diastolic pressures in healthy subjects and organic mitral valve disease. The Ea_{sep} and Ea_{lat} are lower, the E/Ea_{lat} is higher and E/Easep is similar in patients with abnormal septal motion (secondary to LBBB, paced-rhythm, myocardial infarction and cardiac surgery) compared to patients with normal septal motion. The E/Ea_{sep} and E/Ea_{lat} correlated well with PCWP in patients with normal septal motion but not in patients with abnormal septal motion. In patients with abnormal septal motion, TDI methods overestimate PCWP at lower invasive PCWP levels and vice versa.(245)

Regional myocardial function

Diagnosis of ischaemia

CAD is characterised by resting and/or inducible regional myocardial dysfunction. Due to their subendocardial location, the longitudinal muscle bundles of the LV are highly susceptible to ischaemia resulting in the decrease of longitudinal velocities very early with onset of ischaemia. TDI, by virtue of its ability to measure this longitudinal velocity, is a very sensitive tool to detect this ischaemia.

Regional abnormalities of MAV and MDVs at rest are often seen patients with myocardial infarction. Following myocardial infarction, the systolic velocity at each mitral peri-annular site reflects the impaired regional contractility of that

wall. (246;247) The peak systolic amplitude of mitral annular motion is lower at all sites compared to the healthy controls. (247)

Gorcsan J III et al tested the potential of cTDI to quantify regional myocardial dysfunction in open-chest canine model of coronary occlusion using sonicometry as the standard of reference. The peak systolic endocardial velocities from cTDI and myocardial shortening velocity and fractional shortening from sonomicrometry decreased in the territory of coronary occlusion. The peak endocardial velocity was inversely correlated with end-systolic length by sonomicrometry during baseline and induction of ischaemia. (248) In porcine model, Derumeaux et al demonstrated that a reduction in myocardial blood flow assessed by radioactive microspheres mediated by occlusion of the left anterior descending artery resulted in a decrease in systolic shortening measured by sonicometry and systolic velocity measured by pTDI of the septum. There was a significant correlation between the variations of systolic velocity and systolic shortening. Following LAD occlusion, the systolic velocity decreased within 5 seconds and peaked at 1 minute. One minute after reflow, the systolic velocity increased reaching positive values corresponding to the hyperemic phase. It progressively decreased within 5 minutes of reperfusion as the myocardium developed post-ischaemic stunning. (249) In canine model, baseline, endocardial velocities were higher than epicardial velocities. Ischaemia caused a significant and comparable reduction in endocardial and epicardial systolic velocities with the disappearance of the velocity gradient. Systolic velocities significantly correlated with segment shortening in both endocardium and epicardium during ischaemia and reperfusion. In the first minutes after reflow, endocardial velocities showed a greater improvement than epicardial velocities, and the velocity gradient resumed although to a limited extent, indicative of stunning. (81)

Coronary occlusion in humans led to similar changes in MDVs. Edvardsen et al demonstrated a decrease in the Sm and Em in segments supplied by the LAD in a response to LAD occlusion during angioplasty. Furthermore, during early diastole, the ischaemic segments showed a post-systolic contraction pattern. Reversed systolic wall motion during mid systole and marked positive velocity during early diastole was thought to indicate myocardial ischaemia. (250) Bach

et al demonstrated a similar drop in Sm in segments subtended by the angioplasty vessels during occlusive balloon inflation. During early reperfusion, Sm exceeded baseline values. In regions remote from the treated artery, peak Sm increased in the absence of significant stenosis but remained unchanged or decreased in the presence of significant stenosis of the associated vessel. (251) In a similar study, coronary occlusion during angioplasty resulted in the reduction in myocardial velocity in "at risk" segments. Velocity alone had sensitivity and specificity of 68% and 65% respectively for identifying acute ischaemia in segments that were either normal or abnormal at baseline. In "at risk" segments that were visually abnormal at baseline, velocity parameters alone failed to distinguish between baseline and occlusive measurements. The authors concluded that quantitation of regional deformation rather than motion is better in detecting and quantifying acute ischaemic changes in myocardial function, especially in segments with pre-existing abnormal function. (252)

These observations encouraged the application of TDI in detection of inducible ischaemia in conjunction DSE or ESE. Gorcsan III Jr et al investigated the effect of positive and negative inotropy on endocardial velocities. In the canine model, the Sm, Em and Am increased with dobutamine infusion without changes in the heart rate. Esmolol infusion had an opposite effect. Increase in peak endocardial velocity from all sites were significantly associated with changes in fractional shortening and regional stroke work measured by sonicometry and in global LV performance measured by conductance catheters confirming the ability of endocardial velocity to reflect changes in regional contractility. (253) In normal human volunteers, MAV and MDVs were sensitive enough to detect changes in myocardial contractility even at very low doses of dobutamine stimulation. Sa increased significantly with only 1 μg/kg/min of dobutamine and progressively thereafter a linear dose-dependent manner suggesting an incremental dose-dependent alteration in global and regional LV function. These alterations were detected by TDI at doses of dobutamine infusion that was lower than where changes were detected by routine measures of wall thickening or ejection fraction in the same subjects. (254) Yamada et al reported similar progressive increase in Sm with increasing dose of dobutamine in normal segments averaging an increment of 148% at peak dose. The base-apex gradient in Sm persisted at low dose. There were no differences in the

velocities recorded at basal or mid segments of the different walls. Ischaemic and scarred segments demonstrated a significantly lower Sm in all stages of the protocol and the lowest percentage increase in Sm when compared with the normal segments. Basal and mid-ventricular ischaemic segments had similar Sm and percent increment from rest to peak. The Sm responses of ischaemic and scarred segments were similar at low dose. Ischaemic segments were not discernible from nonischaemic segments based on Sm at rest or low dose. However, the ischaemic segments had a significantly lower Sm at peak dose with a tendency to show a lower percentage increase from rest to peak. Sm <12 cm/s at peak dose identified ischaemic segments with a sensitivity of 86% and specificity of 96% for basal and a sensitivity of 81% and specificity of 89% in the mid segments. An increment of <90% in Sm from rest to peak, identified ischaemic segments from normal segments with a sensitivity and specificity of 83% and 87%, respectively.(188) Using cTDI, Katz et al demonstrated that at peak dobutamine stress velocities of abnormal myocardial segments were lower than normal ones. Peak systolic velocity of ≤ 5.5 cm/s had a sensitivity, specificity and accuracy of 96%, 81% and 86% for identifying abnormal segments irrespective of the segmental sites.(255) The mean peak Sm for the hypokinetic and akinetic posterior walls were significantly less than normal controls and correlated with percentage of wall thickening. (256) Using pTDI and quantitative coronary angiography Rambaldi et al predicted a significant proximal RCA stenosis (≥50% diameter stenosis) with a decrease and/or <25% increase in segmental ejection phase velocities of the RV free wall from the 10μg/kg/min of dobutamine to peak stress. This had sensitivity of 82%, specificity of 78%, positive predictive value of 69%, negative predictive value of 88% and accuracy of 79%. (257) In addition to decrease in the Sm with dobutamine, MVG fails to increase in the ischaemic segments but there is a dose-responsive increase in the non-ischaemic segments.(258)

Using visual assessment of wall motion by an expert interpreter as standard reference, Pasquet et al tested the power of TDI (cTDI measured in all segments and pTDI in basal segments) to detect myocardial ischaemia following exercise treadmill testing in patients with known or suspected CAD. Scarred segments had lower Sm than normal segments at rest and stress. Ischaemic segments had a lower Sm and less increment in velocity than normal

segments. The authors concluded that TDI with ESE is feasible and TDI is a useful quantitative tool for interpretation of ESE. (259) The same investigators, using exercise dual isotope SPECT perfusion imaging to identify abnormal myocardial segments, demonstrated that a) resting base-apex gradient of Sm persisted at peak exercise and the increment in Sm with stress was similar in the basal and mid-segments in normal ventricles, b) segments with rest perfusion defects had a lower Sm than normal segments, c) Sm in segments with stress-induced perfusion defect were similar to the normal segments at rest but lower at peak exercise d) Sm of scars were lower than ischaemic segments at rest but similar to them at peak and e) increments in MDV was greater in the normal segments than ischaemic and scarred segments but it was similar in the later to groups. (260) Dagianti et al, using coronary angiogram as the standard reference, demonstrated that Sm at infarct sites were lower than at normal sites at rest in patients with remote myocardial infarction. At peak exercise stress in patients with multivessel disease, Sm at remote regions was significantly lower compared with control subjects. (261) Wilkenshoff et al demonstrated that the Sm of the non-apical segments of all the walls increases with exercise stress in normal subjects. These increases were not altered with adjustment for heart rates. The base-apex gradient persisted in all walls throughout exercise in normal individuals. There was a relatively higher percentage velocity increase in apical and mid segments compared with basal segments.(214)

Sm responses to exercise and pharmacologic stress appear to be different. At least in one study, where the heart rate at peak dobutamine exceeded that after exercise, Sm at peak stress in both normal and abnormal segments was greater with dobutamine than with exercise. The increase in Sm in relation to changes in heart rate induced by dobutamine was greater than by exercise in normal but similar in abnormal segments. Sm correlated better with peak heart rate with exercise than with dobutamine.(262) The velocity of normal myocardial segments increased by 148% when measured by pTDI. (188) When measured by cTDI, it increased by 100% at maximum dose of dobutamine and by 107% with maximal exercise. (259)

In clinical practice, ischaemia is detected when the Sm at peak stress falls below a pre-validated level. These absolute cut-off levels have been derived

both using velocity ranges from normal populations and using more complex mathematical modelling. Absolute cut-off levels are difficult to establish as there is an intrinsic heterogeneity of Sm, as discussed earlier and the normal Sm are influenced by heart rate and loading conditions at peak stress. However, most normal patients develop similar velocities at peak stress, and it is only at the extremes of age that haemodynamics and volumes exert important effects on normal velocities. (263) Although the velocities of basal and mid-wall segments are different at baseline, the relative increases in velocities for each segment are the same at peak stress. A less than normal increment in velocity with maximal stress is indicative of ischaemia. Moreover, there are some suggestions that changes in Sm during ejection do not appropriately reflect changes in myocardial contractile dysfunction when ischaemia is severe. Though the peak velocities during ejection decrease with moderate ischaemia, severe ischaemia and the resulting dyskinesia is reflected in decreased velocities in the isovolumic contraction phase rather than during ejection. (264)

Using cTDI, Cain et al derived normal range of velocities at peak stress of each non-apical segment from subjects with low probability of coronary disease, those with normal wall motion, and those without coronary disease seen on angiography. The lower 20th percentile velocity value for each segment was identified to establish a lowest cut-off value. The intrinsic heterogeneity of Sm precluded the use of a single cut-off level. At peak stress, the lower limits of normal in the basal and mid paraseptal segments were 7 and 5 cm/s, respectively, whereas in the basal and mid–free wall segments, the lower limits were 6 and 4 cm/s, respectively. These cut-off values, detected coronary artery disease with 83% sensitivity, 72% specificity and 80% accuracy compared to coronary angiogram. The sensitivity, specificity and accuracy were 80%, 74% and 77% in the LAD territory, 76%, 64% and 68% in the LCx territory and 56%, 75% and 66% in the RCA territory. (265) The MYDISE investigators used logistic regression models that included systolic velocity at maximum stress, age, sex and peak heart rate to predict coronary artery disease with sensitivity and specificity of 80% and 80% for LAD territory, 91% and 80% for LCx territory and 93% and 82% for RCA territory. Using receiver-operator curves for peak Sm as the only discriminator between patients with normal and stenosed coronary arteries, they obtained cut-offs of 10.3 cm/s in basal anterior segment

with sensitivities and specificities of 63% and 60% for LAD disease, 10.8 cm/s in basal lateral segment with sensitivities and specificities of 69% and 67% for Cx disease and 12.8 cm/s in basal inferior segment with sensitivities and specificities of 69% and 67% for RCA disease. (218) On average, peak systolic velocity increased ≥100% in healthy subjects compared with 50–75% in patients with coronary disease. Sm at peak stress was found to be a better discriminator of disease, than was its change from baseline to maximal stress with dobutamine.(218)

Diagnosis of viability

TDI has been used with LDDSE to detect viability in dysfunctional myocardium and predict its recovery after revascularisation. Using pTDI, Altinmakas et al demonstrated that the Sm of dysfunctional but viable segments increase more than the non-viable ones with 10μg/kg/min of dobutamine. An increase of more than 35% in segmental velocities predicts functional recovery after revascularization with 89% sensitivity and 86% specificity. The sensitivity, specificity, the positive and negative predictive value of the pTDI measurements was higher, though not significantly, compared to visual assessment alone. However, the sensitivity and the negative predictive value significantly increased when visual and TDI assessments were combined. (266) Larrazet et al reported TDI to be at least as accurate as visual assessment for viability detection and more sensitive than it when rest-reinjection Tl-201 SPECT was considered as the reference. When TDI and visual assessment were combined, the agreement between echocardiography and TDI increased further. TDI tended to reveal more viable segments than visual assessment. (267) Ramabaldi et al compared the accuracy of pTDI with LDDSE for detection of myocardial viability confirmed using F18-fluorodeoxyglucose imaging. Sm during low-dose and peak-dose dobutamine were significantly higher in viable myocardium. An increase in Sm using pTDI at low-dose of 1±0·5cm/s indicated viability in that segment while 0±0·5cm/s predicted non-viability. The sensitivity and specificity of the pTDI were 87% and 52% and that of LDDSE 75% and 51% respectively. (268)

Some studies have reported an increased diagnostic accuracy of DSE with application of the TDI techniques. This technique increases the accuracy of

detection of CAD over and above the visual assessment even when used by less expert readers.(198) TDI detects impaired regional LV contractility not seen on visual analysis of images. (269) The Sm correlate to wall motion scoring (259) and independent markers of ischaemia such as SPECT myocardial perfusion imaging. (260) However, there are suggestions that the sensitivity for detecting the presence of CAD using TDI techniques has not been advanced compared with wall-motion evaluation by an expert reader. (164)

Role in dyssynchrony

Regional systolic and diastolic synchronicity can be evaluated by TDI comparing the time to peak systolic contraction and early diastolic relaxation of multiple segments. A number of parameters based on TDI have been proposed to evaluate intra-ventricular dyssynchrony. The delay between the onset of electrical activation (onset of the QRS complex) and the peak of mechanical contraction (the peak systolic velocity either during ejection (Ts) or at any time within the cardiac cycle) is measured in each non-apical segment of the left ventricular or the free wall of the right ventricular. Intra-ventricular dyssynchrony may be measured as the difference in Ts at the basal septal and lateral segments, (270) standard deviation of Ts of all non-apical segments, (271;272) maximum difference of Ts for 6 basal segments, maximum difference of time to peak systolic displacement for 4 segments and maximum difference of time to onset of systolic velocity for 6 basal segments. (273) The difference between the longest and shortest delays between the onset of the QRS complex and the peak systolic velocity measured in each of the 6 basal segments at any time in the cardiac cycle has also been measured. (274) Inter-ventricular dyssynchrony can be measured as the difference between the Ts at the basal segment of the RV free wall and the basal segment of the lateral LV wall or most delayed LV segment. (275) Yu et al demonstrated the presence of intra-ventricular systolic and diastolic dyssynchrony in patients with heart failure with and without prolonged QRS duration. (94)

Tissue Doppler imaging has been extensively used in an attempt to quantify intra- and inter-ventricular dyssynchrony and to predict the response to CRT. Though several small studies reported the value of mechanical dyssynchrony as measured by TDI parameters in predicting response to cardiac

resynchronisation therapy, (270-272;274;276-279) a large multi-centre clinical trial failed to do so. (273) TDI parameters of interventricular delay have not been shown to predict the improvement of cardiac function. (271) In patients with CHF, the degree of intraventricular and interventricular asynchrony and their combination are the best predictive factors of LV functional recovery and reversed remodeling after cardiac resynchronisation therapy. (275) Severe dispersion of regional Ts has been shown to strongly predict responders of reverse remodeling. (271;272) Mechanical dyssynchrony has also been demonstrated in nearly half of the patients with normal QRS duration. (94) Prevalence of responders of reverse remodeling is lower in patients with narrower QRS duration (120–150 ms), possibly due to the less severe mechanical asynchrony as reflected by a lower Ts-SD. This has been confirmed in larger clinical trail. (280)

Conclusion

Tissue Doppler imaging alone and in adjunct to stress echocardiography has application in the assessment of the left ventricle in a wide variety of cardiac conditions. As these conditions are commonly prevalent in patients with suspected heart failure, TDI with DSE is likely to be useful in evaluating these patients.

Chapter 4: Safety and Applicability of DSE with Tissue Doppler Imaging In an Unselected Population of Patients with Suspected Heart Failure.

ABSTRACT

Background: Symptoms suggestive of heart failure (HF) is common in the general population. As these symptoms are usually induced by exercise and are often absent at rest, cardiac function assessed at rest potentially leaves some patients whose cardiac dysfunction occurs only during stress, undiagnosed. The feasibility, safety and the applicability of DSE with cTDI in an unselected population of patients with suspected heart failure were studied. Method: 548 subjects referred to a heart failure clinic with suspected heart failure were screened. 207 of these underwent DSE with cTDI using standard dobutamine atropine protocol. The segmental systolic function, long axis systolic and diastolic functions were visually and quantitative assessed. Results: DSE was applicable to 436 patients. 274 were referred for DSE that was done on 207 patients. DSE was feasible in 183 patients. About 27% of the recruited patients had to be excluded due to poor image quality. Complications occurred in 6 patients: transient ST-elevation in 2 and sustained monomorphic VT in 4. The reproducibility of the cTDI measurements was good. Systolic and diastolic myocardial velocities could be satisfactorily obtained in >90% of the segments. Conclusion: From among the heterogeneous population of elderly subjects with multiple co-morbidities with suspected heart failure expected in heart failure clinic, DSE with cTDI is feasible in only a highly selected group of patients. There may be some safety concerns in this group.

INTRODUCTION

An estimated 5-7% of the Western European population is suspected to suffer from heart failure (HF). (15) Multiple cardiovascular pathologies that culminate in left ventricular (LV) dysfunction leading to HF are likely to be highly prevalent amongst these patients. However, assessment of the LV at rest as recommended in the current guidelines for the diagnosis of HF, (1) may not adequately elicit these functional abnormalities. This potentially leaves a proportion of patients whose cardiac dysfunction occurs only during physiological stress giving rise to symptoms, undiagnosed. Additionally, valuable diagnostic and prognostic information may be missed in patients with and without resting LV dysfunction. Thus evaluation of cardiac function under stress could potentially be useful in assessing patients with suspected heart failure.

Patients encountered in heart failure clinics are often elderly, infirm with musculoskeletal co-morbidities and breathless on exertion, all of which significantly limits their exercise capacity. DSE is very well suited for the assessment of this population. DSE is reported to be feasible in patients with coronary artery disease, (159;281-289) LV systolic dysfunction (290;291) and hypertension (292;293) and in the elderly (294-298). These reports are retrospective analysis of data obtained on patients who underwent DSE for established clinical indications, and selected in terms of their echocardiographic image quality, suitability to tolerate the procedure and the absence of contraindications. The applicability of DSE in an unselected population with multiple cardiovascular and non-cardiovascular co-morbidities is unknown. (159)

The limitations of DSE are its subjective interpretation (182) and dependence on image quality (159) and interpreter expertise. (181) Analysis of myocardial motion using cTDI could potentially overcome these shortcomings. (198) cTDI is used to quantitate the regional and long axis systolic and diastolic function of the LV in patients with wide variety of cardiac conditions. However, there is limited data on the feasibility of this technique in association with DSE. (299) The feasibility, safety and the applicability of DSE with cTDI in an unselected population of patients with suspected heart failure was studied.

METHOD

Patient selection

Between November 2001 and August 2003, subjects referred to a community-based heart failure programme, serving a mixed urban and rural population of 600,000, with a suspected diagnosis of HF, were screened. Physicians were asked to refer any patient in whom the diagnosis of heart failure was being considered including those with breathlessness and/or evidence of fluid retention or receiving a loop diuretic. The diagnosis of HF was based on clinical evaluation by a cardiologist on the basis of the patients' previous and current history and physical examination. In concordance with the ESC definition of HF, (1) most had previous hospital admissions with acute breathlessness, clinical and/or radiological evidence of pulmonary congestion and clinical improvement with diuresis. The inclusion criteria were age above 18 years (no upper limit was set) and referral for assessment of suspected heart failure. The exclusion criteria were refusal or an inability to consent, inadequate echocardiographic window, contraindication to DSE (myocardial infarction, unstable angina, pulmonary oedema or stroke within the last 2 weeks, angina or arrhythmias within last 48 hours, known left main stem stenosis, severe life threatening tachyarrhythmias, severe valvular stenosis, implanted pacemakers, hypertrophic cardiomyopathy, resting systolic blood pressure ≥180 mm Hg, known sensitivity to dobutamine), advanced malignancy and immobility severe enough to constrain acquisition of echocardiographic images. Other cardiovascular conditions in which the physician would consider dobutamine stress unsafe were also excluded. Patients who had only temporary contra-indications for stress echocardiography were recalled for testing later. It was accepted that not all subjects would be suitable for DSE. However, rather than selecting subjects for the study, DSE was offered to all recruited, unless contra-indicated. The reason why DSE was deemed inappropriate or not performed was documented. Written informed consent was obtained. Medical Ethics Committee of the Hull and East Yorkshire NHS Trust approved the protocol.

All subjects underwent routine clinical examination, a 12 lead ECG, chest X-ray, pulmonary function test (hand-held spirometry) and a standardised 6-minute hall walk. The patient underwent full echocardiographic examination using a 2.5-MHz phased-array transducer (GE Vingmed Vivid Five scanner, Horten,

Norway). A standard set of images was acquired at rest. (118) cTD images of 3 cardiac cycles in 3 apical views (4-chamber, 2-chamber and 3-chamber), were stored digitally and reviewed off-line (Echopac 6.3, GE,Vingmed). LV volumes were calculated from manually traced endocardial borders in the apical 4 and 2 chamber views using the modified Simpson's rule and LVEF was calculated. E and A velocity, EDT and IVRT were measured.

Stress echocardiography

Subjects with adequate echocardiographic windows and without any contraindication underwent DSE within 6-8 weeks of referral using a standard dobutamine-atropine protocol, 48 hours after stopping beta-blocker.(103) A patient had to be free of pulmonary oedema, angina or significant arrhythmias for at least 48 hours before the test. The pre-specified end-points were attainment of target heart rate (THR) {85% of (220-age in years)} and/or evidence of ischaemia i.e. new or worsening regional wall motion abnormality, intolerable symptoms of chest pain or severe breathlessness with ≥2 mm flat or down-sloping ST depression or ≥1 mm ST elevation in any of the leads, recurrent ventricular couplets or triplets, single run of non-sustained ventricular tachycardia (defined at ≥5 consecutive ventricular ectopics), sustained ventricular tachycardia or new atrial fibrillation. Side effects of dobutamine, symptoms with no or minor ECG changes, any other arrhythmias, persistent hypotension (reduction in the systolic blood pressure by ≥20 mm Hg on two consecutive recordings) with or without bradycardia or hypertension (systolic blood pressure ≥220 mm Hg) were considered complications of the procedure. The test was "feasible" if a pre-specified end-point was reached or the maximum dose of dobutamine was reached without reaching an end-point. The test was "incomplete" if a test was terminated due to a complication or deterioration of image quality. Intravenous atropine was not administered if there was a history of glaucoma or urinary retention. If needed, dobutamine effects were reversed by a short acting IV beta-blocker, esmolol at a standard dose.

Standard images (103) (3 cycles edited to exclude ectopic beats and without undue translational motion) in grey-scale with superimposed cTD data were acquired at rest and in the final 60 seconds of each stage with breath held in

expiration under continuous 12-lead ECG and intermittent non-invasive blood pressure monitoring. The sector angle and depth were adjusted to achieve highest possible frame rates. Imaging was continued 9 minutes into recovery or till the ECG-changes at peak stress returned to normal. The loops were digitally stored. The 2-D grey scale images were analysed in a quad-screen format and the cTD images were analysed using customised software (Echopac TVI, GE Vingmed). The mitral inflow and the LVOT were interrogated with pulse-wave Doppler at each stage.

Using a 16-segment model of the LV, (118) segmental wall motion was classified as "normal", "hypokinetic", "akinetic", or "dyskinetic" based on a subjective visual evaluation of endocardial motion and degree of wall thickening. Wall motion score (WMS) was assigned to each segment as recommended (1= normal, 2=hypokinesia, 3=akinesia and 4=dyskinesia).(103) Segments with 'mild' or 'questionable' hypokinesia and those appropriately "hyperdynamic" at peak stress was graded normal. Segmental response to dobutamine was classified as "normal", "viable", "biphasic", "ischaemic" or "scar".(103) WMSI (sum of the wall motion scores of the interrogated segments divided by the number of segments interrogated) was calculated at rest, low dose dobutamine and peak stress.

The E and A velocities, EDT and IVRT were measured at rest, low dose of dobutamine and peak stress. If there was fusion of the E and A velocities at peak stress, these were measured at the latest stage (i.e. the highest heart rate) at which separate peak velocities could be appreciated. The EDT and IVRT were corrected for the heart rate using Bazett's formula {EDTc or IVRTc (msecs) = EDT or IVRT (msec)/$\sqrt{}$R-R interval (secs)} to allow comparison of these variables at different heart rates.

In the cTDI mode, the myocardial velocity curves were reconstituted by placing a 5 mm sample cursor at mitral annulus and the midpoint of each of the non-apical segments of the six walls in the 3 apical views. No tracking algorithm or angle correction was used. The systolic myocardial (Sm) and mitral annular (Sa) velocity during ejection, early diastolic (Em, Ea) velocity and late diastolic (Am, Aa) velocity were measured at rest, 10 mcg/kg/min of dobutamine and peak

stress. If the diastolic velocities at peak stress were fused, these were measured at the highest heart rate at which separate velocities could be appreciated. The 6 peri-annular velocities were averaged. (57;58;212) E/Ea was calculated from early diastolic transmitral velocity and the averaged mitral annular velocity.

Reproducibility

A single observer, blinded to the clinical and echocardiographic characteristics of the patients, measured the systolic, early diastolic and late diastolic myocardial velocities and the time to peak velocity at the mitral annulus and the 12 non-apical segments twice in 10 randomly selected patients at rest and peak stress. Differences in the paired measurements were calculated and reported as mean±SD. Confidence limits (95%) of differences were computed and expressed as absolute values and percentages of the average values of paired velocity measurements.

Patient classification

Patients were allocated into one of three groups dependent on symptoms and left ventricular ejection fraction (LVEF).

Group 1: LVEF ≤45% and symptoms of heart failure: 'heart failure-LVSD' (HF-LVSD) group. One patient, with LVEF <45% and no symptoms of heart failure (asymptomatic LVSD), was considered in Group 1.

Group 2: LVEF >45% and symptoms of heart failure: "heart failure with normal ejection fraction" (HFNEF) group.

Group 3: LVEF >45% and no symptoms of heart failure: 'No heart failure' (NoHF) group.

Statistical analysis

All analyses were performed using commercially available software (SigmaStat v 3.5, Systat Software, Inc. San Jose). The continuous variables were described as means and standard deviations and the categorical variables as percentages. The data was tested for normal distribution using the Kolmogorov-Smirnov Normality test. The means between the study groups were compared by Student's unpaired *t* test assuming unequal variance and Mann-Whitney Rank Sum test as appropriate. The data at rest and peak stress within each group

were compared by Student's paired *t* test and Wilcoxon Signed Rank test as appropriate. Multiple groups were compared using ANOVA with post-hoc Bonferoni analysis or ANOVA on Ranks. Proportions were compared using the Chi-square test. A two-tailed p value <0.05 was considered significant.

RESULTS

Five hundred and forty eight non-consecutive but unselected subjects were screened. (Figure 1) Twenty-four (4.4%) patients, who were admitted in hospital at referral died before consenting, 14 (2.6%) (median age 86 years) were deemed unfit to consent, 58 (10.6%) had contraindication to DSE (the commonest being significant valvular lesions) and 16 (2.9%) were not suitable for DSE. Of the 436 (79.6%) subjects eligible for the study, 89 (20.4%) (median age 82 years) refused consent. Three hundred and forty-seven subjects (63.3%) were thus recruited. The attending cardiologists did not refer 73 (21.0%) patients due to inadequate echocardiographic windows. Of the 274 subjects referred for DSE and the test was done in 207 (75.5 %) subjects. Of these patients, 183 patients (feasibility of 88.4%) reached a test end-point.

Feasibility

Sixty-seven referred subjects were excluded from the test. (Figure 1) Patients with persistent or permanent atrial fibrillation developed rapid ventricular response upon withdrawal of beta-blockers. Though the THR was expected to be reached quickly in these patients, it was anticipated that the stress images would be uninterpretable. Twelve patients requested test termination within the first two levels of dobutamine infusion due to subjective symptoms. Patients with resting SBP≥180 mmHg despite replacement of the beta-blockers with other anti-hypertensives were excluded after two attempts. Eight patients with persistent severe heart failure were deemed too unwell for the test. Two patients had pacemakers implanted, 1 for CRT and 1 for complete heart block, between referral and the test. Two patients were awaiting implantable cardioverter defibrillator implantation. One patient was diagnosed with bronchogenic carcinoma.

Of the patients who underwent DSE, the test was "completed" in 183 patients (feasibility of 88.4%) (THR reached in 27, new RWMA 149, angina with ST-

segment depression 5 and was inconclusive in 2). The test was prematurely terminated in 24 patients: image deteriorated during the test in 9 (4.3%), 7(3.3%) developed NSVT without evidence of ischaemia, hypotension in 6(2.9%) and hypertension in 2(1%). The 9 patients whose images deteriorated very early in the test have been included "DSE not done" group for further analysis.

Baseline characteristics

The clinical characteristics of the study population are described in Table 1. The recruited patients were younger, predominantly male and with less valvular heart disease than those not recruited. Subjects aged ≥75 years were less frequently recruited (38.6% of those recruited versus 57.7% of the non-recruited, p=0.000). The subjects who "completed" DSE were younger, had lower mean BMI and a lower prevalence of COPD. Elderly patients completed DSE less frequently (33.5% amongst those who did versus 44.9% amongst those who did not, p=0.031). Only 28.8% had normal BMI. Chronic and paroxysmal AF was present in 19% and 8% respectively in subjects who underwent DSE compared to 25% (p=0.26) and 6% (p=0.47) respectively in subjects who did not. There were no differences in prevalence of risk factors and medication use between the two groups. The prevalence of heart failure symptoms and abnormal LV systolic and diastolic parameters was similar in the groups that did and did not undergo DSE. (Figure 2)

Response to stress

The response to stress of the 200 patients is shown in table 2. The mean peak dose of dobutamine needed to reach an end-point was similar in patients with LVSD and those without and in those who did and did not reach THR (29.9±9.2 µgm/kg/min versus 32.1±7.8 µgm/kg/min respectively, p=0.064), a pre-specified end-point (31.3±8.5 µgm/kg/min versus 30±7.6 µgm/kg/min respectively, p=0.681) or developed RWMA (31.2±8.4 µgm/kg/min versus 31.3±8.5 µgm/kg/min respectively, p=0.921). The THR was reached in 83 (41.5%) subjects, 22(26.5%) of who were in persistent AF during DSE. The mean peak dose of dobutamine in these patients was 31.2±8.5 µgm/kg/min.

Sixteen (8%) patients, all of whom were in sinus rhythm, needed atropine. Seven (40%) reached THR (concomitant RWMA in 3, NSVT in 1) and 9 patients

(new RWMA in 7, non-diagnostic test in 2) did not. Atropine did not affect the maximum heart rate (124±15 with versus 124±13 without, p=0.933) or % of the THR achieved (95.9±7.8% with and 96.3±10.6% without, p=0.903). The proportion of patients achieving THR (44% versus 41%, p=0.849) or a diagnostic test (88% versus 92%, p=0.55) with and without atropine was also similar. The resting heart rates were higher in the patients who reached THR compared to those who did not (79±15 v 74±12, p=0.012). Atrial fibrillation at rest was more prevalent in patients who reached THR (27.8% v 13.7%, p=0.021). Amongst patients in sinus rhythm, there was no difference in the resting heart rates of patients who did and did not reach THR (77±14 v 74±12, p=0.120). A diagnostic result was achieved most frequently (34.6%) at 30 µgm/kg/min of dobutamine followed by 40 µgm/kg/min (32.7%).

Reasons for discontinuation of the test

The reasons for test termination are shown in table 3. Stress induced ischaemia was identified in 156 (78%) patients, manifesting as new RWMA in 146 and ischaemia on ECG with chest pain in 10.

Major Complications

Six patients (3%), all with new RWMA, had major complications (sustained VT and MI). There were no deaths. Four patients (mean age 74±6 years, 3 male, mean LVEF 28±5%, with prior MI, and with RWMA at peak stress, 2 in sinus rhythm and 2 in atrial fibrillation) endured haemodynamically stable self-terminating sustained ventricular tachycardia at peak stress. They were monitored overnight without any further therapy. . Two patients (75 years (LVEF 19%) and 79 years (LVEF 33%), males, previous MI, new RWMA) had transient anterior ST elevation with minor increase in troponin but no new Q-waves. They were both treated with intravenous heparin and nitrate.

Minor complications

Minor complications (hypotension, hypertension and all other new onset arrhythmias) were seen in 70 (35%) patients leading to test termination in 15 (7.5%).

Hypotension was seen in 17 (8.5%) patients (5 had prior MI, 5 developed RWMA). These patients were younger (64±8 years v 69±10 years, p=0.04), had higher mean LVEF (56±19% v 46±17%, p=0.02), lower prevalence of LVSD (23.5% v 56.3%, p=0.010) and comparable systolic (147±25 mmHg v 140±22 mmHg, p=0.200) and diastolic (86±10 mmHg v 81±13 mmHg, p=0.150) blood pressure compared to those that did not. LVOT gradient increased in 6 patients, 4 of whom were bradycardic. Hypotension led to test termination in 6 patients (all with normal LVEF, 3 of whom had increased LVOT gradient and bradycardia). Compared to others with hypotension, these patients were younger (57±4 years v 68±8 years, p=0.03) and had higher resting diastolic pressure (95.5±3.1 mmHg v 80.6±8.9 mmHg, p=0.001). Three other patients (1 with bradycardia) had hypotension with increased LVOT gradient (2 reached THR and 1 had RWMA). Hypotension was associated with chest pain and ischaemia on ECG in 2 patients (both with normal LV function but without new RWMA at 80% of THR) and NSVT in 2 patients (normal LV function) at 97% and 91% of the THR respectively. Three patients with hypotension needed fluid resuscitation and 3 with additional bradycardia responded to atropine alone.

Hypertension (≥ 220 mmHg) was seen in 14 (7%) patients (all known hypertensives) leading to test termination in 2 (1%). The test was terminated for ischaemia on ECG in 3, achieving THR in 1 and developing new RWMA in 8. Hypertension settled spontaneously after termination of protocol in all except 3 patients who needed intravenous nitrates.

The commonest dysrrhythmias included ectopic ventricular and supraventricular activity. These did not lead to test termination. Induced ventricular dysrrhythmias (p=0.461) and AF (p=0.504) were as frequent amongst patients who received atropine as those that did not. The mean peak dose of dobutamine in patients who developed significant ventricular dysrrhythmias was similar to that in patients who did not (31.7±8.2 µgm/kg/min versus 31.1±8.5 µgm/kg/min, p=0.773). Five patients (3 with LVSD, mean EF 33.2±10.3% and 2 without LVSD or RWMA at THR) developed AF. Intravenous esmolol was used in 4 patients with AF and rapid ventricular rates that did not respond to discontinuation of dobutamine. Bradycardia was seen in 4 patients, all in association with increased LVOT gradient. All had normal LV systolic function.

Non-sustained ventricular tachycardia was seen in 18 (9%). The mean peak dose of dobutamine (33.9±7.0 μgm/kg/min versus 30.9±8.5 μgm/kg/min, p=0.156), the mean ejection fraction (49±14% versus 46±18%, p=0.53) and the prevalence of LVSD (44% versus 54%, p=0.42) were similar in patients who did and did not develop NSVT. Atropine was administered to one patient. The test was terminated in 7(3.5%) patients (1 with AF and 2 with previous MI one of whom had PCI to LAD, 2 with symptomatic hypotension and mean LVEF 59±6%) before an end-point. Of the other 11 patients (1 with AF, 8 with LVSD: mean LVEF 37±13), new RWMA developed below THR in 7 and at THR in 3 while 1 attained THR without any RWMA. One patient had atropine. The mean peak dose of dobutamine was similar in patients who did and did not reach end-points (35.5±5.2 μgm/kg/min versus 31.4±9 μgm/kg/min, p=0.244). NSVT was terminated in all patients on discontinuation of dobutamine.

Chest pain was induced in 36(18%) patients (22% had known angina, 42% had previous MI and 28% had previous revascularisation). Two had STEMI with RWMA below the THR. ST depression led to test termination in 10 patients (5 developed new RWMA, 2 were hypotensive and 3 hypertensive). Twenty-four patients had no ST changes (12 had RWMA below the THR, 10 at THR and 2 reached THR without any RWMA). Chest pain was as frequent in patients who received atropine than those who did not (19% versus 18%, p=0.935). Chest pain accompanied the induced AF in 5 patients 2 of who did not show any RWMA. Thirty-one patients needed sublingual and 4 intravenous nitrate.

The test was non-diagnostic for inducible ischaemia in 17(8.5%) patients (pre-mature termination in 15 and test end-point not reached in at maximum dose in 2). Echocardiographic data of 174 patients could be analysed completely (90 patients with HF-LVSD, 41 with HFNEF and 43 with NoHF). All subsequent analysis pertains to this group of patients.

Reproducibility

Overall intraobserver variability of the annular and myocardial velocities at rest and stress was low (<10% at rest and ≤15% at stress) (tables 4). At rest, the highest variability of the systolic velocity was seen in the posterior mitral

annulus, septal basal and middle segments. The highest variability of the early diastolic velocity was seen in lateral mitral annulus, lateral basal and posterior middle segments. The late diastolic velocity was most variable at the posterior mitral annulus, anteroseptal basal and anterior middle segments.

Regional wall motion assessment

2784 segments of the left ventricle were visually scored at baseline, low dose and peak dose of dobutamine totalling 8352 observations. (Figure 3) Fewer segments could be visually assessed in the HF-LVSD group compared to the other two groups at all levels of stress. Fewer segments were assessed at stress compared to rest in the NoHF group ($p=0.041$) but not in the HF-LVSD ($p=0.686$) or the HFNEF ($p=0.098$) groups. The three segments of the anterior wall were the most difficult to score and those of the septal wall the easiest.

Regional myocardial velocities were quantitatively analysed in 2088 segments (12-segment model) at baseline and each dose of dobutamine totalling 6264 observations. Segments could be quantitatively evaluated more frequently than visually in all ($p<0.01$) except the HFNEF group. (Figure 3) Myocardial velocities could be measured more frequently in the NoHF group compared to the other two groups at low dose ($p=0.000$) and peak stress ($p=0.000$) but not at rest ($p=0.096$). The levels of stress did not affect quantitative assessment in the HFNEF ($p=0.13$) and NoHF group ($p=0.79$) but velocities were measured less frequently at peak stress ($p=0.000$) in the HF-LVSD group. Fewer basal segments ($p=0.000$), but not the mid-segments ($p=0.093$), could be measured at peak stress than at rest and low dose dobutamine in the HF-LVSD group but not in the other two. The middle segments could be interrogated less successfully than the basal segments at all levels of stress in all the three groups. The segments could be interrogated least frequently at all levels of stress compared to the others were the middle segment of the anterior wall due to inadequate visualisation and that of the anteroseptal wall due to poor alignment.

Mitral annular velocities were measured at 1044 sites totalling 3132 observations. It could be measured in 99%, 97.3% and 100% of the instances in the HF-LVSD, HFNEF and NoHF groups respectively ($p=0.000$). Fewer

observations could be made at peak stress compared to rest and low dose (p=0.000) in the HF-LVSD group but not in the others.

The wall motion response to stress could be visually characterised in 94.1% segments, 93.4% in the HF-LVSD, 96.8% in the HFNEF groups and 93.2% in the NoHF (p=0.004) and least commonly in the anterior wall. The inability to assign a response to a segment was due to the failure to score that segment at peak stress (p=0.001) in the NoHF group and at all levels of stress in the HF-LVSD and HFNEF groups.

Comparison between visual and quantitative assessment

Segmental wall motion could be estimated both visually and quantitatively on 91.8%, 94.0% and 95.4% instances in the three groups respectively (p<0.001). Neither modality could assess a segment 0.9-1.9% instances; most frequently in the HF-LVSD group (ANOVA, p=0.01). (Figure 4A) Fewer assessments were made visually only than by TDI only in all, except the HFNEF group. A response characteristic to stress could be assigned to 91.0%, 92.7% and 92.6% segments both visually and quantitatively in the three groups respectively (p=0.39). Neither modality could assign a response characteristic to 1-2.9% of segments most frequently in the HF-LVSD group (ANOVA, p<0.05) (figure 4B). Larger number of segments was assigned a response characteristic on the basis of TDI observations only compared to visual assessment only in the normal group.

A segment could not be visually assessed on 333 (5.3%) instances, most frequently in the HF-LVSD group (p<0.001) (figure 5 Panel 1A). TDI could assess segments on 73% of these attempts. The proportion of observations that could not be made visually but could be made quantitatively was similar in the three groups (ANOVA, p=0.57). A segment could not be assessed by TDI on 180 (2.9%) instances; least commonly in NoHF group (p<0.001). (figure 5 Panel 1B) Of these, higher proportion of observations could be done visually in the HFNEF group (ANOVA, p<0.001). A segment that could not be assessed quantitatively is less likely to be assessed visually (p<0.001). A response characteristic could not be visually assigned to 119 (5.7%) segments. 62% of these segments could be assessed by TDI (figure 5 Panel 2A). This was least

likely in the HFNEF group (p=0.03). A response could be assigned using TDI to similar proportion of segments in the three groups (p=0.12). A response could not be assigned using TDI to 97 (4.6%) segments; most commonly in the HF-LVSD group (p=0.01). (figure 5 Panel 2B) The proportion of these segments that could be visually assessed was the highest in the HFNEF group (p=0.003).

Diastolic assessment

E could be measured in all patients at rest and peak stress. The A wave and thus the E/A ratio could be measured in 77%, 78% and 93% patients at rest (p=0.054) and 69% 76% and 91% patients at stress (p=0.023) in the three groups respectively. The proportions were similar at rest and stress (p=ns, rest v stress). The failure to measure E/A was exclusively due to AF at rest or induced by stress. Of the 136 patients who were in sinus rhythm under stress, fusion of the E and A waves was seen in 38(28%) patients all of whom reached heart rates higher than 110 bpm. The EDT could be measured in all patients at rest and peak stress. IVRT could not be measured in 1 patient in each of the heart failure groups.

The averaged Ea could be calculated in all and 98.8% patients with and without LVSD at rest and in 97.8% and 98.8% patients at stress. Aa could be calculated in all patients in sinus rhythm in both groups (75.6% and 72.2% patients with LVSD and 85.7% and 83.3% patients without at rest and stress respectively).

Ea could be measured more sites at rest than at peak stress (96.9% v 90.4%, p=0.000 in patients with LVSD and 98.8% v 97.0%, p=0.047 in patients without). Amongst the patients in sinus rhythm, Aa could be measured more frequently at rest than at peak stress (96.8% v 92.6%, p=0.007) in patients with LVSD but not in patients without (100% v 99.8%, p=0.310). Ea and Aa could be measured at fewer sites in patients with LVSD compared to those without (Ea: at rest, p=0.031; at peak stress, p=0.000; Aa: at rest and peak stress, p=0.000). In patients with and without LVSD, Em and Am could be measured in fewer mid segments compared to the basal segments at rest and at peak stress (p<0.001 for all). Em and Am could be measured in fewer segments (both basal and mid) at peak stress compared to rest in all patients (p<0.001 for all). Ea/Aa ratio could be calculated for fewer annular sites in patients with than those without

LVSD at rest and at peak stress (p=0.000). Ea/Aa ratios could be calculated at fewer annular sites at peak stress compared to rest in patients with LVSD (p=0.034) but not in patients without (p=0.310). The average annular E/Ea could be measured both at rest and peak stress in 168 patients; 85, 40 and 43 in the three groups respectively.

DISCUSSION

To the best of our knowledge this is the only report on the feasibility of DSE with cTDI in the assessment of an unselected population of patients with suspected heart failure in an ambulatory setting. The study included a heterogeneous population of subjects who were mostly elderly with multiple cardiac and non-cardiac co-morbidities.

An unselected population of patients with suspected heart failure that can be expected in a heart failure clinic were screened. DSE was offered to all recruited subjects. Previous studies (159;281-298;300) that have reported feasibility of DSE are retrospective analysis of data obtained on patients who underwent DSE for established clinical indications, and selected in terms of their echocardiographic image quality, suitability to tolerate the procedure and the absence of contraindications. Thus the information on the applicability of DSE to a heterogeneous population expected in a heart failure clinic is limited. About a third of the screened population had to be excluded. Death of 4% of the screened patients before recruitment is unsurprising given the high mortality (about 20%) amongst newly diagnosed patients with heart failure during index admission. (25;26;301) About 10% had contraindication to DSE. Even though the contraindications to the DSE in this study were set conservatively, we are unaware of any estimate of prevalence of conditions that would preclude DSE in this population. The median age of the population screened for this study was 78 years, a decade higher than that included in most feasibility reports. Except for studies in the elderly, (294-298) most feasibility reports include patients who are younger than what could be expected in a heart failure population. This study accurately represents the population that suffer with heart failure the prevalence of which increases rapidly with age (1;15;302) with 15% of people over 85 suffering from it. (302) Co-morbidities precluded 3% of the screened patients from DSE. About 16% (median age 82 years) did not consent for the

study. Though the reasons for refusal were not recorded, it could be presumed to be due to discomfort of the test, inconvenience, travel and travel costs as sighted as reasons in some studies. 3% (median age 86 years) subjects were adjudged incompetent of consenting. Impediments to consenting for studies in the elderly include impairment of cognition, inability to communicate etc. (303)

After screening, 21% of the subjects were excluded due to poor acoustic windows. Some authors have suggested that an inadequate acoustic window precludes the performance of successful DSE in only ~5% of patients.(288;304) This may be an underestimate when applied to an unselected population. (159) Our experience matches the estimate that 10-20% of non-selected patients have suboptimal endocardial border visualisation even with tissue harmonic imaging without contrast. (305) Deterioration of endocardial border definition during DSE precluded analysis of images in another 6%. This conforms to reports that 0-6% of patients selected for DSE had to be excluded for poor image quality. (282;289;298;306)

In the absence of established clinical indication for DSE, patients, especially the elderly, were intolerant to subjective symptoms e.g. musculoskeletal pain. Beta-blockers were withdrawn 48 hours before the test. This resulted in a higher incidence of exclusion due to high ventricular response in patients with persistent atrial fibrillation and loss of control over blood pressure.

Complications

The overall incidence of ventricular arrhythmias was higher than previously reported (Table 5). Resting regional wall motion abnormality, history of previous myocardial infarction and arrhythmias were common in these patients. Only 1 patient received atropine and the mean peak dose of the dobutamine was similar to the rest of the patients. This is consistent with previous reported experience that induction of ventricular tachycardia during DSE is not related to the addition of atropine (182;307) and is more frequently seen in patients with prior history of ventricular arrhythmias or baseline wall motion abnormalities. (159) Its relation to the peak dose of dobutamine is also reported to be uncertain. (289) Stress induced RWMA was common in these patients suggesting that stress induced ischaemia is likely to have precipitated these

arrhythmias. However ventricular arrhythmias during DSE have not been related to inducible RWMA. (289;307) About 44% of the patients with NSVT had normal LVEF and no inducible ischaemia. Three-fourth of these patients did not have previous MI or resting RWMA. In these subjects, the arrhythmia may be attributed to dobutamine-induced β_1-receptor stimulation or reduction in plasma potassium. (308)

Beta-blockers were stopped 48 hours before testing. This resulted in lower number of non-diagnostic tests (8.5%) compared to previous estimates (10%). (287;288) This however, resulted in uncontrolled ventricular rates in patients with AF leading to exclusion of some of these patients and increased incidence of ventricular arrhythmias especially amongst patients with inducible ischaemia. The increased incidence of ventricular arrhythmias, however, did not necessitate termination of tests before ischaemic end-points were reached thus maintaining the diagnostic yield of the test. Beta-blockers reduce ventricular arrhythmias by limiting ischaemia and decreasing the susceptibility of the myocardium to the beta-adrenergic effect of dobutamine. (289)

The incidence of hypotension during DSE varies between 5-38% depending on the definition used. (288;309-311) The incidence of hypotension in our study was considerably lower than that reported by others using comparable cut-offs. (309-311) Hypotension led to test termination in 3% patients compared to 0-7% in previous reports. Stress-induced hypotension has been associated with older age, (296;309;310) higher resting systolic blood pressure in some (309;310) but not all studies (296) and symptoms in the younger but not older patients. (296) The patients with symptomatic hypotension leading to test termination were younger compared to those in whom the test could continue and had higher resting diastolic but not systolic blood pressure.

Fewer patients complained of chest pain in our study than previously reported (table 5). MI occurred in 1% patients. MI is rare during DSE. The higher incidence in this study could be related to withdrawal of beta-blocker and the troponin based definition of infarction. However it can occur due to intense coronary spasm in normal coronary arteries. (284)

Reproducibility of data

Interobserver variability of echocardiographic measurement has been assessed using 'real-time' pulsed tissue Doppler in one study. The 95% confidence intervals for standard deviations expressed as a percentage of the mean, were 10–16% for longitudinal velocities and 14–24% for radial velocities. (200) Good reproducibility has been reported for off-line measurements of peak systolic velocity even by inexperienced observers. (197) In keeping with the latter study, the intraobserver variability for mitral annular and regional myocardial systolic and diastolic velocities was low.

Feasibility of TDI

Myocardial velocity was obtainable in 95-99% of segments interrogated at all stages of the protocol. Myocardial velocities could be most frequently measured in the NoHF group reaching success rates of 99% at all levels of stress. Most, (188;214;260;312) but not all (299;313;314) studies have reported similar feasibility. The lower proportion of analysable segments (90%) in the MYDISE study (299) resulted from non-analysable waveforms from the mid-anterior septum interrogated in the parasternal long axis view and the four apical segments interrogated in apical view. The higher yield of interpretable velocity curves in our study resulted from interrogation of the anteroseptal segments in the apical long axis view allowing better ultrasound beam alignment and the exclusion of the apical segments.

Measurement of regional myocardial velocities was least successful in the HF-LVSD group especially at peak stress. A segment could not be assessed either visually or quantitatively most frequently in the HF-LVSD group. Interrogation of the walls of dilated, spherical, often scarred and dyssynchronous ventricles may have resulted in uninterpretable myocardial velocity traces. Despite this limitation, success rate for quantitative evaluation of segments was consistently higher compared to visual assessment in this group. Both visual and quantitative were equally successful in the HFNEF group.

The three segments of the anterior wall were the most difficult to score visually. Visualisation of anterior or lateral walls may be suboptimal during echocardiography and worsen during stress.(305) The middle segments could

be quantitative interrogated less successfully than the basal segments at all levels of stress in all the three groups. The segments that could be interrogated least frequently at all levels of stress were the middle segment of the anterior wall due to inadequate visualisation and that of the anteroseptal wall due to poor alignment. This mirrors the experience of the MYDISE investigators.(299) The success rate of quantitative assessment was consistently higher than visual assessment. Depending on the level of stress and the population of patients examined, 92-98% of the segments examined could be visually assessed. This concurs with the reported proportion of segments that could be scored visually (83-97%) in various studies. (214;313;314)

TDI supplemented visual assessment of wall motion quite appropriately. Myocardial velocities could be measured in similar proportion of segments (70-77%) that could not be visually assessed in all three groups. But as the HF-LVSD group had higher absolute number of non-visualised segments, TDI seemed to benefit this group the most. Concurrence between the visual scoring and myocardial velocity was modest at rest, being the lowest in the HF-LVSD group. Published comparison between conventional visual assessment of regional wall motion and TDI analysis is lacking.

Diastolic measures

Feasibility of diastolic assessment of the LV during stress is limited by the difficulties in the measurement of the diastolic waves and velocities. Fusion of the diastolic waves occurs at peak heart rates. Najos-Valencia et al could not be designate Em and Am velocities in 1.5% of 756 segments tested at rest and 21% at peak stress because of fusion between the E and A waves at peak heart rates.(186) Fusion prevented assessment of diastolic function in 40% (257) and 71% (188) cases in other studies. This problem was avoided by measuring the diastolic velocities at the highest heart rates where they could be separately measured. Analysis of diastolic velocities at sub-maximal stress seemed to be a reasonable approach for diagnosis of stress-induced diastolic dysfunction firstly because ischaemia induces diastolic dysfunction occurs earlier than systolic (315) and secondly, heart failure patients with exercise intolerance are unlikely to achieve maximal heart rates during day-to-day physical activity that make them breathless. Interpretation of the patterns of diastolic waves under stress is

further complicated by the presence of resting changes in relative magnitudes of these velocities. The ratio of Ea and Aa may be permanently inverted in regions of the myocardium supplied by stenotic arteries.(79) Age, hypertension and/or LV hypertrophy may have similar effect. This may conceal the effect of stress induced ischaemia on these variables or at least make interpretation difficult. The high prevalence of these conditions in patients with suspected heart failure could adversely affect the evaluation of diastolic function under stress in these patients. The reproducibility of these measurements has been reported to be suboptimal and probably less than that obtainable with systolic velocity.(299;312) Intraobserver variability in this study was <10% at rest and <15% at peak stress.

LIMITATIONS

The subjects underwent DSE as part of a research project. A significant proportion of eligible patients that did not consent for a research procedure may have done so if it was clinically indicated. DSE was offered to an unselected population of patients attending the heart failure clinic a substantial proportion of whom would never be considered for DSE in a real-world situation. This led to a high exclusion contrary to clinical experience.

CONCLUSION

DSE is feasible in patients with suspected heart failure only when they are appropriately selected for the test. DSE is applicable to a small portion of patients attending the heart failure clinics. The safety of DSE in an unselected population may be a concern. Both systolic and diastolic assessment of these patients is feasible using cTDI both at rest and stress and may supplement visual interpretation. DSE may have important influence on management of these patients but that needs to further assessed.

Table 4.1 Baseline characteristics of the study population

	Screened/ not recruited (n=201)	*Screened/ recruited (n=347)*	*DSE done (n=200)*	*DSE not done (n=147)*
Age (years) (mean±SD)	76±10	71±11*	69±10	72±11**
Age (yrs) range (median)	42-95 (78)	29-92 (72)	42-92 (70)	29-90 (74)
Males (%)	51.6	61.4***	62.5	59.9
BMI (mean±SD)	27.9±8.2	28.6±5.8	27.0±5.3	29.9±6.2*
Risk factors for CAD				
H/O Smoking (%)	64.6	71.9	77.0	76.9
Diabetes (%)	14.3	19.6	18.5	21.1
Family history (%)	29.1	35.2	32.5	38.8
Hypertension (%)	35.2	38.9	32.3	48.3
Obesity (%)	-	-	16.4	52.5*
History of				
Angina (%)	30.1	33.5	33.2	36.3
Revascularisation (%)	10.4	11.2	11.5	10.9
Myocardial infarction (%)	32.4	33.4	31.0	36.7
Valvular disease (%)	14.3	3.2*	0	0.7
COPD (%)	11.4	14.9	10.1	18.5***
Drugs				
Loop diuretics (%)	73.8	74.9	75.2	74.8
ACEI or ARB (%)	65.1	66.1	68.6	65.9
Beta-blockers (%)	66.5	69.8	69.1	70.3
Aspirin (%)	80.6	84.6	86.6	83.8
Wafarin (%)	16.2	19.1	18.9	19.6
Spironolactone (%)	12.1	13.8	12.6	15.2
Systolic BP (mmHg)	148±28	142±29	140±26	139±27
Diastolic BP (mmHg)	84±12	86±14	82±16	83±14
Sinus rhythm (%)	70.3	73.5	72.8	69.6
QRSd (ms)	98±20	97±21	101±20	100±19
RR interval (ms)	810±152	812±159	818±153	809±149
Heart rate (bpm)	78±12	76±15	76±11	79±11
Echocardiography				
IVSd	1.3±0.4	1.3±0.4	1.3±0.4	1.4±0.5
IVSs	1.6±0.6	1.6±0.5	1.6±0.3	1.6±0.1
LVPWd	1.3±0.4	1.3±0.4	1.3±0.4	1.3±0.5
LVPWs	1.7±0.8	1.7±0.5	1.7±0.1	1.7±0.6
LVIDd (cm)	5.5±1.2	5.6±1.2	5.6±1.2	5.6±1.2
LVIDs (cm)	4.2±1.3	4.4±1.4	4.4±1.4	4.3±1.4
LVEDVol (ml)	127±74	135±80	134±69	136±102
LVESVol (ml)	80±61	82±58	82±52	81±72
EF (mean±SD)	42±15	45±16	45±16	46±17

p value for comparison between the DSE done and not done groups. *p<0.001, **p<0.01, ***p<0.05

Table 4.2. Haemodynamic response to stress.

	LSVD (n=107)	Normal EF (n=93)	p
DSE End-point reached at			
40 µg/kg/min+atropine n (%)	9 (9.3)	6 (6.5)	0.623
40 µg/kg/min n (%)	34 (29.9)	31 (36.6)	0.397
30 µg/kg/min n (%)	34 (34.6)	34 (33.3)	0.971
20 µg/kg/min n (%)	29 (25.2)	19 (20.4)	0.524
10 µg/kg/min n (%)	1 (0.9)	3 (3.2)	0.517
Peak dose of dobutamine	31.1±8.3	31.5±8.7	0.631
HR (rest)	77±15	75±13	0.531
HR (peak stress)	125±14	123±13	0.236
Target HR	129±8	128±9	0.544
% of THR reached	96.7±10.3	95.8±10.6	0.860
% of THR reached			
≥ 100 % n (%)	42 (39.3)	41(44.1)	0.489
> 90 % n (%)	87 (82.2)	70 (83.9)	0.760
> 80 % n (%)	99 (92.5)	86 (92.5)	0.798
> 70 % n (%)	107 (100.0)	93 (100.0)	-
SBP (rest)	135±24	146±20	<0.001
SBP (peak stress)	170±26	162±22	0.169
DBP (rest)	80±13	84±11	0.016
DBP (peak stress)	95±8	89±8	0.002

Table 4.3. Reasons for termination and side-effects observed during DSE.

	Reason for termination	Complication
NSVT n(%)	7(3.5)	18(9.0)
PVCs n(%)	-	64 (32)
PSVCs n(%)	-	26 (13)
Atrial fibrillation/flutter n(%)	-	5 (2.5)
Bradycardia n(%)	-	4 (2)
Chest pain without ST depression n(%)	-	24 (12)
Dyspnoea n(%)	-	3(1.5)
Nausea n(%)	-	7(3.5)
Headache n(%)	-	2 (1)
Shivering n(%)	-	1 (0.5)
Dizziness n(%)	-	1 (0.5)

Table 4.4. Intra-observer variability in the systolic, early diastolic and late diastolic of the mitral annulus, basal and mid segments of the lateral, septal, anterior, inferior, posterior and the anteroseptal walls at rest and peak stress.

	REST									STRESS							
Segments	Sm Diff (Mean±SD)	95% CI	%	Em Diff (Mean±SD)	95% CI	%	Am Diff (Mean±SD)	95% CI	%	Sm Diff (Mean±SD)	95% CI	%	Em Diff (Mean±SD)	95% CI	%	Am Diff (Mean±SD)	95% CI	%
L_MA	0.21±0.51	0.32	5.6	-0.04±0.75	0.46	8.3	0.11±0.57	0.35	5.2	0.60±0.91	0.56	6.05	0.05±0.74	0.46	7.09	0.39±0.71	0.44	5.30
L_B	0.15±0.28	0.18	4.3	-0.51±0.74	0.46	9.8	0.02±0.49	0.31	7.1	-0.11±0.76	0.47	7.01	-0.23±0.74	0.46	9.48	-0.30±1.38	0.86	13.00
L_M	0.22±0.24	0.15	4.9	-0.06±0.32	0.20	7.3	0.12±0.34	0.22	6.1	-0.55±0.98	0.61	12.35	-0.23±0.63	0.39	10.63	-0.17±0.84	0.52	13.89
S_MA	0.03±0.23	0.14	3.5	0.02±0.33	0.20	5.5	0.26±0.37	0.23	3.7	-0.09±0.29	0.18	2.21	0.02±0.19	0.12	2.89	0.30±0.37	0.23	2.68
S_B	0.05±0.65	0.40	9.3	0.05±0.66	0.41	9.6	-0.10±0.64	0.40	6.8	-0.53±0.95	0.59	7.86	0.24±0.60	0.37	8.29	-0.13±0.69	0.43	5.19
S_M	-0.05±0.50	0.31	9.8	0.08±0.39	0.24	6.7	-0.28±0.44	0.27	6.9	-0.22±0.53	0.33	5.90	0.07±0.53	0.33	9.38	0.39±0.85	0.53	7.97
A_MA	0.24±0.20	0.13	2.4	0.23±0.28	0.18	3.4	0.23±0.56	0.35	5.6	0.35±0.55	0.34	3.42	-0.20±1.05	0.65	11.36	0.31±0.82	0.51	5.92
A_B	0.02±0.45	0.28	7.1	-0.23±0.40	0.25	5.6	0.08±0.42	0.26	6.7	-0.01±0.52	0.32	4.04	0.04±0.92	0.57	13.65	-0.12±0.75	0.46	7.14
A_M	-0.02±0.24	0.15	7.6	-0.10±0.33	0.20	8.4	-0.06±0.33	0.21	9.8	0.09±0.87	0.54	9.93	0.05±0.60	0.37	12.54	-0.21±0.91	0.57	15.73
I_MA	-0.08±0.41	0.26	5.6	-0.16±0.36	0.23	5.5	0.22±0.38	0.24	3.3	-0.30±0.59	0.37	4.65	-0.33±0.73	0.45	9.03	0.62±0.64	0.40	4.58
I_B	-0.18±0.51	0.32	6.9	-0.07±0.34	0.21	4.8	0.13±0.52	0.32	5.1	-0.45±1.26	0.78	10.02	0.14±0.45	0.28	6.17	0.42±0.54	0.34	3.48
I_M	-0.07±0.16	0.10	3.2	0.01±0.45	0.28	9.0	0.09±0.31	0.19	4.3	0.12±0.85	0.53	9.32	0.03±0.33	0.21	5.98	0.82±1.07	0.66	9.77
P_MA	0.09±0.70	0.43	8.1	-0.34±0.43	0.27	5.1	0.40±0.85	0.53	8.1	-0.26±0.29	0.18	2.10	-0.25±0.58	0.36	5.77	0.41±0.84	0.52	6.26
P_B	-0.03±0.27	0.17	3.8	0.10±0.65	0.40	7.6	-0.21±0.36	0.22	4.8	-0.26±1.43	0.89	11.18	-0.08±0.53	0.33	6.49	0.02±0.39	0.24	3.11
P_M	-0.10±0.47	0.29	9.5	0.12±0.46	0.29	9.6	-0.07±0.21	0.13	3.6	0.06±1.05	0.65	10.12	0.36±0.90	0.56	13.41	0.56±0.76	0.47	8.48
A_SMA	0.10±0.39	0.24	5.6	0.05±0.34	0.21	5.2	0.42±0.58	0.36	6.5	0.01±1.17	0.73	9.28	-0.21±0.81	0.50	12.69	-0.02±0.39	0.24	3.23
A_SB	-0.16±0.49	0.30	8.3	-0.14±0.26	0.16	4.6	0.13±0.57	0.35	7.4	0.44±1.19	0.74	10.53	-0.06±0.41	0.25	8.14	0.00±0.61	0.38	5.37
A_SM	0.04±0.33	0.21	7.9	0.07±0.30	0.19	5.2	-0.04±0.22	0.14	4.6	0.19±1.07	0.66	11.62	0.14±0.37	0.23	7.78	0.25±1.00	0.62	11.65

CI, confidence interval of the difference (presented as absolute values and percentages of the average values of Sm, Em and Am velocities); Diff, difference between paired measurements (Mean±SD). L, lateral; S, septal; A, anterior; I, inferior; P, posterior; AS, anteroseptal. MA, mitral annulus, B, basal segment, M, middle segment

Table 4.5. Feasibility of DSE in some selected studies.

					Indication for test termination									Side effects that did not lead to test termination						
	Year	n	feasibility	Age	VF	MI	VT	NSVT	AF/ SVT	Brady	Low BP	High BP	CP	NSVT	AF/ SVT	Brady	Low BP	High BP	CP	Others
Baudhuin et al	1993	136	-	66±5	-	-	-	-		-	-	-	-	11			12.5	3.7		5.9
Mertes et al	1993	1118	-	60±12	-	-	2.1			0.2	3.2	0.9	12.7	4.2	4.1	3.1	-	-	28	3.2
Picano et al	1994	2949	88.4%		0.1	0.1	4.6		1.5	2.1		0.8	-	-	-	-	-	-	-	2.5
Poldermans et al	1994	650	98%		0.2	-	0.5	1.9	1.2											
Poldermans et al	1994	179	92%	75	-	-	-	-	1.1	-	1.1	-	2.8	-	-	-	-	-	-	-
Gordon et al	1995	127	-	65±11	-	-	0.8	2.4	-	-	-	-	-	-	3.2	-	-	-	16.5	29
Cornel et al	1996	318	97.5%	58±10	-	-	0.3	0.9		-	1.9	-	17.9	3.8	1.3	-	9.4	-	-	0.9
Anthopouloset al	1996	120	90%	75.3±3	-	-	-	-	1.7	-	6.7	1.7	-	-	0.8	-	-	-	31	-
Secknus et al	1997	3011	86.2-96.3%	66±12	-	0.03	0.2	0.6	0.9	-	3.5	0.8		1.8	3.0	-	7	2	25	
Hennesey et al	1997	474	96.6%	59±12	-	-	0.2	1.3		0.2	0.2	0.2	0.6	1.7	4	0.8	-	-	-	-
Elhendy et al	1997	1164	91.5%	60±12	-	-	-	1.7		-	1.5	0.1	5.9	4.8	4.8	-	4.8		26	11/0.9
Hiro et al 106>75	1997	732	-	62±12	-	-	-	1.4						36.1	19.3					
Poldermans	1998	200	93%	63	-	-	1.5	-	0.5	-	1.5	-	-	2.5	1.5	-	11	-	-	-
Cortigiani et al	1998	368	97.6%	63±11	-	-	0.3	1.1	0.3	-	0.8	0.3	-	-	-	-	-	-	-	-
Mathias et al	1999	4033	90%	56.4	-	-	-	1	0.4	-	0.4	1.5	0.2	3.6	0.8	-	5	2	11	
Poldemans et al	1999	1659	93.7%	62	0.2	-	0.8	-	0.4	-	0.4	0.2	-	2.7	1.3	-	4	-	-	0.2
Sitges et al	2000	122	94	64±12	-	-	-	-	-	-	-	-	-	4	5	1.5		7.5		
Cortigiani et al	2001	636	97%	60±11	0	0	2	0	0	-	0	0		8	2	-	5	4		
Cortigiani et al	2002	959	91.3%	65±10	-	-	0.1	3.4	-	0.3	2.2	1.1	-	6.6	4.0		3.5	2.2	-	4.6
Previtali et al	2002	135	93.3%	74±3	-	-	-	3.0	0.7	-	5.9	1.5	-	-	-	-	-	-	-	0.7

Figure 1

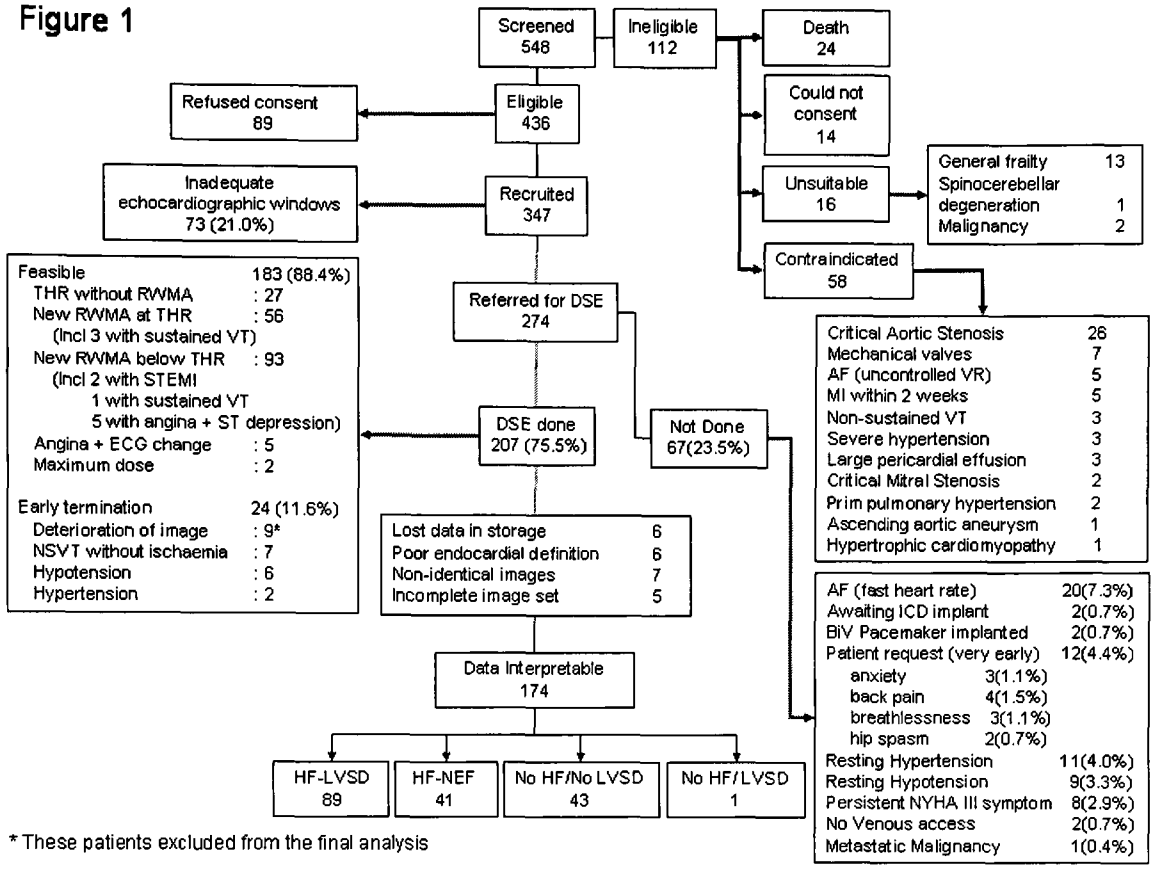


Figure 4.1. The journey of the screened patients through the study.

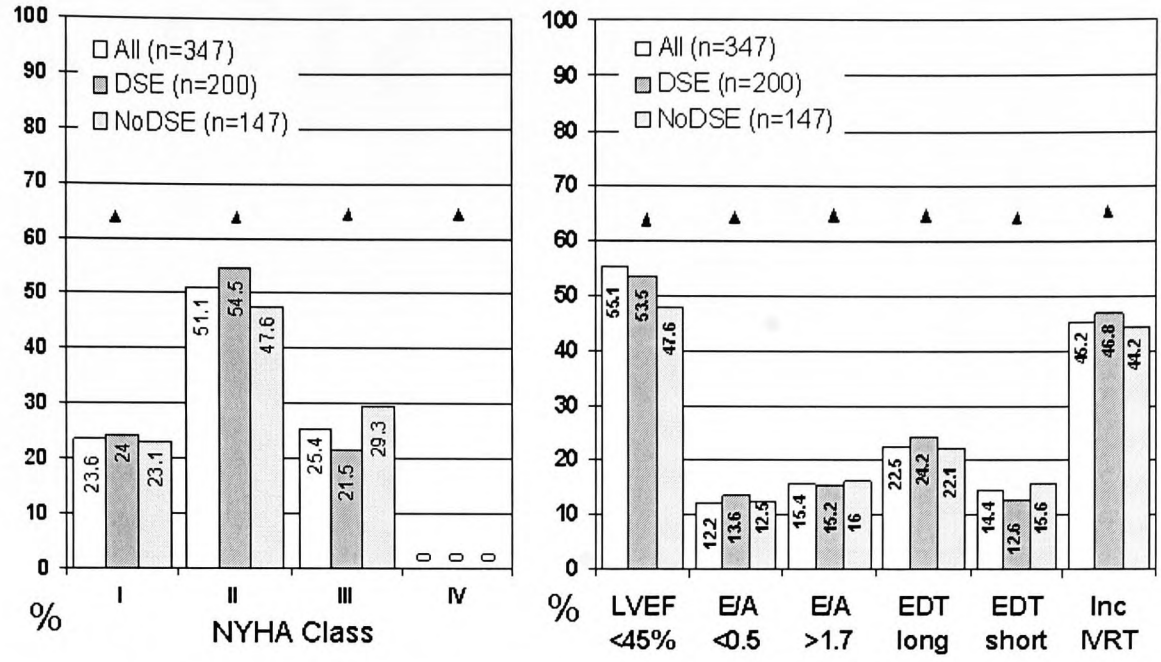


Figure 4.2. Prevalence of HF symptoms, systolic and diastolic left ventricular impairment at rest in the recuited population.

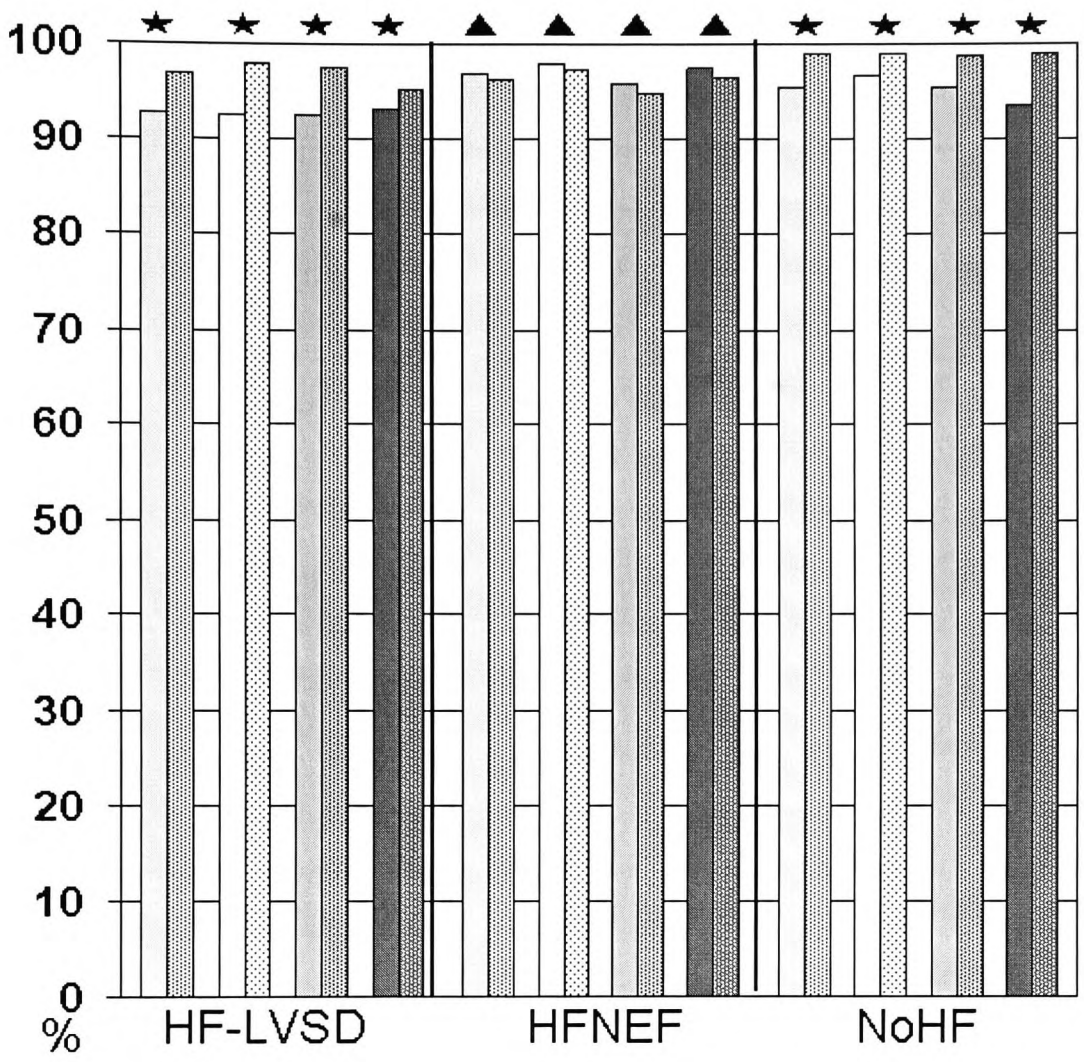


Figure 4.3. Proportion of segments that could be assessed visually (plain bars) and quantitatively (dotted bars) overall, at rest, low dose and peak dose of dobutamine in the HF-LVSD, HFNEF and No-HF groups.

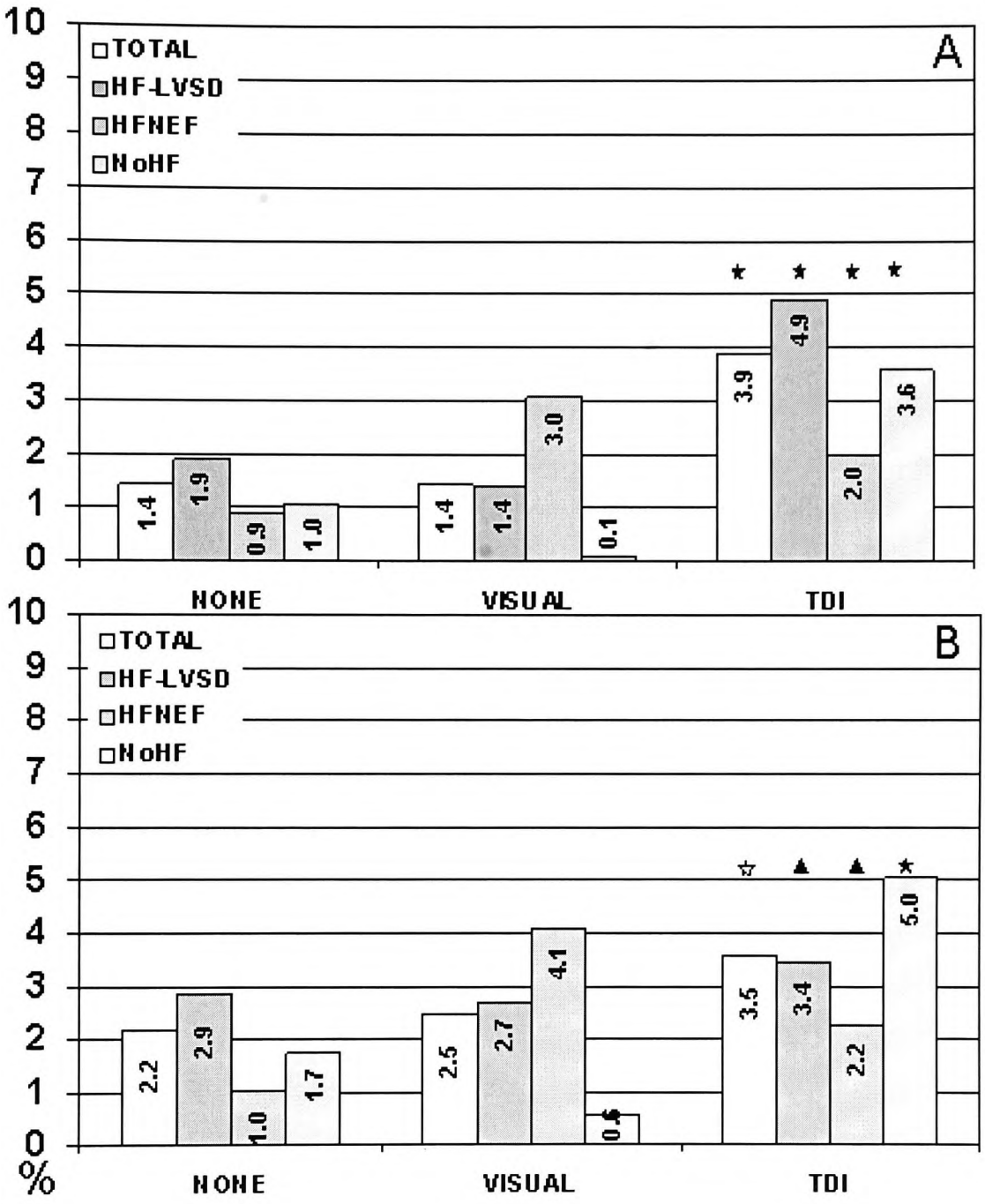


Figure 4.4. A: % of instances where a wall motion of a segment could be assessed visually only, TDI only and neither. B: % of segments where a wall motion response could be assigned visually only, TDI only and neither. ★ $p<0.01$, ☆ $p<0.05$, ▲ p=ns versus visual.

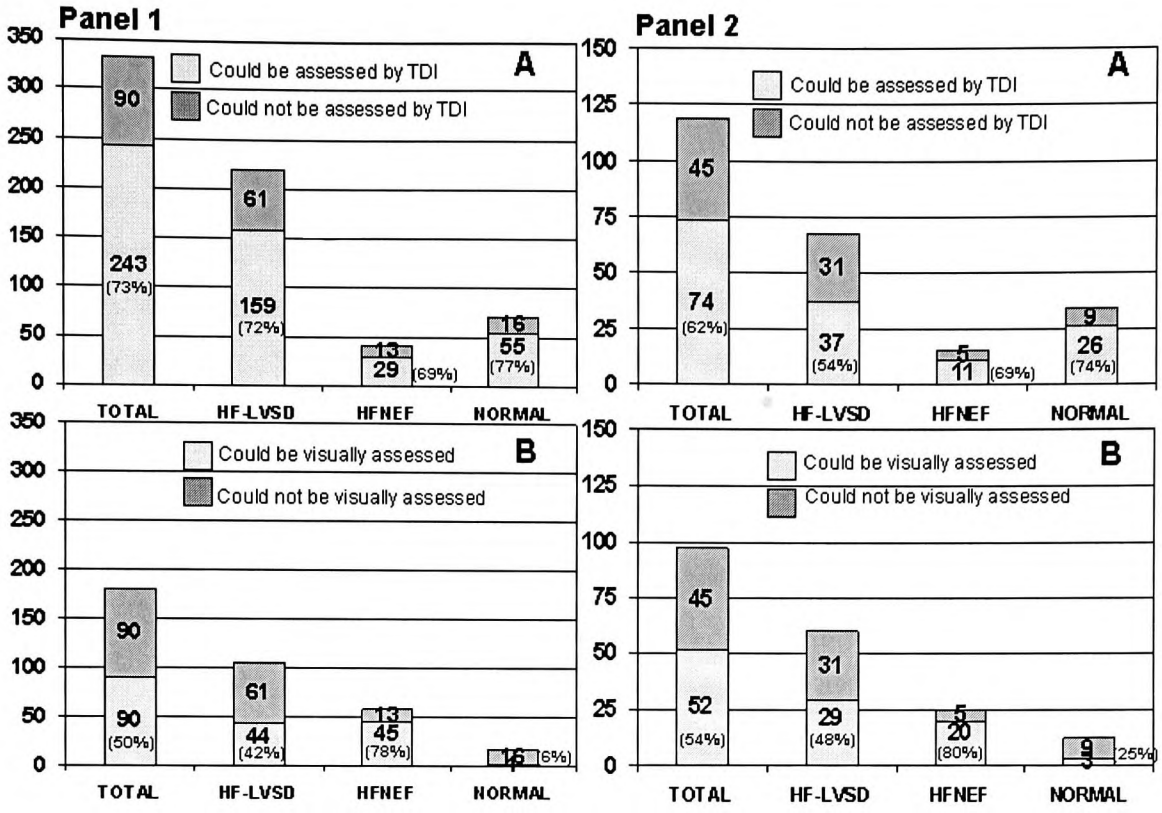


Figure 4.5. Panel 1: A. Instances where TDI could and could not assess segments that could not be visually assessed. B. Instances where segments that could not be assessed by TDI, could and could not be visually assessed. Panel 2: A. Instances where segmental response to stress could and could not be assigned using TDI in segments that could not be visually assessed. B. Instances where segmental response to stress could and could not assigned visually in segments that could not be assessed by TDI.

Chapter 5: Dobutamine Stress Echocardiography with colour tissue Doppler imaging in an unselected population of patients with suspected heart failure.

ABSTRACT

Background: Exercise commonly induces or exacerbates symptoms in subjects with suspected heart failure. Guidelines recommend resting echocardiography for assessment of cardiac function in these patients. This is likely to miss stress-induced left ventricular dysfunction that may be the aetiology of the symptoms in patients with normal resting ejection fraction.

Method and results: 209 of 274 patients with suspected heart failure underwent DSE with cTDI. DSE was fully analysable in 174 patients (90 with HF and left ventricular systolic dysfunction (HF-LVSD), 41 with HF and normal ejection fraction (HFNEF) and 43 with no HF (NoHF)) with 89% feasibility. Prognostically significant improvement in global, regional and long-axis function was seen in dysfunctional ventricles in all three groups. Stress impairment in Ea was seen in the HFNEF but not the other groups with associated increase in the E/Ea ratio. The transmitral Doppler failed to detect any difference in the diastolic function with stress. LV outflow tract gradient increased with stress.

Conclusion: DSE can only be applied to a selected population of patients that are referred to a heart failure clinic. It reveals findings that are not seen at rest but may have therapeutic and prognostic implications. The increase in the LVEDP with stress in patients with HFNEF may explain the exercise intolerance in this group of patients. The therapeutic and the prognostic implication of these findings need to be tested in outcome studies.

INTRODUCTION

Resting echocardiography has conventionally been the mainstay of assessment of patients with suspected HF.(1) Confirmation of the diagnosis of HF has been straightforward in patients with LVSD. However, the diagnosis of HF has been difficult to confirm or exclude in an estimated 1-3% of the Western European population with symptoms suggestive of HF but normal LVEF at rest. (15) Considerable uncertainties in the diagnosis of HF, has been reported in this group of patients in primary and secondary. (20;34)

Multiple cardiovascular pathologies that may result in HF may or may not give rise to abnormal LV function at rest or affect conventionally measured LVEF. These pathologies are likely to be highly prevalent in patients with suspected HF. Although symptoms in patients with suspected HF are often absent at rest and almost universally induced or exacerbated by exercise, most studies, and indeed the current guidelines have focused on assessing cardiac function at rest.(1) This strategy may be inadequate in the assessment of patients with suspected HF. Resting echocardiography may be sufficient to confirm HF secondary to LVSD, but it often fails to suggest an aetiological diagnosis or provide prognostic information. On the other hand, the very diagnosis of HF is put to jeopardy in the presence of symptoms without abnormal LVEF on resting echocardiography. The genesis of symptoms in these patients may be related to transient but extensive changes in global or regional systolic or diastolic dysfunction induced by exercise. Resting echocardiography potentially leaves a proportion of these patients undiagnosed.

Thus evaluation of cardiac function under stress in patients with suspected HF could potentially delineate the role of exercise induced stress in the genesis of their symptoms. It would potentially identify ischaemia as aetiology of LVSD in patients with low LVEF and as the cause of breathless in those without. It would detect viability or the lack of it in dysfunctional segments of impaired ventricles. It would also unmask changes in LV global or regional systolic or diastolic function in response to stress in patient with normal LVEF.

In the present study the effect of pharmacological stress on the prevalence and severity of the abnormalities of cardiac function that could cause or contribute to the symptoms of HF in an unselected population of subjects suspected of having heart failure was studied. Conventional DSE supplemented by cTDI was used in this assessment.

METHOD

Patient selection

All consecutive subjects with a suspected diagnosis of HF who underwent DSE were included for the study. These patients were selected from a screened cohort assessed in a community-based heart failure programme as described in Chapter 4. Written informed consent was obtained. Medical Ethics Committee of the Hull and East Yorkshire NHS Trust approved the protocol.

Patients with LVEF ≤45% and HF were designated as HF-LVSD group, LVEF >45% and HF as HFNEF group and LVEF >45% and no HF as NoHF group. One patient, with asymptomatic LVSD was considered in HF-LVSD.

Clinical evaluation

All subjects underwent a routine clinical examination, 12-lead ECG, chest X-ray, pulmonary function test (hand held spirometry) and six-minute hall walk. Demography, medical and drug history and cardiovascular risk factors were recorded. Hypertension was defined as a previous blood pressure recording on two separate occasions of >140 mmHg systolic or >90 mmHg diastolic or the ongoing prescription of anti-hypertensive medication. Myocardial infarction was defined according to World Health Organisation criteria. Ischaemic heart disease was defined as a history of myocardial infarction, unstable angina or angiographic evidence of >50% stenosis of one or more coronary arteries with or without a past history of revascularisation. Patients underwent physical examination, a 12-lead ECG, chest X-ray and pulmonary function tests. Body mass index (BMI) >25 was

considered overweight and that >30 as obese. Airways disease was diagnosed if FEV1/FVC ratio was <75%.

A standard echocardiographic examination was undertaken. LV mass, chamber volumes and ejection fraction were measured. (118) Left ventricular hypertrophy (LVH) was defined as LV mass index >134 gm/m^2 in men and >110 gm/m^2 in women and LVSD as LV ejection fraction of <45%. LVSD was considered moderate-to-severe if resting WMSI was >1.6. Diastolic volume index >75 ml/m^2 and systolic volume index >30 ml/m^2 were considered abnormal. (118) The E, A, EDT and IVRT were measured. LV diastolic dysfunction was defined as per age related normal values. (66) Impaired diastolic compliance was defined as E/A>1.7 and EDT<138 msec. Pseudonormalisation of the E/A ratio was diagnosed in the presence of reversed Ea/Aa ratio. The peak systolic velocity was measured using the pulse wave Doppler sample volume at the LVOT.

Stress echocardiography

Subjects underwent DSE using standardised dobutamine-atropine protocol 48 hours after stopping beta-blockers. The image acquisition is described in detail in Chapter 4.

Hibernation in ≥4 or ≥6 segments of myocardium was considered to be prognostic. (172;316) Contractile reserve (CR) was defined as the change in WMSI (ΔWMSI) i.e. the difference between the resting and low dose WMSI. Improvement in WMSI ≥0.2 and 0.4 were considered prognostic. (26;317) CR at low dose was also determined as the ratio of number of segments with improved wall motion scores at low dose to the number of segments scored at this dose expressed as a percentage. The proportion of patients with contractile reserve in at least 25% of ventricular myocardium was also determined. (318)

The IVRT and EDT were corrected for heart rate using the Bazett's formula to compare observations at rest and peak stress {EDTc=EDT(msec)/√R-R(sec)}. The LVOT maximum velocity ≥2.5 m/sec was considered raised.

Resting averaged periannular Sa <2.8 cm/sec was considered prognostically abnormal. (319) The velocities were considered "abnormal" at rest if it was <mean±2SD of published normal value for that segment for that age. (212) At each wall ΔSa (the difference between mitral annular velocity at rest and at low dose of dobutamine) was calculated. An increase in the Sa >1 cm/sec from rest to low-dose dobutamine in walls with low resting velocities was considered to denote "significant viability". (268) A segment was identified being abnormal at peak stress if the Sm was ≤ 5.5 cm/sec. (255) A segment was labelled "normal" if the velocity was normal at rest and increased at peak stress, "ischaemic" if velocity decreased or failed to increase at higher dose and "scar" if the velocity was abnormal at rest and did not change with stress. The response was considered "biphasic" if a segment that was abnormal at rest improved at low dose and then worsened at high dose. These segments were designated viable and ischaemic.

Ea/Aa<1 was considered abnormal. The mitral inflow pattern was considered "pseudo-normalised" if the Ea/Aa ratio was <1 in the presence of a normal E/A ratio. E/Ea were calculated. E/Ea at rest, (191;204) and stress (183;192) was used as an estimate of the LVEDP. As velocities measured by cTDI are 20% less than that measured by pulse-wave TDI, (320) the measured Ea was corrected to obtain the corresponding value in pulse-wave TDI. The E/Ea was then calculated at rest and stress using these new values. E/Ea<8 was considered normal, 8-15 was intermediate and >15 was high. (193)

Reproducibility

As described in Chapter 4.

Statistical analysis

As described in Chapter 4.

RESULT

274 subjects were referred for DSE. DSE was done in 207 (76%). Test end-points were reached in 183 (88.4%). (Figure 1) DSE data was completely analysable in 174 (83.3%) subjects: HF-LVSD group (n=90), HFNEF group (n=41) and NoHF

group (n=43). All subsequent analysis pertains to these patients. Table 1 describes the baseline characteristics of the population.

Resting Echocardiography (Table 2)

The mean LV mass was highest in the HF-LVSD group. WMSI was >1 in 41-49% patients without LVSD. The A velocity could not be measured in 24.4%, 21.9% and 7.0% patients in the three groups respectively due to AF during imaging (p=0.054). LV diastolic dysfunction was common (about 50%) in the three groups. 6.7% patients of the HF-LVSD group had restrictive LV filling. Low Sa and Ea were most prevalent and reversed Ea/Aa was least prevalent in HF-LVSD group.

Systolic function (global)

WMSI and Sa (figure 2 and 3)

WMSI was higher in the HF-LVSD group compared other groups at rest and all levels of stress with no differences between the HFNEF and NoHF groups. WMSI improved with low dose dobutamine in the HF-LVSD (2.27±0.49 v 2.01±0.54, p=0.001) and NoHF (1.15±0.24 v 1.03±0.11, p=0.005) groups but not in the HFNEF (1.15±0.25 v 1.01±0.04, p=0.39) group. The Sa in the HF-LVSD group was lower than in others both at rest and peak stress with no differences between the HFNEF and NoHF groups. The Sa increased with stress in all the three groups. The increase in the Sa from rest to peak stress was 2.15±1.60 cm/sec in the HF-LVSD group (p=0.018 v normals and p=0.009 v HFNEF), 2.85±1.37 cm/sec in HFNEF (p=0.731 v normals) and 2.95±1.75 cm/sec in the normal group (p=0.006, Single factor ANOVA).

The prevalence of abnormal WMSI and Sa and its change with stress are described in figure 3. Resting WMSI was >1 in 73.6% patients overall, 71.1% of whom improved with low dose dobutamine. Of the 82 (47%) ventricles with resting WMSI ≥1.6, 61(74.4%) improved with low dose dobutamine. WMSI decreased by ≥0.2 in 50.0%, 23.5% and 47.6% of the ventricles that were abnormal at rest in the HF-LVSD, HFNEF and NoHF groups (p=0.132). It decreased by ≥0.4 in 32.2%, 17.6% and 28.6% in the three groups (p=0.132). Normal Sa at rest was least frequently seen in the HF-LVSD group (p<0.001). Sa improved in 80.4% of patients

with reduced velocities at rest, overall. Of the 67.8%, 24.4% and 25.2% walls that had low Sa at rest in the HF-LVSD, HFNEF and normal groups, 60.9%, 65% and 58.5% improved by >1 cm/sec with low-dose dobutamine respectively suggesting "significant viability" in these walls.

Systolic function (Regional)

WMS and Sm (figure 3)

The segmental wall motion response to stress could be characterised in 94.1% segments. The rest are excluded from further analysis. Of the dysfunctional segments at rest, 41.6%, 54.4% and 94.7% in the HF-LVSD, HFNEF and NoHF groups respectively showed viability with low dose dobutamine and 35.8%, 54.4% and 93.4% subsequently became ischaemic at peak dose. The rest showed sustained improvement. Of the dysfunctional segments at rest, 28.4%, 19.6% and 1.3% in the HF-LVSD, HFNEF and NoHF groups respectively were scars. Of the segments that were normal at rest, 32.9%, 4.7% and 8.3%segments were ischaemic in the three groups

Of the patients with WMSI>1 at rest, 57.8% patients in the HF-LVSD group had viability in ≥4 dysfunctional segments compared to 23.5% in the HFNEF group and 33.3% in the normals (p=0.01). Viability was seen in ≥ 6 dysfunctional segments in 38.9%, 17.7% and 33.3% patients in the three groups respectively (p=0.239). Of the patients with WMSI>1, contractile reserve was seen in 82.2%, 64.7% and 76.2% patients in the HF-LVSD, HFNEF and normal groups respectively (p=0.253) and contractile reserve of ≥ 25% was seen in 42.2%, 17.7% and 14.3% patients (p=0.016).

The median number of segments that were normal, reversibly abnormal (i.e. had a viable, ischaemic or biphasic response) and irreversibly abnormal (i.e. scarred) was 1 (range 0-14), 8 (range 1-16) and 4 (range 0-15) in the HF-LVSD group compared to 14 (range 5-16), 0 (range 0-8) and 0 (range 0-5) in the HFNEF group and 13 (range 1-16), 1 (range 0-12) and 0 (range 0-1) in the NoHF respectively.

Sm could not be measured on 181 (2.9%) occasions. The segments without response characteristic were excluded. Amongst the segments that were dysfunctional at rest, 83.3%, 85.2% and 84.2% in the three groups respectively were viable (p=0.892) and 17.9%, 14.8% and 8.9% segments (p=0.071) showed a biphasic response. An ischaemic response was seen in 33.7%, 27.9% and 30% of the segments that were normal at rest and 5.6%, 5.7% and 6.9% of the segments that were abnormal at rest in the three groups respectively.

Mitral Inflow (Figure 4)

E/A became abnormal with stress in 65%, 25% and 36% of the patients (p=0.045) who were normal at rest and remained abnormal in 81%, 67% and 73% patients (p=0.499) who were abnormal at rest in the HF-LVSD, HFNEF and NoHF groups respectively. E/A was pseudonormalised in 29.4%, 56.3% and 62.5% in the three groups (p=0.001) at rest and 21%, 71% and 56.4% patients at peak stress (p=0.000). The prevalence did not change with stress (p=0.269 in HF-LVSD, 0.225 in HFNEF and 0.581 in NoHF).

EDT failed to shorten with stress in 34.4%, 43.9% and 30.2% patients in the HF-LVSD, HFNEF and NoHF groups respectively. The EDTc increased with stress in 52.2%, 58.5% and 53.5% (p=0.795, HF-PLVF v normal, p=0.641) patients in the HF-LVSD, HF-PLVF and NoHF groups and decreased in the rest. Amongst patients with high EDTc at rest, it increased further with stress in 21.7% 28.6% and 38.9% patients (p=0.486), decreased to above normal range in 13.0%, 14.3% and 16.7% patients (p=0.948) in the HF-LVSD, HFNEF and No-HF group respectively. No one in the NoHF group had low EDTc at rest. Amongst patients with low EDTc at rest, it decreased further with stress only in the HF-LVSD group.

IVRT was normal at rest in 47.8%, 65.9%, 58.1% patients in the three groups (p=0.135). It failed to shorten with stress in 21.1%, 46.3% and 34.9% patients in the three groups (p=0.011, HFNEF v normal, p=0.285). IVRTc increased in 55.0%, 67.5% and 58.1% patients (p=0.413, HFNEF v normal, p=0.513) in the three groups. IVRTc increased to >105 msec in 54.8%, 56.3% and 62.5% patients (p=0.878) with resting IVRTc<105 msec in the three groups. Amongst patients with

IVRTc≥105 msec at rest, it decreased to <105 msec in 28.8%, 28% and 14.8% patients (p=0.357).

The E/A ratio decreased in the HF-LVSD group but did not change with stress in the other two. The IVRTc did not change in the HF-LVSD group but got prolonged in the other two. EDTc however did not change with stress in any group.

Mitral annular diastolic velocity (Figure 4 and 5)

The Ea could be measured in all patients at rest. The average peri-annular Ea was lower than normal at rest in 24.4%, 4.9% and 2.3% in the three groups respectively (p=0.000). Amongst the patients with normal Ea at rest, it decreased with stress in 20.6%, 69.2% and 42.9% in the HF-LVSD, HFNEF and NoHF group respectively (p=0.000, p=0.017 HF-PLVF v NoHF group) and increased in the rest. The Ea decreased by ≥20% in 11.1%, 31.7% and 20.9% patients in the three groups respectively (p=0.016, HFNEF v NoHF, p=0.261) while it increased by ≥ 20% in 61.1%, 9.76% and 30.23% in the three groups respectively (p=0.000, HFNEF v NoHF, p=0.02).

Ea/Aa could be measured in >70% patients at rest and peak stress. Ea/Aa was <1 in 71.4%, 84.4% and 85% patients in the three groups (p=0.171) at rest and 84.1%, 90.6% 89.7% under stress (p=0.576) (p for rest v stress: 0.086 for HF-LVSD, 0.450 for HFNEF and 0.526 for NoHF). Of the patients with Ea/Aa>1 at rest, it decreased to <1 in 66.7%, 60% and 83.3% (p=0.324) patients in the three groups with stress. Ea/Aa increased to >1 with stress in 8.9%, 3.7% and 8.8% (p=0.681) of the patients with Ea/Aa<1 at rest, in the three groups.

•

The mean Ea velocity in the HF-LVSD group was lower than HFNEF group that was similar to the normal group at rest. At peak stress, Ea in the HFNEF group was lower compared to the normal group but was similar to the HF-LVSD group. In the HF-LVSD group, Ea and Aa increased with stress and their ratio remain unchanged. In the HFNEF group, Ea decreased, Aa increased but their ratio does not change. In the normal group, Aa increases but there are no changes in the Ea or Ea/Aa. It decreased with stress in the former but not in the later group.

Left atrial pressure

E/Ea could be measured in 98.9%, 97.6% and 100% patients at rest and 95.6%, 100% and 100% patients at stress in three groups. 5.4%, 52.2% and 25% of the patients that had normal resting E/Ea in the HF-LVSD, HFNEF and NoHF groups, had high E/Ea at peak stress. (Figure 4) Among the patients with high E/Ea ratio at rest, it remained high at peak stress in 43.3%, 92.2% and 87.6% patients in the HF-LVSD, HFNEF and NoHF groups. E/Ea decreased to normal in 46.7%, 7.8% and 12.4% patients in the three groups.

At rest, E/Ea HF-LVSD>HFNEF=NoHF (HF-LVSD v HFNEF and NoHF, p=0.000) and HFNEF v NoHF, p=0.391) (figure 5). At peak stress, the E/Ea in the HF-LVSD group was similar to the other groups (p=0.128 v HFNEF, p=0.206 v NoHF group) with HFNEF>NoHF (p=0.002). With stress, E/Ea decreased in HF-LVSD (0.000), increased in HFNEF (p=0.002) and remained unchanged in NoHF group (p=0.598)

In the HF-LVSD group, most patients had E/Ea >15 at rest and 8-15 at stress. Most HFNEF patients had E/Ea 8-15 at rest and >15 at stress. Most NoHF had E/Ea 8-15 at rest and stress. In the HF-LVSD group the prevalence of E/Ea 8-15 increased and that of >15 decreased with stress. In the HFNEF group prevalence of E/Ea >15 increased with stress. (Figure 6A). More than 70% of the patients in the HF-LVSD and HFNEF groups with resting E/Ea<8, worsened with stress compared to 43% in the NoHF group. All HFNEF and 89% of NoHF patients with resting E/Ea 8-15 either remained so or worsened and 39% of HF-LVSD and 11% of NoHF patients improved with stress. Of the patients with resting E/Ea ratio >15, 44% improved in the HF-LVSD group compared to 8% and 12.5% in the HFNEF and NoHF groups (figure 6B).

LVOT gradient

The velocity could not be measured in 1 patient in the HF-LVSD group and 2 in the HFNEF group at peak stress. The maximum velocity (Vmax) was ≥1.5 m/sec in 2.3%, ≥2.0 m/sec in 0.6% and ≥ 2.5 m/sec in 0% patients at rest and 36.3%, 14.0% and 5.8% patients at peak stress. None, 20.5% and 4.7% of patients in HF-LVSD,

HFNEF and NoHF had Vmax ≥2.5 m/sec at peak stress ($p<0.001$). Vmax increased with stress in 87.6%, 97.4% and 100% patients ($p=0.016$) and increase was ≥20% in 66.3%, 84.6% and 88.4% ($p=0.007$) in the three groups. The average velocity in the HF-LVSD group was lower than both the other groups at rest and at peak stress ($p<0.05$, ANOVA) with no difference between the HFNEF and NOHF groups. It increased with stress in all the three groups ($p<0.001$ for all three groups).

DISCUSSION

Evaluation of subjects with suspected heart failure using TDI supplemented DSE has identified new or worsening regional, global and long axis systolic and diastolic dysfunction. Prognostic volumes of dysfunctional but viable myocardium was found not only in those with reduced LVEF but also in those without. The improvement of overall LV function, as measured by WMSI, with LDDSE matched these changes. The prevalence of hibernating myocardium in patients with HF and LVSD was similar to that previously reported. (321;322) These findings may have prognostic significance. In medically treated patients with post-infarction LVSD, the extent of hibernating myocardium, determined either by the degree of improvement of WMSI or by the proportion dysfunctional segments that improve with LDDSE, predicts survival. (323) The extent of myocardial hibernation and/or ischaemia determines the improvement in LVEF in patients with ischaemic and non-ischaemic cardiomyopathy treated with carvedilol (324-326) and bucindolol. (327) In a meta-analysis where half of the patients had their viability tested using DSE, revascularisation offered a higher prognostic benefit compared to medical therapy for patients with chronic CAD and LVSD with viable myocardium while absence of viability was associated with no significant difference in outcomes, irrespective of treatment strategy. (115) The extent of hibernating myocardium predicts survival, improvement in LVEF and functional status after revascularization in chronic ischaemic LVSD. (173;176;316-318) Contractile reserve however, did not predict outcome in one study. (318) Ischaemia was detected in 35%, 6% and 10% of dysfunctional segments in the three groups. Myocardial ischaemia detected by DSE was predictive of cardiac death in ischaemic cardiomyopathy treated medically after adjustment for LVEF in some (175;323;328) but not all studies.

(318;329) The prevalence of coronary disease is between 5-67% in patients with HFNEF. Studies with higher prevalence of CAD reported higher annual mortality rate in contrast to those that excluded patients with coronary disease. 84 Despite this high prevalence of CAD, there is paucity of data on the extent of hibernation in patients with normal LVEF presenting with symptoms suggestive of heart failure.

The trans-mitral variables of LV diastolic function that either became abnormal or continued to remain abnormal with stress were common in all the three groups. This is consistent with some (77;80;186) but not all studies. (75;76) The interpretation of these changes during DSE is constrained by the influence of multiple factors on these variables during various stages of the test. These variables are influenced not only by the relaxation properties of the myocardium in diastole but also by the pre- and after-load of the ventricle, age and sex of the subjects, presence or absence of LV hypertrophy, heart rate, intraventricular conduction abnormalities, PR interval etc. During dobutamine stress testing, many of these factors are altered depending on the stage of the test making rest-stress comparisons difficult. Lowering of after-load due to the vasodilatory effects of low dose dobutamine may "truly" improve an abnormal resting diastolic filling pattern. Increase in the left atrial pressure due to stress-induced ischaemia may pseudonormalise the resting delayed relaxation pattern. These may underestimate the prevalence of diastolic abnormality at peak stress. Trans-mitral velocity that measures global LV diastolic function may not be altered if only small areas of regional dysfunction are induced with stress. Fusion of the E and A waves and shortening of the diastolic timings at higher heart rates are additional problems.

Sa and Sm are well-established indices of longitudinal LV global and regional systolic function. (213;330;331) Resting Sa <2.8 cm/s predicted survival in patients with LVSD. (319) Basal Sm at peak stress of <6 cm/s predicted cardiac death and non-fatal infarctions in patients with known or suspected coronary artery disease, 60% of whom had resting RWMA. (332) Investigators have reported the ability of Sm to identify dysfunctional segments with fair degree of accuracy. Sm (cTDI) of the non-apical segments of ≤ 5.5 cm/sec at peak stress identified visually abnormal segments 96% sensitivity, 81% specificity and 86% accuracy irrespective whether

the segment was basal or mid-wall. (255) Sm (pTDI) <12cm/s distinguished ischaemic from non-ischaemic segment with sensitivity and specificity of 86% and 96% for the basal regions, and 81% and 89% for the mid segments. A percentage increase in Sm of <90% from rest to peak identified ischaemic segments from normal segments with a sensitivity and specificity of 83% and 87%, respectively. (188) TDI is able to detect improvements in the velocity of contraction earlier than that possible visually, (254) making it a sensitive tool for detection of viability in hypocontractile segments with low dose DSE. (333;334) Rambaldi et al demonstrated that improvement of systolic velocity, measured by pTDI, of 1±0·5 cm/s predicted myocardial viability confirmed with F18-fluorodeoxyglucose-SPECT, with a sensitivity of 87% and a specificity of 52%. (268)

Ea, an index of diastolic relaxation at rest (202;335;336) and during sinus tachycardia (183) is relatively load independent (193;202;204;209) making it more suitable for assessment of such function during DSE. However, this has rarely been assessed during DSE. (185;188) The response of Ea to stress is influenced by a number of physiological processes often with opposing effects. Sa and Ea are positively and non-linearly correlated across a wide range of LVEFs at rest. (61;62) This is due to the inter-dependence of the systole and diastole. During systole, the longitudinal shortening and "twisting" motion of the myocardial fibres compresses the elastic cardiac elements generating potential energy that is stored within the coiled fibres of the myocardium. This creates early diastolic restorative forces that produce diastolic recoil that contributes to the Ea velocity. It is thus conceivable that inotropic stimulation during dobutamine stress would result in a parallel increase in both the Sa and Ea. The lusitropic effect of dobutamine is also likely to increase in the Ea velocity. On the other hand, dobutamine stress induced ischaemia, hypertension and tachycardia may impair diastolic relaxation and reduce Ea. Stress-induced ischaemia impairs both regional (184;185;188) and global left ventricular diastolic relaxation (77;80) and this occurs earlier than the impairment of systolic contraction. (187) Even transient, reversible episodes of ischaemia can impair LV relaxation and elevate LV filling pressures (74) Ischaemia induced by dobutamine stress (188) and coronary occlusion (81) causes regional impairment of myocardial relaxation of ischaemic segments even when systolic

contraction is preserved. (79) Stress-induced tachycardia worsens ischaemic diastolic relaxation by increasing myocardial oxygen demand and decreasing coronary perfusion time. It shortens the diastole allowing less time for relaxation. This is further amplified in hypertrophied and fibrosed myocardium that is unable to generate a higher rate of diastolic relaxation causing the diastolic pressures to increase. (85;189) Stress-induced elevation of systolic blood pressure, slows LV relaxation due to increased afterload with a resultant increase in the LA pressure. (82) In hypertensives, a rapid increase in SBP at rest 94 or following exercise (183) results in deterioration of LV diastolic function without worsening systolic function. Similar changes in response to stress have been demonstrated in patients with HFNEF. (84) Sa and Ea increased with stress in HF-LVSD group. This is likely to have resulted from the inotropic and lusitropic effect of dobutamine. As Ea was measured at submaximal stress to avoid the problem of fusion, significant hypertension and tachycardia are unlikely to have affected it. The degree of ischaemia at these stages was also likely to be low but probably severe enough to impair diastolic but not systolic function. The effect of dobutamine induced augmented systole may have overridden the negative effect of low-grade ischaemia on Ea resulting in net increase of Ea. On the other hand, Sa increased and Ea decreased with stress in the HFNEF patients. The difference in the ultrastructural and functional properties of the myocardium between these groups (337-344) may have affected this diverse response. The low-grade hypertension and tachycardia at submaximal stress, when Ea was measured, may have been enough to reduce Ea in the presence of an abnormally relaxing myocardial substrate. The effect of ischaemia on diastolic function may also have been intensified in the presence of such a substrate.

In the HFNEF group, most patients with high resting E/Ea ratio remained so at stress while it worsened in 70% of patients who were normal at rest. The E/Ea increased with stress in a substantially more patients in the HFNEF group than in the NoHF group. This is consistent with invasive findings of impaired diastolic relaxation and a rise in the left atrial pressure during exercise in patients with HFNEF. (183)

In the NoHF group, the E, Ea, Aa increased with stress with no change in the E/Ea or Ea/Aa ratios. This response was similar to that of normal subjects. (194)

LIMITATIONS

Pharmacological rather than exercise stress was used in this study. Exercise being the most physiological stressor would have been preferable. Supine bicycle ergometry was not available. Treadmill exercise, the available form of exercise stress in our setting, has several limitations. Only 40% of patients tested for CAD, can perform a truly diagnostic exercise test. (101;102) This proportion is likely to be even lower in the elderly patients, with musculoskeletal or neuromotor problems, general frailty and breathlessness, that were studied. The heart cannot be continuously imaged. Thus the time of onset of ischaemia and changes in the cardiac function at each level of exercise cannot be precisely identified. Myocardial viability, a prognostically important component of left ventricular evaluation in patients with heart failure, cannot be assessed. Ischaemia induced wall motion abnormalities may resolve if imaging is not completed quickly after the completion of exercise. Even under "study" conditions, about a third of new RWMA that develop at peak exercise may resolve by the time images were acquired after exercise. About 29% patients may be missed if imaging is performed only after exercise. (105) In 31% of patients with positive exercise echocardiography, the new RWMA at peak exercise resolved at post-exercise imaging obtained within 80 seconds of exercise termination. (106) It was envisaged that imaging was unlikely to be completed in a significant proportion of the subjects studied within 60-90 minutes of completing exercise. However, as both exercise and dobutamine have a similar accuracy for the detection of coronary disease; (107-109) it was felt that DSE would not be inferior to exercise for studying the patients with suspected heart failure.

The procedural limitations affecting DSE and cTDI influenced the study. The absence of universally accepted gold standard definition of LV diastolic dysfunction and the influence of heart rate and loading conditions on the diastolic mitral inflow velocities made interpretation if these changes difficult. These variables had to be assessed at sub-maximal stress to avoid fusion of the diastolic velocities. This was

considered reasonable, as these breathless patients are unlikely to achieve age-predicted maximal heart rates during daily living. Moreover, sub-maximal stress is likely to be adequate to unmask LV diastolic dysfunction as the later is induced by ischaemia earlier than systolic dysfunction. The E/Ea measured using cTDI is higher than previously reported with pTDI. (20;345) The conversion used (21) may be somewhat arbitrary. Without measured NT-proBNP the diagnosis of heart failure in patients with normal ejection fraction was clinical.

The study groups were not compared to "true" healthy controls. The mean age of the HFNEF and the NoHF groups was similar. A proportion of patients with HFNEF who were very elderly may not have been recruited, as seen in other research studies, driving down the mean age in this group. The prevalence of diabetes, hypertension, COPD and LV hypertrophy all of which may affect diastolic function was also similar. This resulted in similar prevalence of resting LV diastolic dysfunction in these groups as reflected in the measured echocardiographic variables.

The therapeutic and prognostic implications of the findings in this heterogeneous group of patients were not tested. However, studies on better-defined populations suggest that the implications are likely to be significant.

CONCLUSION

TDI supplemented DSE is feasible only in a very selected group of patients that are referred to a heart failure clinic. It reveals information on cardiac function that is not identifiable at rest but have diagnostic, therapeutic and prognostic implications. DSE may be especially useful in evaluating patients with symptoms suggestive of heart failure but normal ejection fractions. The increase in the LVEDP with stress in patients with HFNEF may explain the exercise intolerance in these patients. The therapeutic and prognostic implication of the data in a heterogeneous group of subjects with suspected heart failure needs to be tested in larger outcome studies.

Table 5.1 Baseline characteristics of the study population

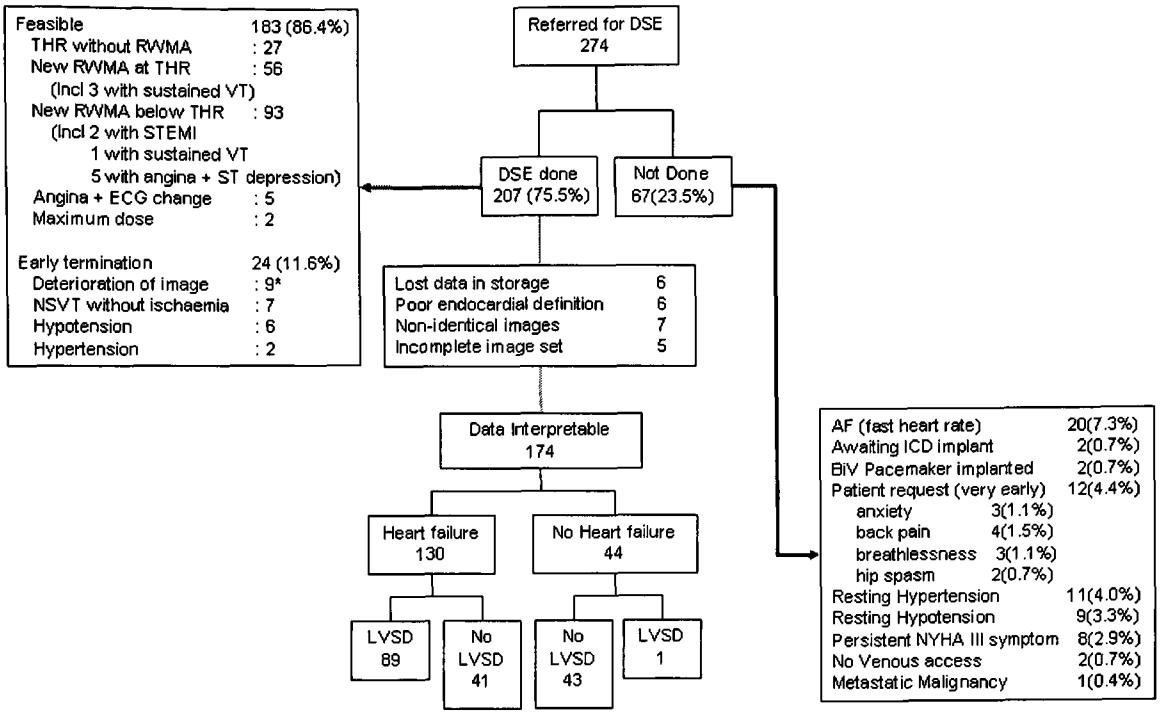
	HF-LVSD (n=90)	HFNEF (n=41)	No HF (n=43)	HFNEF v NoHF (p)	ANOVA (p)
Age (years) (mean±SD)	68±9	70±11	68±11	0.37	0.51
Age (yrs) range (median)	43-88(69)	42-86(74)	46-89(69)	-	-
Males (%)	80.0	46.3	51.2	0.05	0.00
BMI (mean±SD)	27.45±3.6	26.64±4.8	26.65±3.3	0.99	0.38
NYHA (I/II/III/IV) (%)	1/31/58/0	0/27/14/0	43/0/0/0	0.00	0.00
Risk factors for CAD					
H/O Smoking (%)	64.4	63.4	62.8	1.00	0.98
Diabetes (%)	18.9	19.5	13.9	0.79	0.74
Family history (%)	35.5	31.7	32.5	1.00	0.89
Hypertension (%)	64.4	63.4	46.5	0.30	0.12
History of					
Angina (%)	61.1	63.4	23.3	0.00	0.00
Revascularisation (%)	28.9	9.7	0.0	0.03	0.00
Myocardial infarction (%)	47.8	29.3	7.0	0.03	0.00
Valvular disease (%)	8.9	7.3	9.3	0.95	0.94
COPD (%)	26.7	24.4	30.2	0.87	0.83
Drugs					
Loop diuretics (%)	74.4	75.6	26.5	0.00	0.00
ACEI or ARB (%)	67.8	68.3	44.2	0.08	0.02
Beta-blockers (%)	68.8	70.7	37.2	0.01	0.00
Aspirin (%)	86.7	87.8	34.9	0.00	0.00
Wafarin (%)	8.1	9.7	0.0	0.11	0.13
Spironolactone (%)	23.3	4.9	0.0	0.34	0.00
Systolic BP (mmHg)	134±24	148±22	145±18	0.50	0.00
Diastolic BP (mmHg)	80±13	85±11	83±11	0.47	0.04
6-min walk test (m)	217±139	174±109	363±96	0.00	0.00
Sinus rhythm (%)	74.4	78.1	90.7	0.65	0.09
Heart Rate	76±15	76±14	75±13	0.69	0.76

Table 5.2: Resting echocardiographic characteristics

	HF-LVSD (n=90)	HFNEF (n=41)	No HF (n=43)	HFNEF v NoHF (p)	ANOVA (p)
IVSd	1.3±0.3	1.4±0.4	1.3±0.4	0.31	0.55
IVSs	1.5±0.4	1.7±0.5	1.6±0.4	0.30	0.05
LVPWd	1.4±0.5	1.3±0.3	1.2±0.4	0.61	0.38
LVPWs	1.8±0.5	1.7±0.3	1.7±0.5	0.81	0.64
LVIDd (cm)	6.4±0.9	4.7±1.1	5.0±0.9	0.16	0.00
LVIDs (cm)	5.2±1.0	3.1±1.0	3.5±0.8	0.16	0.00
LV mass (gm)	411±178	248±114	249±95	0.95	0.00
LV mass index (gm/m^2)	218±81	139±65	139±54	0.97	0.00
LVH n(%)	54 (60.0)	22 (53.7)	23 (53.5)	-	0.69
LVEDVol (ml)	135±55	71±26	83±33	0.06	0.00
LVESVol (ml)	92±44	24±12	34±17*	0.00	0.00
LVEDVIsmp	74±31	39±14	46±17	0.06	0.00
LVESVIsmp	50±26	14±7	19±9**	0.01	0.00
LVEDVol high n (%)	38 (42.2)	1 (2.4)	3 (7)	-	0.00
LVESVol high n (%)	70 (77.8)	2 (4.9)	6 (13.9)	-	0.00
EF (mean±SD)	33±9	66±9	60±10*	0.00	0.00
WMSI >1 n (%)	90 (100)	17 (41.4)	21(48.8)	0.50	0.00
WMSI ≥1.6 n (%)	77 (85.6)	0	0		
E/A <0.5 (%)	22.1	9.4	0	-	0.00
E/A >1.7 (%)	26.5	3.1	2.5	-	0.00
EDT long n(%)*	14 (15.7)	14 (34.2)	13 (30.2)	-	0.03
EDT short n(%)*	20 (22.2)	4 (9.8)	1(2•3)	-	0.01
IVRT long n(%)	48 (53.3)	14 (34.2)	18 (41.9)	-	0.10
Mod-sev MR n(%)	34 (37.8)	7 (17.0)	3 (7.0)	0.18	0.00
Mod-sev TR n(%)	17 (18.9)	4(9.8)	2(4.7)	0.33	0.05
Mild AS n (%)	3 (3.3)	2 (4.9)	2 (5.6)	0.80	0.76
Raised PAP n (%)	21 (23.3)	2 (4.9)	2 (5.6)	0.82	0.00
LVDD %	55.6	43.9	53.5	0.38	0.45

Low Sa %	87.8	31.7	34.9	0.70	0.00
Low Ea %	24.4	4.9	2.3	0.56	0.00
High Aa %	2.2	7.3	9.3	0.70	0.17
Ea/Aa<1 %	48.9	65.8	79.1	0.35	0.00
Normal E/Ea %	7.8	9.8	16.3	0.38	0.32

LVIDd, LV internal diameter in diastole. LVIDs, LV internal diameter in systole. LVEDvol, LV end-diastolic volume. LVESvol, LV end-systolic volume. EF, ejection fraction. MR, mitral regurgitation; TR, tricuspid regurgitation; AS, aortic stenosis; PAP, pulmonary artery pressure. LVDD, LV diastolic dysfunction; EDT, E-wave decelarartion time; IVRT, isovolumic relaxation time; *age dependent cut-off values.



* These patients excluded from the final analysis

Figure 5.1. The patient journey.

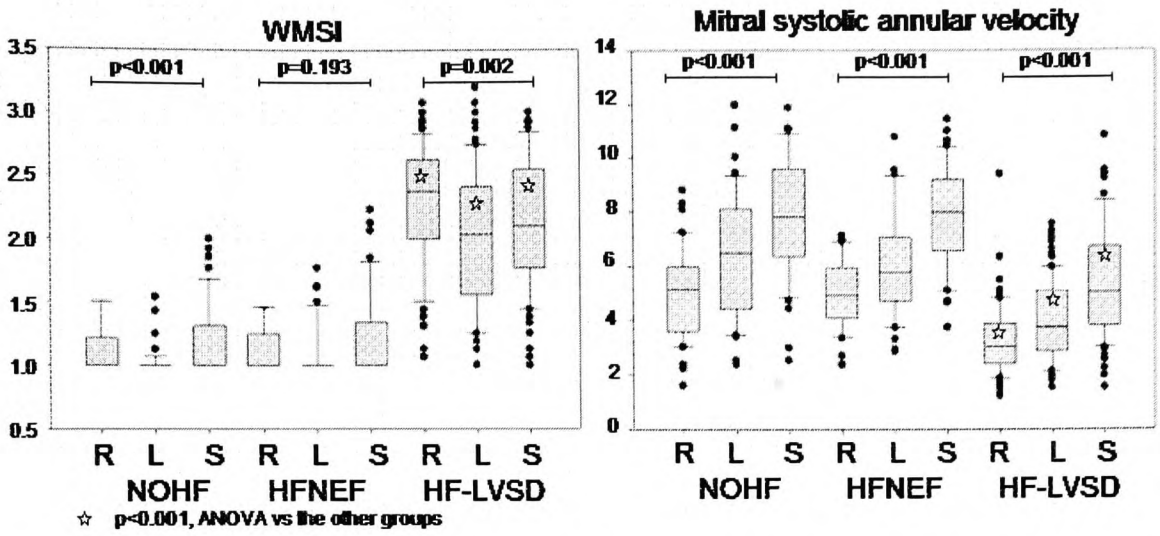


Figure 5.2. Median, interquartile range, 95% confidence and outlying results for wall motion score index and mitral annular systolic velocity in the three groups at rest, low dose dobutamine and peak stress.☆p<0.001, ANOVA vs the other groups.

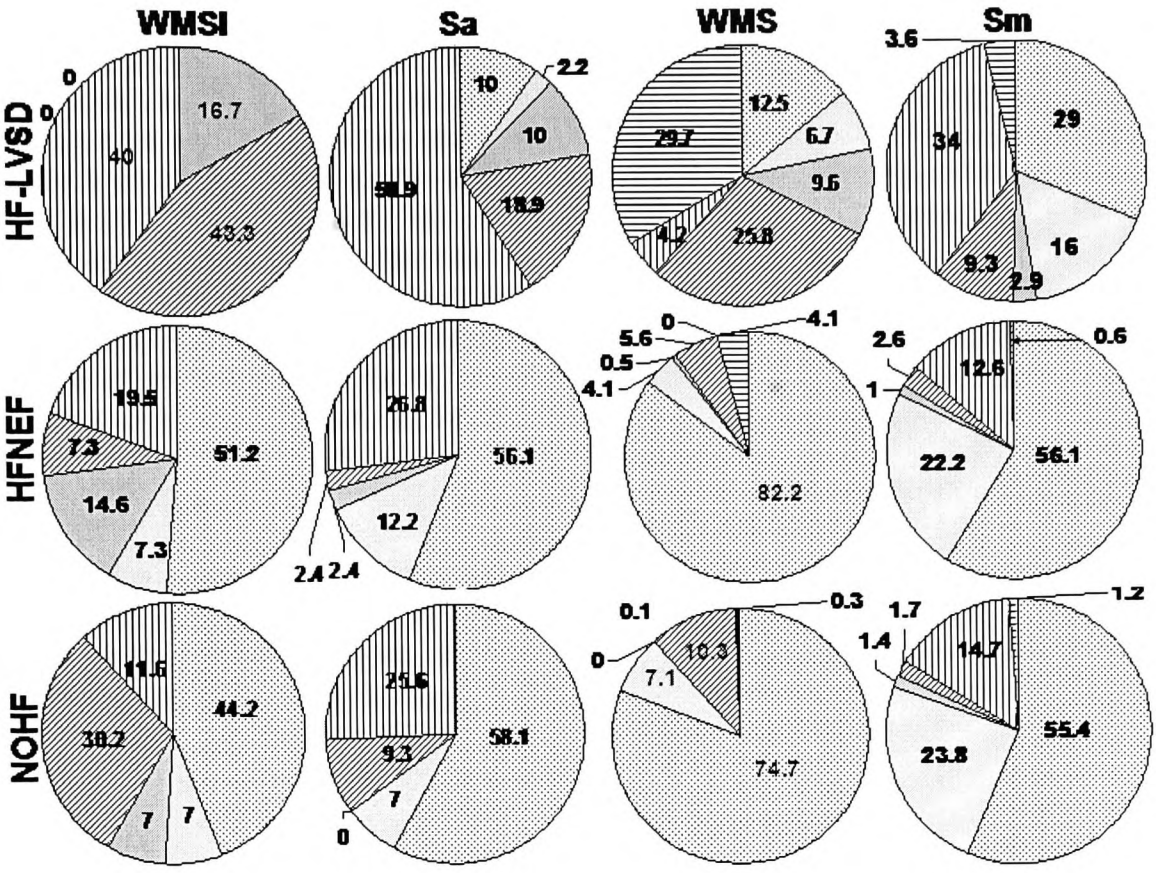


Figure 5.3. Pie-chart showing the response of the ventricles to stress in the three groups. WMSI and Sa are reported as % of the total number of patients studied. Segmental WMS and Sm are reported as % of the total number of segments studied. The small % of segments not accounted for include the ones that either could not be assessed at rest and/or stress or a response to stress could not be determined.

N-N, normal at rest with normal response to stress (normal). N-I, normal at rest and worsened with stress (ischaemic) A-I, abnormal at rest and worsened with stress (ischaemic) A-B, abnormal at rest with biphasic response to stress (viable and ischaemic) A-SI, abnormal at rest with sustained improvement with stress (viable and non-ischaemic) A-S, abnormal at rest with no change with stress (scar).

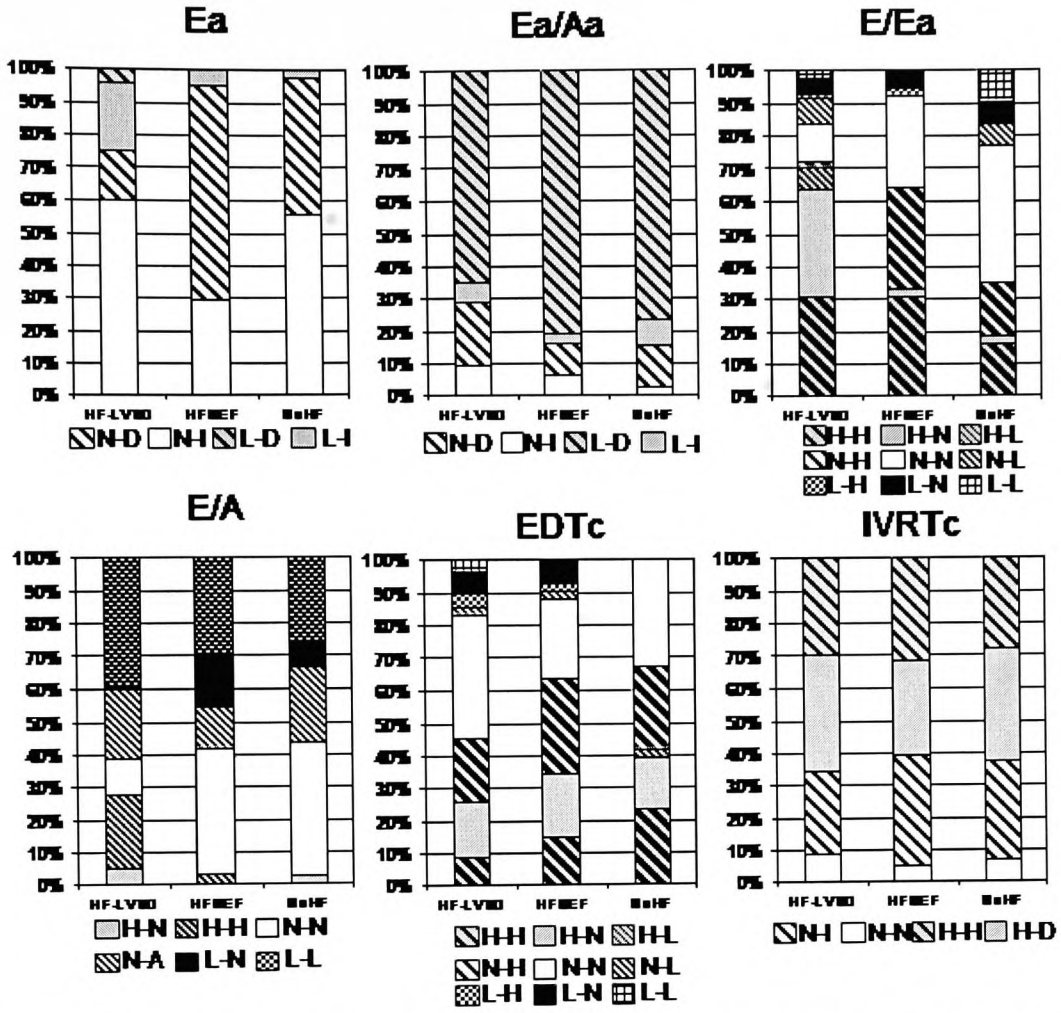


Figure 5.4. Changes (first letter denoting the resting and second, the stressed state) in the prevalence of the diastolic variable as a % of the total number of patients. H, high; N, normal; L, low; D, decreased; I, increased; A, abnormal

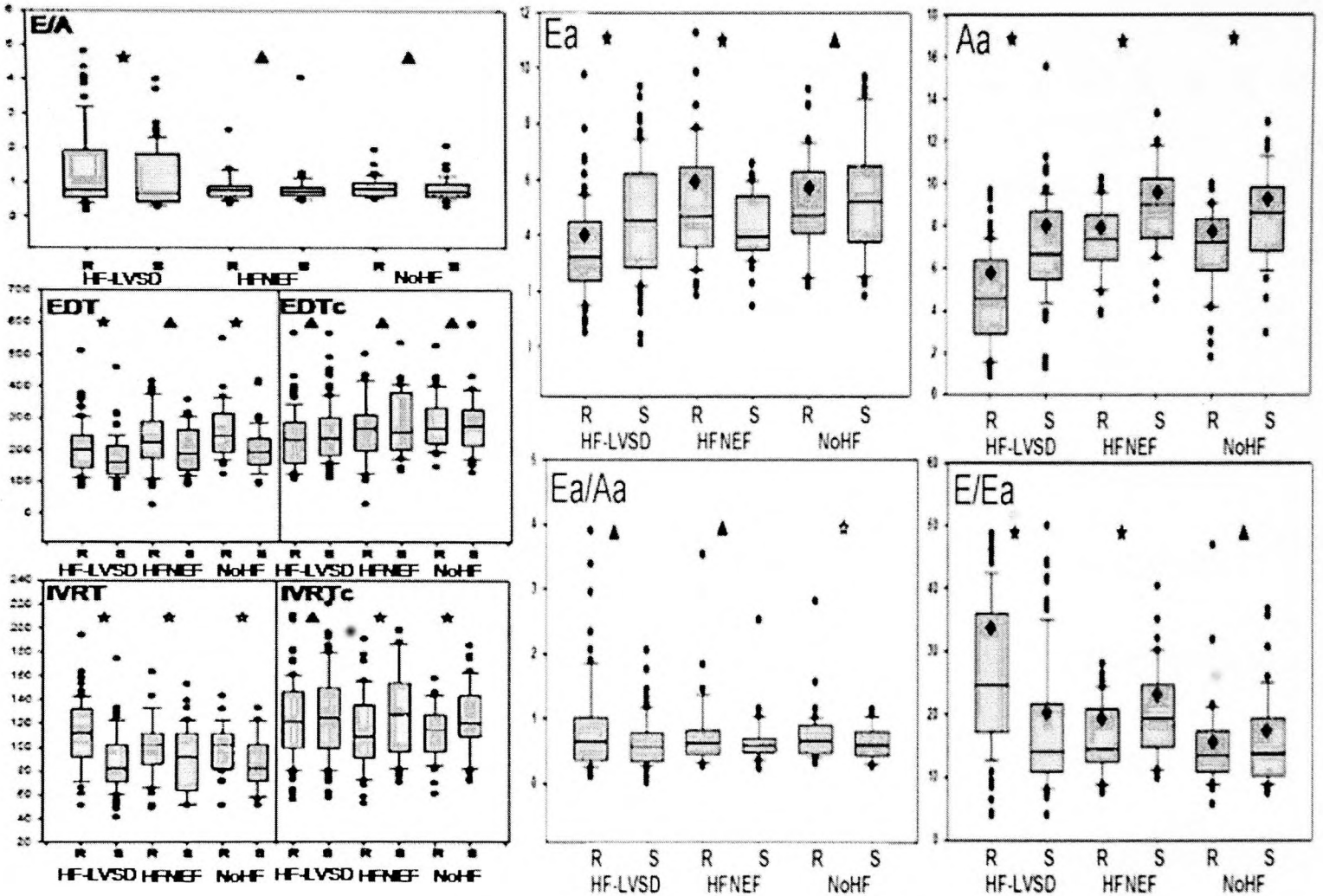


Figure 5.5. Median, interquartile range, 95% confidence and outlying results for mitral inflow and annular diastolic parameters in the three groups at rest and peak stress. ★p<0.001, ☆p<0.01, ☆p<0.05, ▲p=ns. ◆p<0.001, ◇p<0.05 for ANOVA.

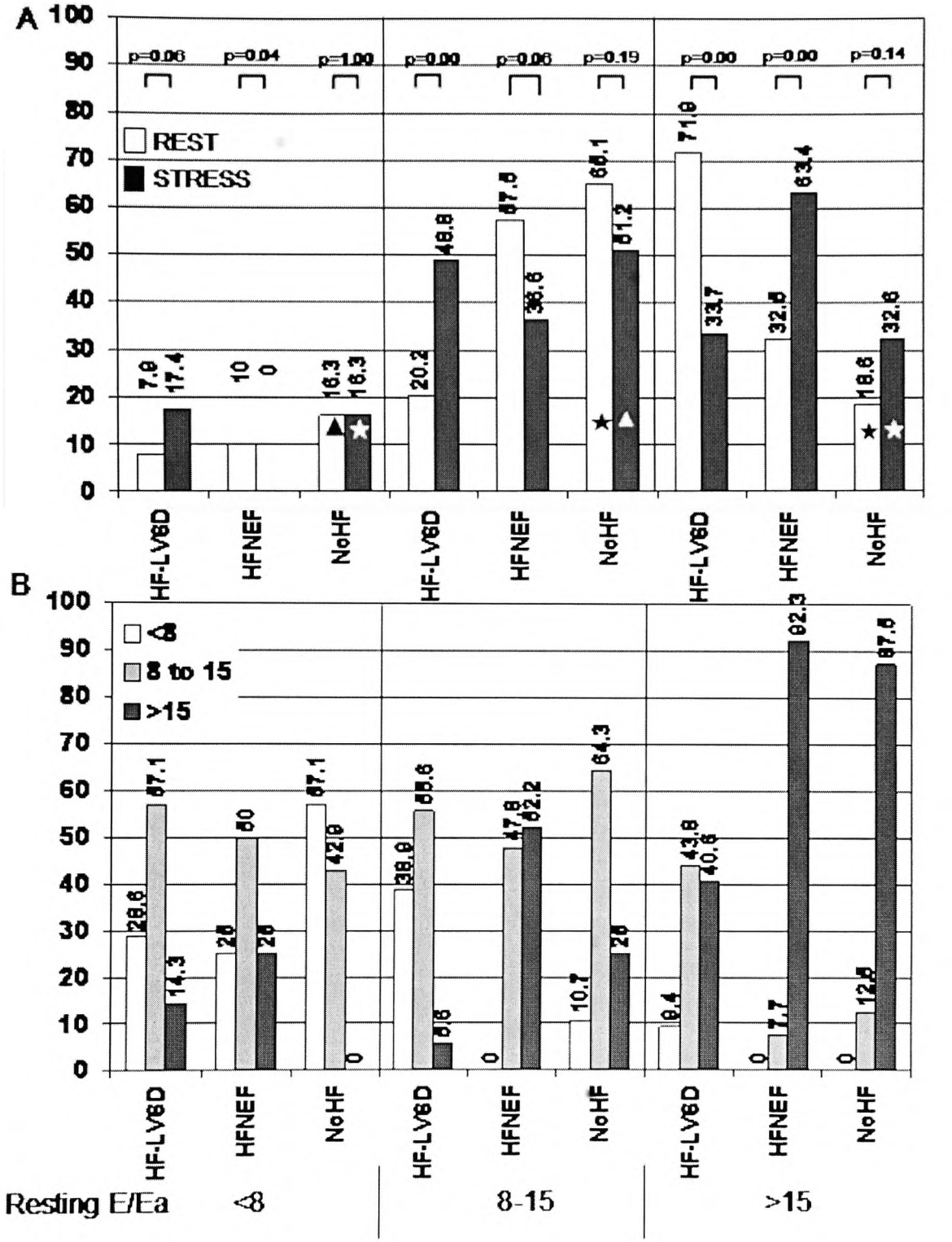


Figure 5.6. A. Changes in the prevalence of E/Ea ratios amongst patients with resting E/Ea <8, 8-15 and >15 in the three groups. B. Patients with E/Ea <8, 8-15 and >15 at peak stress as a % of patients with resting E/Ea <8, 8-15 and >15.

Chapter 6: Impaired Diastolic Reserve in Patients with Heart Failure and Normal Ejection Fraction. *Circ Heart Fail 2009 Oct 30. [Epub ahead of print]*

ABSTRACT

Background: The genesis of symptoms in patients with heart failure (HF) and normal ejection fraction (HFNEF) is unclear. Most investigations of HFNEF have focused on cardiac function at rest though most of these patients are breathless only on exercise. Stress induced impairment in systolic or diastolic function could result in these symptoms.

Method and results: Forty-one patients with HFNEF and 29 controls underwent DSE with cTDI. Regional wall motion score and wall motion score index (WMSI) and regional myocardial systolic velocity (Sm) were measured at and peak stress. Sa, Ea and Aa were averaged over the 6 peri-annular sites. Sa, but not the Ea, Aa or Ea/Aa ratio, was lower and the E/Ea ratio was higher in the HFNEF than controls at rest. Global, regional and long axis systolic function did not worsen with stress in the HFNEF group. The Ea decreased and the E/Ea increased with stress in the HFNEF but not in controls. The 6-minute walk distance was shorter and negatively correlated to the E/Ea ratio at rest and stress only in the HFNEF group.

Conclusion: Impaired diastolic reserve resulted in stress-induced increase in the left ventricular end-diastolic pressure (LVEDP) in patients with HFNEF giving rise to exercise intolerance.

INTRODUCTION

The clinical syndrome of heart failure may arise in the absence of any substantial abnormality of conventionally measured LVEF. Epidemiological studies suggest that up to half of subjects with heart failure have a normal LVEF.(13;29;51-53;346) The genesis of the symptoms of HF in the absence of reduced global LV systolic function is uncertain and may reflect a great deal of heterogeneity. Misdiagnosis may account for a proportion of cases.(55) Transient LVSD may occur due to ischaemia or arrhythmia (56) although serial echocardiographic studies have suggested that this is rare. (63) Many patients do have subtle forms of LVSD e.g. selective impairment of long-axis systolic and diastolic dysfunction at rest that do not manifest as a major impairment of global LVEF. (57;58)

Most investigations of HFNEF have focused on cardiac function at rest, yet most patients are breathless only on exertion. The pathophysiological basis of the exercise induced symptoms and signs in these patients with HFNEF has not been well characterised.

DSE is a standardised method of assessing the heart under stress. Using cTDI with DSE, global, regional and longitudinal systolic and diastolic function can be measured. (193;204) These techniques were used to test the hypothesis that stress induced diastolic impairment occurs and might contribute to exercise induced breathlessness in patients with HFNEF.

METHOD

Patient Selection

Patients with a suspected HFNEF were identified from a community-based heart failure programme. The diagnosis of HF was based on clinical evaluation by a cardiologist on the basis of the patients' previous and current history and physical examination in concordance with the ESC definition of HF.(1) Most patients had previous hospital admissions with acute breathlessness, clinical and/or radiological evidence of pulmonary congestion and clinical improvement with diuresis. The patients with pacemakers, severe valvular disease, prosthetic heart valves, inadequate echocardiographic window and contraindication to DSE were excluded.

From a cohort of 200 consecutive patients with suspected heart failure who were referred between January 2002 and June 2003, 41 subjects (HFNEF group) were identified who matched the study criteria. Twenty-nine other subjects without a history of diabetes, hypertension, angina, myocardial infarction, with normal ECG, echocardiogram, and whose breathlessness was thought to be due to other problems (13 with obesity, 8 with obstructive airways disease, 1 with restrictive airways disease, 5 with obesity and obstructive airways disease and 2 with undetermined cause) acted as controls (control group). All subjects gave written informed consent. The Medical Ethics Committee of the Hull and East Yorkshire NHS Trust approved the protocol.

Study protocol

Following clinical evaluation, resting echocardiography the patients underwent a DSE supplemented with cTDI using a standard dobutamine atropine protocol. The procedure is detailed earlier.

Statistical analysis

As described earlier.

RESULT

Patients with HFNEF (table 1) had a higher prevalence of hypertension, diabetes and previous myocardial infarction and greater use of ACEI or ARB and beta-blockers. The mean BMI and the prevalence of obesity were similar in each group. The mean FEV1/FVC ratio was higher in the HFNEF group but a similar proportion in each group had a ratio <75%. The blood pressure and LVEF were higher on average in patients with HFNEF.

Reproducibility

The intra-observer variability for all velocities was <10% at rest (Sa: 2.4-8.1%; Ea:3.4-8.3%; Aa: 3.3-8.1% and Sm:3.2-9.8%) and 13% at stress (Sa: 2.1-9.3%; Ea:2.9-12.7%; Aa: 2.7-6.3% and Sm:4.1-12.4%). The reproducibility of the annular measurements was better then that of the myocardial segments.

Response to stress

No major adverse event occurred during DSE (table 1). The final dose of dobutamine was higher in the controls. The blood pressures increased with stress in both groups. Intraobserver variability of the measured myocardial velocities remained low at rest (<10%) and peak stress (<15%).

The WMSI was similar in both groups at rest and at stress and did not worsen with stress in either group (figure 1). Fifty one percent and 59% patients at rest (p=0.540) and 68% and 69% patients at peak stress (p=0.952) had WMSI of 1 in the HFNEF and control groups respectively (p=0.115 rest v stress in HFNEF and p=0.412 rest v stress in controls). The increases in WMSI did not exceed 20% in any subject. 96.5% segments in the HFNEF group and 91.6% in controls could be assigned a response to stress (p<0.001). Except for a higher prevalence of scars in the HFNEF group, the segmental response to stress was similar in the two groups (table 1).

Six patients in the HFNEF group and none in the control group had low Sa at rest. The Sa (figure 1) was lower in the HFNEF group than the controls at rest and peak stress but increased with stress in both groups. Sa increased from rest to stress in all subjects with increase of >20% seen in 37/41 (90.2%) and 26/29 (89.7%) in HFNEF and controls respectively. The Sa was higher in the controls in all the walls at rest and most walls at peak stress. With stress, it increased in all walls in both groups (table 2).

The mean Sm for each non-apical segment of the HFNEF group was similar to that of the controls at rest and peak stress except those for the inferior basal and anteroseptal basal segments that were higher in the controls at peak stress. It increased for all the segments of both groups in response to stress (table 2). Amongst the segments that could be assessed quantitatively at rest (97.2% in the HFNEF and 98.9% in controls) Sm was low in 18.4% and 9.9% segments in the HFNEF and controls respectively (p=0.001). Amongst the segments that could be

assessed quantitatively at rest and stress, the Sm decreased with stress in 27.6% segments in the HFNEF group compared to 28.7% in controls (p=0.727).

The averaged LVOT gradient of the HFNEF group was similar to controls both at rest and peak stress and increased with stress in both groups (table 2). The highest LVOT gradient recorded were 13.5 and 8.4 mmHg at rest and 52.1 and 46.2 mmHg at peak stress in the HFNEF and controls respectively. The highest increases in the LVOT gradient with stress were 47.7 and 39.7 mmHg in the two groups respectively.

Conventional measures of LV diastolic function (table 2) were similar in both groups at rest and stress. With stress, the E/A ratio remained unchanged and the IVRT and EDT shortened in both groups. The heart rate corrected IVRT increased in the HFNEF group but not in controls and EDT did not change in either group. Diastolic LV dysfunction at rest was seen in 39% of subjects (14 with slow isovolumic relaxation and 2 with restrictive filling pattern) with HFNEF and 52% of the controls (15 with slow isovolumic relaxation) respectively (p=0.292).

The changes in the prevalence of the diastolic variables are shown in figure 2. E/A decreased with stress by >20% in 26% and 33% patients in HFNEF and controls respectively (p=0.53). Amongst the subjects with normal EDT at rest, it increased or failed to decrease in 50% in the HFNEF and 42% in controls (p=0.606). Amongst the patients with normal IVRT at rest, it failed to decrease in 58% and 43% in the two groups (p=0.37).

At rest, E/Ea ratio in the HFNEF group was higher than the controls (figure 3). At peak stress, the Ea and Ea/Aa were lower and the E/Ea ratio higher in the HFNEF group compared to controls. The Ea and Ea/Aa ratio decreased and the Am and E/Ea ratio increased in the HFNEF group with stress. In the controls, all the variables remained unchanged with stress except Aa that increased.

The Ea decreased by at least 20% in 47.5% and 17.3% (p=0.009) and increased in the same amount in 7.5% and 24.1% (p=0.05) in the HFNEF and controls

respectively. E/Ea ratio increased by ≥ 20% in 72.5% and 31.0% (p=0.001) subjects in the two groups respectively. Amongst those whose Ea decreased with stress the E/Ea increased in 97.1% patients in the HFNEF group and 58.3% in the controls (p=0.001).

The distance walked in 6 minutes was shorter in the HFNEF group compared to controls. On univariate analysis, (table 3) E/Ea (p<0.001), Ea (p=0.008), E (p<0.001), A (p=0.028) at peak stress; E/Ea (p<0.001), EDT (p=0.045), E (p=0.042), A (p=0.014) at rest and age (p=0.003) correlated with the 6 minute walk distance.

There was a negative correlation between the distance walked and the E/Ea ratio at rest and stress (figure 4) in the HFNEF group.

DICUSSION

This study excludes stress-induced LVSD as a common cause of symptoms in patients with HFNEF. Obesity and obstructive airways disease are also unlikely to account for these symptoms. Impaired diastolic relaxation provoked by stress associated with increased LV end-diastolic pressure (LVEDP) is likely to reduce exercise tolerance in these patients.

The symptoms in patients with HFNEF have been attributed to obesity, respiratory disease and myocardial ischaemia. (55) This study does not support these hypotheses. High BMI and abnormal spirometry were equally prevalent in the HFNEF and control groups. Search for myocardial ischaemia, transient but extensive enough to impair global LV systolic function has rarely been undertaken in these patients. In most studies history of CAD, electrocardiographic evidence of myocardial infarction or ischaemia and coronary angiography has been used to as evidence of ischaemia. (55;89) Ischaemia was systematically evaluated in only 1(n=20) (88) of the 11 studies (n=763) reviewed by Choudhury et al and was found to be absent. (89) Preserved LV systolic function during episodes of pulmonary oedema has been reported in hypertensives. (63) Studies have suggested exclusive diastolic impairment in patients with HFNEF. (90;91) In our

HFNEF patients global, regional and long axis systolic function did not worsen with stress suggesting that ischaemia-induced systolic dysfunction is an unlikely cause of heart failure. The lack of evidence of LVSD in patients with HFNEF may be due to the remoteness of its estimation relative to the episode of heart failure. (52) Though the LV function was not assessed in relation to an episode of heart failure, it is unlikely that these symptoms were due to LVSD, in the absence of stress-induced systolic abnormalities.

Impaired LV long-axis systolic function at rest has been reported in HFNEF. (57;58;60) Consistent with these studies, the resting Sa was lower in the patients compared to controls. Baicu et al (91) argued that the impaired resting long axis systolic function reported in these studies (57;58;60) resulted from the inclusion of a substantial number of the patients LVEF <0.50 into the HFNEF group. None of our HFNEF patients had LVEF <0.50. Contrary to a previous report (59) the Sm of most segments in the two groups were similar at rest. The Sa and Sm increased during stress in the HFNEF group as in controls suggesting improvement rather than a deterioration of the long axis function with stress.

Effect of stress on diastolic function

The changes in the indices of diastolic function in the controls were consistent with the effects of exercise on these indices in normal middle-aged subjects. (194) The effect of stress on LV diastolic indices has rarely been studied in patients with HFNEF. Kitzman et al demonstrated a increase in LV filling pressure with exercise in 7 patients with heart failure and preserved systolic function. (183) Similar changes have been reported in normotensive patients with normal LVEF without inducible myocardial ischaemia and exaggerated SBP response to exercise (83) and in about a third of patients with conventional indications for cardiac catheterisation. (184) Though these studies did not assess the effect of stress on the diastolic indices specifically in patients with HFNEF, our conclusion that stress impairs LV diastolic relaxation resulting in an increase in the LVEDP in patients with HFNEF is consistent with these findings. The causal relation between exercise intolerance and stress induced diastolic impairment seen in our study has also

been demonstrated in patients with exercise intolerance and normal LV systolic function. (184;239)

Mechanisms of stress induced diastolic dysfunction

The diastolic dysfunction induced by dobutamine stress may have resulted from ischaemia, increased systolic blood pressure and induced tachycardia. Impaired ventricular relaxation may be a manifestation of early ischaemia. Myocardial ischaemia impairs ventricular relaxation earlier than systolic contraction. (187) In patients with coronary artery disease ischaemia induced by pacing, (78) dipyridamole, (77) dobutamine (76;80) and exercise (75) results in a transmitral flow pattern consistent with delayed relaxation. Even transient, reversible episodes of ischaemia can impair LV relaxation and elevate LV filling pressures. (74) Regional impairment of myocardial relaxation of ischaemic segments has been seen at rest even when systolic contraction is preserved (79) and after dobutamine stress (188) and coronary occlusion. (81)

Stress-induced tachycardia may have worsened ischaemic diastolic relaxation by increasing myocardial oxygen demand and decreasing coronary perfusion time. Shortening the diastole allows less time for relaxation. This is further amplified in hypertrophied and fibrosed myocardium that is unable to generate a higher rate of diastolic relaxation causing the diastolic pressures to increase. (85;189)

Stress-induced elevation of systolic blood pressure, may have contributed. Elevated SBP slows LV relaxation due to increased afterload with a resultant increase in the LA pressure. (82) In hypertensives, a rapid increase in SBP at rest (63) or following exercise (83) results in deterioration of LV diastolic function without worsening systolic function. Similar changes in response to stress have been demonstrated in patients with HFNEF.(84)

LIMITATION

Pharmacological stress used in this study may differ qualitatively from exercise. This choice permitted us to investigate patients who were elderly with poor exercise capacity and mobility. The problem of inadequate image quality due to the

increased rate and depth of breathing after exercise stress was eliminated. The lack of diagnostic gold-standard for diastolic heart failure made diagnosis difficult. The diastolic blood flow and annular velocities were measured at sub-maximal heart rates to avoid the problem of fusion of these velocities at peak stress. This strategy was reasonable considering that these breathless patients were unlikely to generate maximal heart rates during daily living. The E/Ea ratio measured was higher than previously reported. (193;204) This is because myocardial velocities measured by cTDI in this study are lower than that measured by pulsed TDI. (196) The left atrial diameter measured in the parasternal long axis view may not have reflected the true increase in LA size that often occurs in the apico-basal direction in patients with HFNEF. The study group was heterogeneous comprising of patients with IHD, myocardial infarction, hypertension and diabetes, all of which may have influenced LV relaxation. Some of the subjects in the control group had obesity and COPD both of which may have affected the LV diastolic function. This may have underestimated the difference in the diastolic parameters between the groups. The study involved small number of patients and the findings need to be confirmed on a larger population.

CONCLUSION

Stress does not commonly induce systolic dysfunction in patients with HFNEF. It is unlikely that exercise intolerance is due to global regional or long axis systolic dysfunction or other non-cardiac causes. Abnormalities in diastolic function are often induced or exacerbated by stress in these patients, whether or not the final diagnosis is thought to be diastolic heart failure. Stress-induced impairment of early diastolic relaxation with consequent rise in the LVEDP is the likely cause of exercise intolerance. This study suggests that routine stress echocardiography may be useful in fully evaluating these patients. However, utility of the test is uncertain till it is shown to predict symptoms, morbidity, mortality and effects of treatment.

Table 6.1. Clinical characteristics of the HFNEF and controls.

	HFNEF (n=41)	Controls (n=29)	p
Age (yrs)	70±11	66±11	0.14
Male n (%)	19(46)	17(59)	0.31
BMI	26.6±4.2	26.53±3.4	0.92
Overweight/Obesity n (%)	25(61)	21(72)	0.32
Current smoker n (%)	24 (58)	16 (55)	0.78
Hypertension n (%)	26 (63)	0 (0)	<0.001
Diabetes n (%)	8 (19)	0 (0)	0.01
Previous MI n (%)	12 (29)	0 (0)	<0.001
Drug history			
Loop diuretics (%)	31 (76)	22 (76)	0.98
ACEI or ARB (%)	28 (68)	3 (10)	<0.001
Beta-blockers (%)	29 (71)	2 (7)	<0.001
Aspirin (%)	36 (89)	24 (83)	0.55
Spironolactone (%)	2 (5)	0 (0)	0.23
NYHA II-III n (%)	40 (98)	25 (86)	0.69
Heart rate (bpm)	76±14	76±13	0.89
SBP (mm Hg)	148±22	135±12	0.01
DBP (mm Hg)	85±12	78±8	0.01
FVC (l)	2.7±1.3	2.2±0.9	0.67
FEV_1 (l/min)	2.1±1.0	1.6±0.79	0.09
FEV_1/FVC (%)	80±7	71±16	0.003
FEV_1/FVC <75% n (%)	16 (39)	13 (45)	0.63
QRS duration (ms)	95±21	94±21	0.90
6 min walk test (m)	174±109	373±100	<0.001
Resting Echocardiography			
LA (cm)	3.84±0.80	3.66±0.69	0.36
LV mass (gm)	248±115	234±92	0.59
LV mass index (gm/m^2)	139±65	129±50	0.47
LVH n (%)	25 (61)	13(45)	0.19
EDVsmp (ml)	70.6±26.0	76.8±23.1	0.31
ESVsmp (ml)	24.5±12.4	30.0±13.2	0.08
EDVIsmp (ml/m^2)	39.2±13.8	41.8±10.8	0.41
ESVIsmp (ml/m^2)	13.6±6.9	16.3±6.4	0.11

EF (%)	66±9	62±8	0.02
Stress Response			
Final dobutamine dose	29±9	34±8	0.02
THR	127±9	131±9	0.14
HR reached	124±13	124±13	0.76
% of THR reached, (%)	98±10	95±10	0.17
THR reached n (%)	24(59)	14(48)	0.39
SBP (mm Hg)	176±21	170±12	0.23
DBP (mm Hg)	98±11	97±5	0.81
Test Termination			
THR n (%)	10(24)	9(31)	0.54
THR+RWMA n (%)	12(29)	4(14)	0.13
RWMA n (%)	6(15)	5(17)	0.77
Hypertension n (%)	1(2)	1(3)	0.80
Hypotension n (%)	4(10)	5(17)	0.36
NSVT n (%)	5(12)	1(3)	0.20
Ischaemia n (%)	2(5)	3(10)	0.38
Pain/Breathlessness n (%)	1(2)	1(3)	0.80
Segmental Response			
Normal (%)	82.2	86.2	0.07
Ischaemic (%)	10.2	7.3	0.10
Scar (%)	4.1	0	0.00

CAD, Coronary artery disease; IHD, ischaemic heart disease; NYHA, New York Hear Association; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; HR, heart rate; THR, target heart rate; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 second, LA, left atrial diameter; EDVsmp, left ventricular end-diastolic volume by Simpson's; ESVsmp, left ventricular end-systolic volume by Simpson's; EDVIsmp, left ventricular end-diastolic volume index by Simpson's; ESVIsmp, left ventricular end-systolic volume index by Simpson's; EF, ejection fraction.

Table 6.2. The echocardiographic variables at rest and stress in the HFNEF and control groups.

	REST		p	PEAK STRESS		p
	HFNEF (n=41)	Controls (n=29)		HFNEF (n=41)	Controls (n=29)	
Mitral annular systolic velocities (mean±SD)						
LMA (cm/s)	5.4±1.7	6.8±1.5	0.00	8.1±1.9*	9.6±1.6*	0.004
SMA (cm/s)	4.6±1.3	5.2±1.1	0.02	7.4±2.5*	9.1±2.1*	0.01
AMA (cm/s)	5.3±1.6	6.1±1.5	0.04	7.9±2.5*	8.7±2.6*	0.20
IMA (cm/s)	5.0±1.4	5.8±1.3	0.01	8.1±2.6*	8.9±2.0*	0.21
PMA (cm/s)	5.2±1.5	6.4±1.3	0.00	8.3±1.8*	9.5±2.0*	0.01
ASMA (cm/s)	4.4±1.4	5.6±1.0	0.00	7.5±2.3*	8.6±1.8*	0.03
Myocardial Segmental Velocities (mean±SD)						
LB (cm/s)	4.1±2.1	5.0±1.9	0.06	6.5±2.5*	7.5±2.1*	0.09
SB (cm/s)	4.6±1.3	4.9±1.2	0.39	7.6±2.5*	8.5±2.1*	0.13
AB (cm/s)	4.1±1.8	4.0±1.9	0.83	6.6±2.9*	6.7±2.6*	0.96
IB (cm/s)	5.1±1.6	5.4±1.2	0.30	7.7±2.8*	9.1±2.0*	0.02
PB (cm/s)	4.5±1.8	5.2±1.8	0.16	7.2±2.6*	7.8±2.3*	0.31
ASB (cm/s)	3.9±1.5	4.5±0.9	0.06	6.8±2.2*	7.9±2.0*	0.03
LM (cm/s)	3.0±2.2	3.5±2.0	0.27	5.2±2.6*	5.6±2.0*	0.50
SM (cm/s)	3.5±1.2	3.3±1.0	0.40	6.2±2.5*	6.7±2.4*	0.45
AM (cm/s)	2.4±2.1	2.7±1.5	0.54	4.7±2.6*	4.4±2.5**	0.60
IM (cm/s)	3.7±1.3	3.8±1.3	0.78	6.2±2.5*	7.1±2.6*	0.12
PM (cm/s)	3.2±2.0	3.8±1.6	0.25	5.9±2.4*	6.0±2.8*	0.93
ASM (cm/s)	3.1±1.7	3.2±1.0	0.89	6.3±2.2*	6.7±2.1*	0.44
LVOT Vmax (cm/s)	109±28	113±20	0.51	186±73*	172±52*	0.87
LVOT Pmax (mmHg)	5.0±2.7	5.2±1.8	0.73	15.4±12.8*	14.0±8.9*	0.62
Diastolic variables median (IQR)						
E (cm/s)	68(54-95)	65(53-75)	ns	77(65-91)***	70(54-93)***	ns
A (cm/s)	77(71-92)	81(68-96)	ns	97(88-114)*	97(80-108)	ns
E/A	0.83(0.61-0.94)	0.77(0.6-0.9)	ns	0.73(0.62-0.84)	0.73(0.56-0.89)	ns
IVRT ms	102(91-112)	107(82-115)	ns	92(69-111)***	82(71-92)*	ns
EDT ms	235(184-286)	244(194-306)	ns	189(140-265)***	183(153-214)**	ns
IVRTc ms	109(91-134)	114(96-133)	ns	127(98-153)*	120(109-135)	ns
EDTc ms	267(198-309)	268(226-328)	ns	257(203-362)	252(214-298)	ns

L, lateral; S, septal; A, anterior; I, inferior; P, posterior; AS, anteroseptal; MA, mitral annulus; B, basal segment; M, middle segment; E, early mitral inflow velocity; A, late mitral inflow velocity; IVRT, isovolumic relaxation time; EDT, E wave decelaration time; IVRTc, isovolumic relaxation time corrected for heart rate; EDTc, E wave decelaration time corrected for heart rate. Rest versus stress: *$p<0.0001$, **$p<0.01$, ***$p<0.05$

Table 6.3.Correlation of 6 minute walk distance to the clinical and echocardiographic parameters

	HFNEF		Cont		ALL	
	Rest	Stress	Rest	Stress		
Age (yrs)	-0.4569***		-0.3020		-0.3895****	
BMI	0.0551		0.0285		0.0200	
SAP	-0.1505		0.2296		-0.0624	
DAP	-0.2159		0.2308		-0.1417	
LA	0.0649		-0.0220		-0.0648	
LV mass index	-0.0300		0.1246		-0.0553	
EDVIsmp	0.2906		-0.1073		0.1821	
ESVIsmp	0.2877		-0.1620		0.2281	
EF	-0.2318		0.0521		-0.2928**	
FEV1	0.0751		0.2818		0.0158	
FEV/FVC	-0.2882		0.0450		-0.1302	
WMSI	-0.2585	-0.2578	-0.2266	-0.1425	-0.3143***	-0.2902**
LVOT Pmax	-0.1980	0.1409	0.0076	-0.1096	-0.0734	-0.0068
E	-0.3249*	-0.5276****	0.4898***	0.3457	-0.1644	-0.2093
A	-0.4299***	-0.3950**	0.2316	0.3108	-0.1745	-0.1212
E/A	-0.0580	-0.1868	0.3279	0.0824	-0.0126	-0.1584
EDT	0.3151*	0.2452	-0.2597	-0.0311	0.1270	0.0542
IVRT	0.0464	0.0962	0.1045	-0.2735	0.0689	-0.0858
IVRTc	-0.0537	0.1069	0.2116	-0.2490	0.0223	-0.0839
DTc	0.2004	0.2761	-0.1882	0.0099	0.1178	0.0772
Sa	0.2455	0.2811	0.2848	0.2784	0.4493****	0.4106****
Ea	0.2578	0.4164***	0.4212	0.1934	0.3048	0.5652****
Aa	0.0895	0.3359	-0.0421	0.0882	0.1911	0.2630*
Ea/Aa	0.1758	0.1617	0.4751***	0.0660	0.1547	0.3978****
E/Ea	-0.6260****	-0.7621****	0.0826	0.1904	-0.4780****	-0.6649****

*p<0.05, **p<0.02, ***p<0.01, ****p<0.001

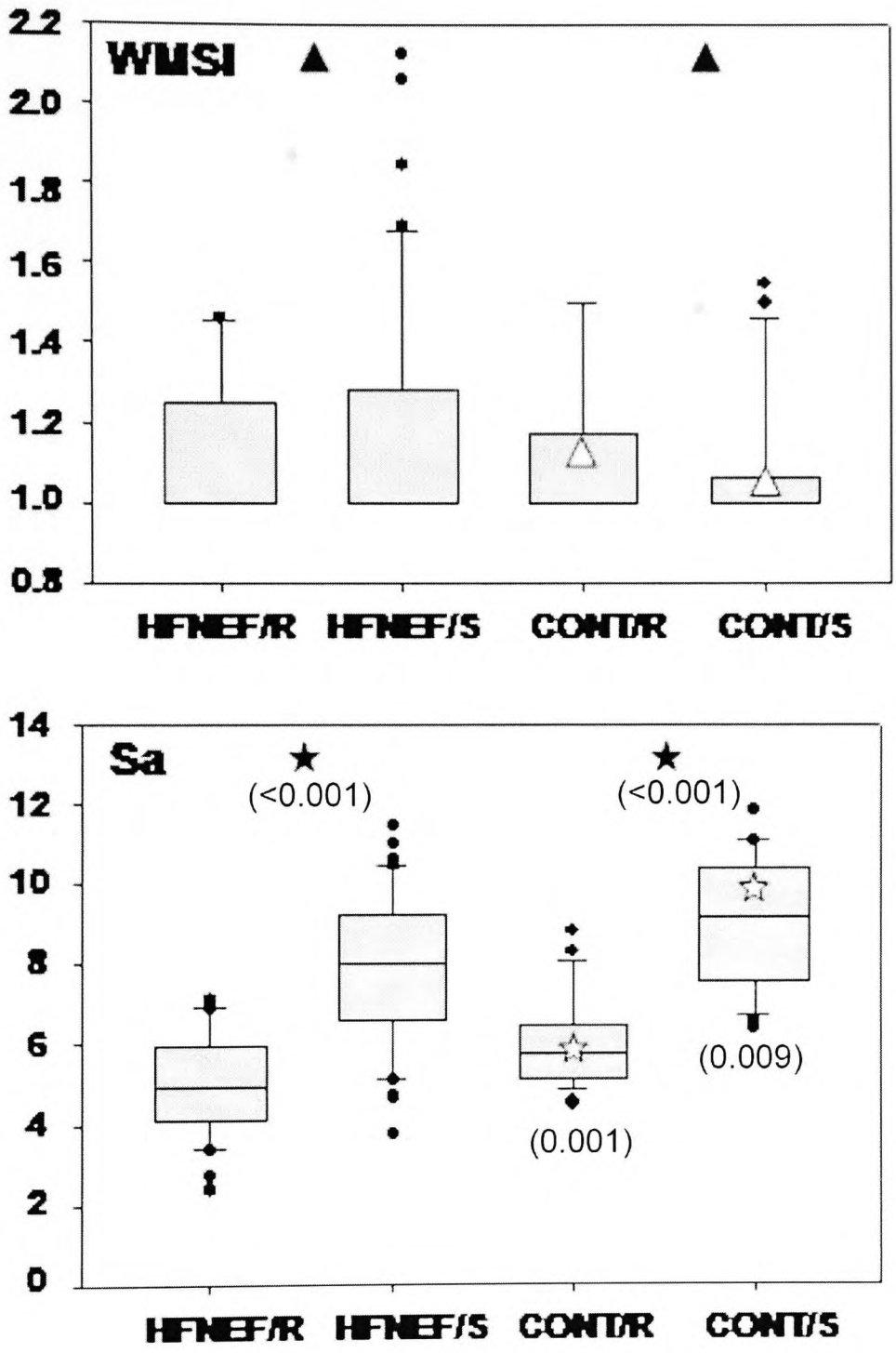


Figure 6.1. Median, interquartile range, 95% confidence and outlying results for WMSI, Sa of the HFNEF and controls at rest and peak stress. ☆p<0.001 and △p=ns comparing HFNEF v controls at rest and peak stress. ★p<0.001 and ▲p=ns comparing rest v peak stress in the HFNEF and controls.

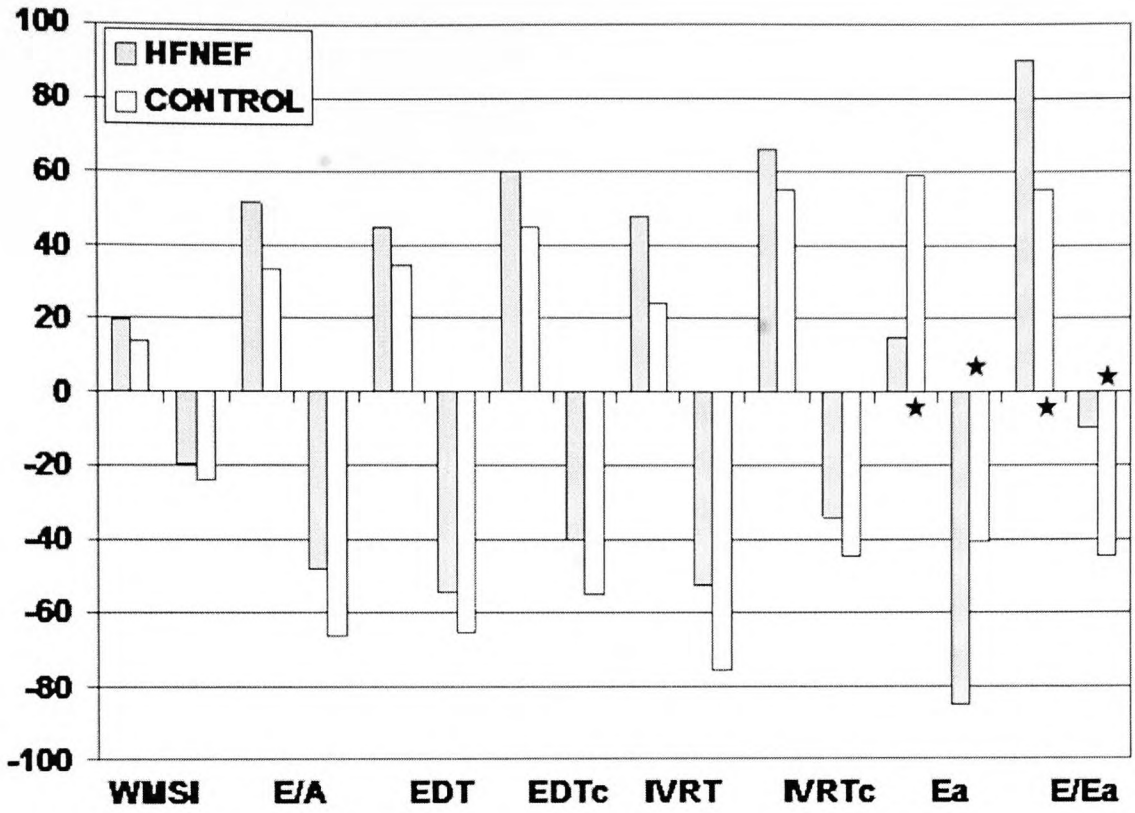


Figure 6.2. The % of patients in whom measurements increased (+) or decreased (-) with stress. ★ $p<0.001$.

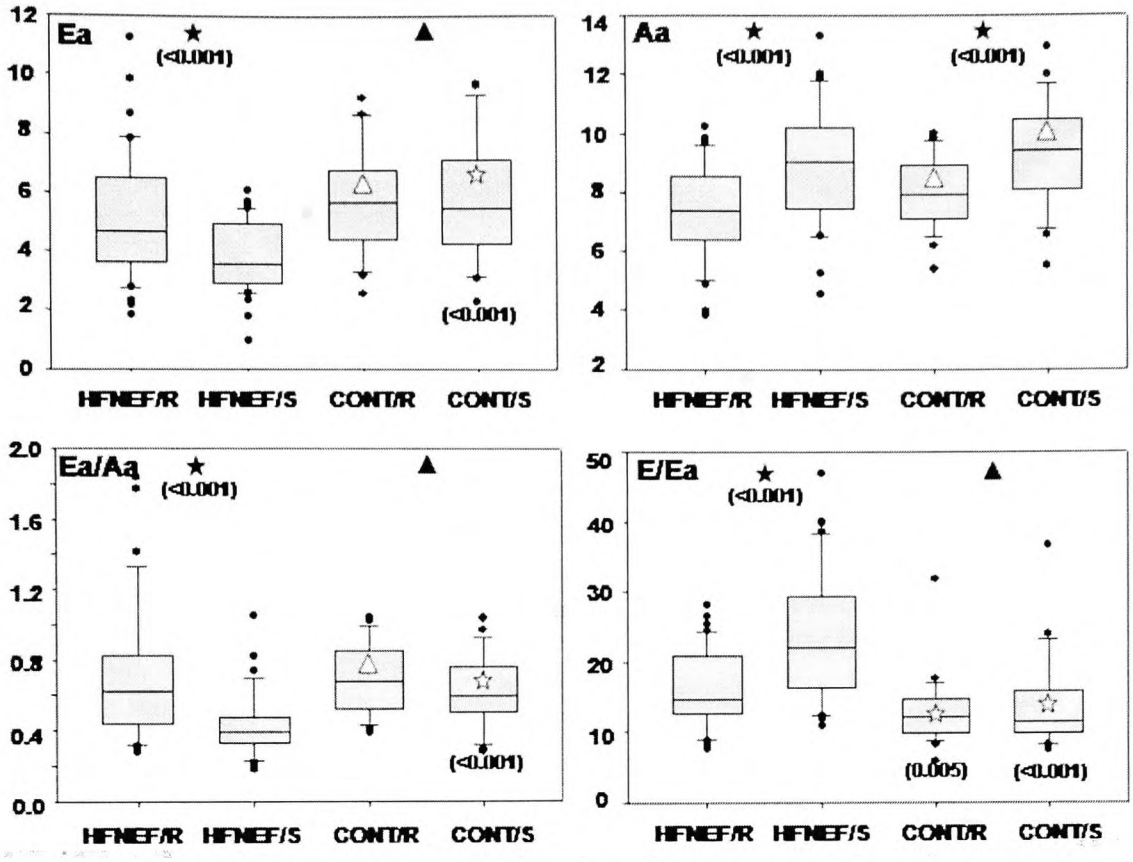


Figure 6.3. Median, interquartile range, 95% confidence and outlying results for Ea, Aa, Ea/Aa and E/Ea of the HFNEF and controls at rest and peak stress. ☆ p<0.001 and △ p=ns comparing HFNEF v controls at rest and peak stress. ★ p<0.001 and ▲ p=ns comparing rest v peak stress in the HFNEF and controls.

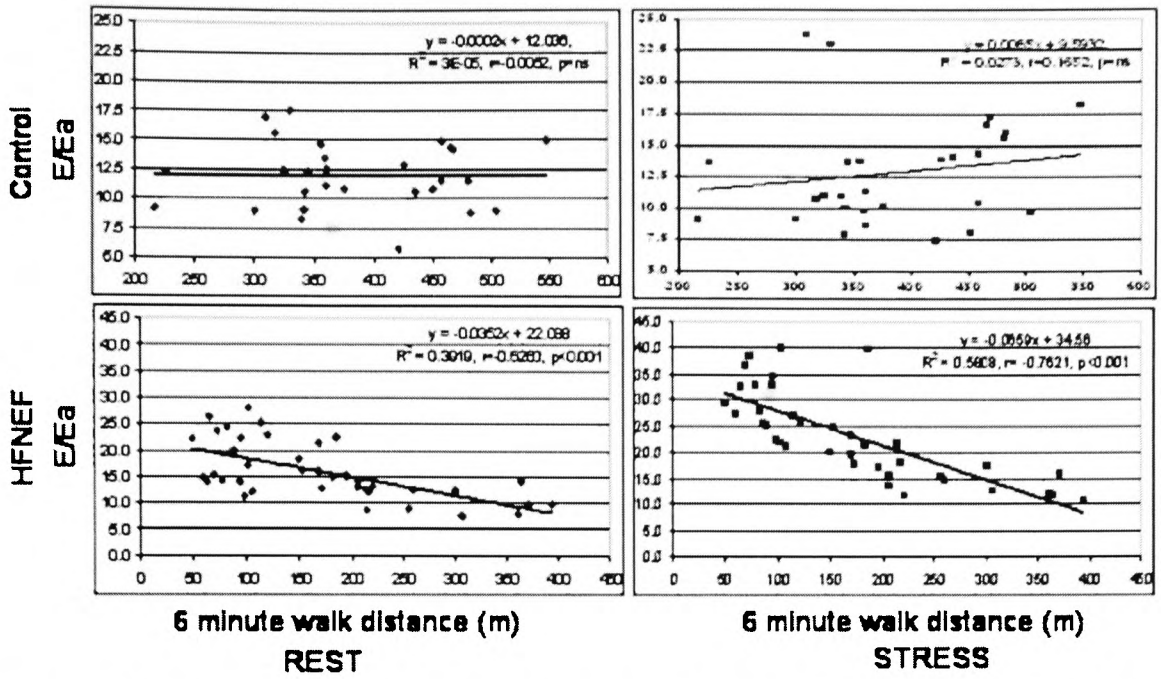


Figure 6.4. The relation between the 6 minute walk distance (m) and the E/Ea ratio in the controls (upper panel) and HFNEF (lower panel) at rest (left panel) and stress (right panel).

Chapter 7: The Effect of Pharmacological Stress on Intraventricular Dyssynchrony in Left Ventricular Systolic Dysfunction. *Eur J Heart Fail. 2008 Apr;10(4):412-20.*

ABSTRACT

Background: Cardiac resynchronisation therapy (CRT) improves symptoms and exercise capacity in many patients with heart failure (HF) who have left ventricular systolic dysfunction (LVSD) and markers of dyssynchrony. LV dyssynchrony is conventionally measured at rest but the symptoms of heart failure occur predominantly on exercise. Induction or exacerbation of dyssynchrony during stress might identify additional patients who could benefit from CRT.

Methods and Results: Seventy-seven patients (47 with QRSd<120 ms and 30 with QRSd>120 ms) with heart failure due to left ventricular systolic dysfunction and 22 normal subjects underwent DSE using colour tissue-Doppler imaging. Left intraventricular dyssynchrony was measured as the standard deviation of the time to peak velocity from the onset of the QRS (Ts-SD) and the difference between the maximum and minimum time to peak velocity (Tscor-diff) in the 12 non-apical segments at rest and during peak stress. Timings were corrected for heart rate. The mean values of these indices increased with stress in both groups of patients but not in control subjects ($p<0.001$). The prevalence of conventionally-defined dyssynchrony also increased with stress.

Conclusion: In patients with heart failure, the severity and the prevalence of intraventricular dyssynchrony increase with stress. Whether stress-induced dyssynchrony will identify patients who might benefit from CRT awaits further research.

INTRODUCTION

Left ventricular mechanical dyssynchrony is present in 30-50% of patients with heart failure and LV systolic dysfunction (LVSD) at rest, depending on the population studied and the definition of dyssynchrony applied. (93-96) The optimal method for assessing dyssynchrony is unclear. Prolonged QRS duration (QRSd), widely perceived as a marker of cardiac dyssynchrony, was a universal entry criterion for the randomised controlled trials demonstrating clinical and echocardiographic benefits of cardiac resynchronization therapy (CRT). (347;348) However, QRSd is a crude indicator of mechanical dyssynchrony (93;95) and QRSd prior to implantation and its reduction with CRT are poor predictors of therapeutic response. (349) Some non-randomised observations have suggested that direct measurement of mechanical systolic dyssynchrony before implantation may improve prediction of response to CRT either alone or in addition to QRSd but conclusive evidence is lacking. (271;350-354) These studies have considered dyssynchrony as a relatively stable phenomenon that neither changes during cardiovascular stress nor during prolonged follow-up. (348) The failure of current approaches to consistently identify therapeutic response, especially the long-term response, may reflect a failure to appreciate the potential for dyssynchrony to be a dynamic problem. The possibility that the prevalence and severity of LV dyssynchrony change when the ventricle is subjected to stress was investigated.

METHOD

Patient selection

Inclusion criteria were NYHA class II-IV symptoms despite the use of diuretics and, unless not tolerated or contraindicated, treatment with ACE inhibitors or angiotensin receptor antagonists and beta-blockers for at least 3 months, LV ejection fraction (LVEF) <40% and sinus rhythm. Exclusion criteria were an acute coronary syndrome in the previous 6 months, significant valvular abnormality or a technically inadequate echocardiogram. The study population was divided into two groups: WQRS group (QRSd ≥120 ms) and NQRS group (QRSd < 120 ms). The aetiology of heart failure was considered to be ischaemic if there was evidence of previous myocardial infarction or angiographic evidence of >50% stenosis in major coronary arteries. Subjects, referred for the investigation of cardiac function, with a

low probability of ischaemic heart disease, without a history of myocardial infarction, diabetes, hypertension, with normal resting ECG and echocardiography and no inducible ischaemia on DSE (DSE), acted as controls.

Following a clinical examination and ECG every subject underwent standard transthoracic echocardiography followed by DSE. All subjects gave written informed consent and the Medical Ethics Committee of the Hull and East Yorkshire NHS Trust approved the protocol.

Echocardiography

A standard set of images was recorded digitally at rest using GE Vingmed System V scanner (Horten, Norway) equipped with a 2.5 to 5-MHz phased-array transducer and analysed off-line. LV volumes and LVEF were assessed using the biplane modified Simpson's rule.

Stress echocardiography

Protocol

As described in Chapter 4.

In the cTDI mode, a sample cursor was placed at the midpoint of each of the 12 non-apical segments of the lateral, septal, anterior, inferior, posterior and anteroseptal walls in the 3 apical views and myocardial velocity curves were reconstituted. The onset of the QRS to the peak of the T wave was taken as systole. The time to peak systolic velocity (Ts) was measured from the onset of the QRS complex to the peak of the myocardial systolic velocity during ejection in each of the 12 segments at rest and at peak stress. (271;354) Ts was corrected for heart rate (Tscor) using the Bazett's formula (Tscor=Ts/$\sqrt{}$R-R) to allow comparison between the Ts of any segment at rest and at peak stress. (191) Any segment that developed the highest positive velocity after systole with low flat velocity profile during ejection phase was excluded from the analysis.

Intraventricular dyssynchrony was measured as the standard deviation of the Ts and Tscor of all 12 segments (Ts-SD and Tscor-SD) (94;271;272;354) and the

maximum difference in the Ts (Tsdiff) and Tscor (Tscordiff) between any two of the 12 segments. (272) A segment was labelled as "delayed" if the Ts or Tscor was > the mean+2SD of controls in that state (i.e. rest or stress). The prevalence of systolic dyssynchrony was defined as % of patients with Ts-SD, Tscor-SD, Tsdiff or Tscordiff of > the mean+2SD of controls in that state. All timings were calculated as the average of 2 to 3 consecutive cardiac cycles. All images were analysed by a single investigator (SC) blinded to the clinical characteristics of the patient.

Statistical analysis

As described before.

Intraobserver variability in the Ts measured at the 12 non-apical segments was calculated in a sample of 10 randomly selected patients at rest and at peak stress totalling 240 pairs of measurements. It was reported as mean±SD. Confidence limits (95%) of differences were computed and expressed as absolute values and percentages of the average values of paired velocity measurements.

RESULTS

Between January 2002 and March 2003, 77 patients with heart failure (mean age 68±9 years, 60 (78%) males) were enrolled (47 (61%) in NQRS group and 30 (39%) in WQRS group) (Table 1). Patients were in New York Heart Association class II (n=42), III (n=26) and IV (n=9). The QRSd, LV volumes and WMSI at rest were higher in the WQRS group. Twenty-two controls (mean age 67±12 years, 14 (64%) males) were also enrolled. Controls and patients had similar characteristics apart from measures of LV dysfunction. All controls and 31 (40%) patients reached the target heart rate (THR), 33 (43%) reached >90%, 8 (10%) reached >80% and 5 (7%) reached >70% of the THR. There were no major adverse events or limiting side effects during the study. Of those with heart failure, 32/77 (41.5%) complained of chest discomfort with or without minor ST-segment depression. The heart rate, systolic and diastolic blood pressure and the rate-pressure product were higher at peak stress than at rest in all three groups (Table 2).

Segmental Time to Peak Velocity (Ts) at rest and during stress

At rest, Ts could be measured in 261/264 (98.9%) segments in the control group compared to 896/924 (97.0%) segments in patients with heart failure (p=0.23). At peak stress, Ts could be measured in 260/264 (98.4%) segments in the control group and 906/924 (98.1%) in patients with heart failure (p=0.84). The overall intraobserver variability (Table 3) was low (range 1.2-5.9% at rest and 1.0-9.6% at peak stress). The variability was highest in the basal segment of the anteroseptal wall at rest and in the basal segment of the septum at peak stress.

In patients with heart failure, the Ts was delayed in most myocardial segments at rest and in all myocardial segments at peak stress compared to controls (Figure 1). Ts was shortened in most segments during stress except postero-basal, lateral-mid and postero-mid segments where Ts was similar to or delayed compared to resting values. Comparing patients with NQRS and WQRS, the mean Ts of each segment was similar at rest but at peak stress, the postero-basal, lateral-mid and postero-mid segments in the WQRS group were delayed compared to the NQRS (Figure 1).

Correction for heart rate (Tscor) had little effect on the overall pattern (Figure 1). The Tscor shortened in all segments with dobutamine stress in controls. It failed to shorten in any segment and increased in the mid-segments of the lateral and posterior walls in patients with and without wide QRS. At rest, Tscor was delayed in 6/264 (2.3%) segments in the control group compared to 73/564 (12.9%) in the NQRS (p<0.001) and 81/360 (22.5%) in the WQRS (p<0.001) (p<0.001 comparing patient QRS groups). At peak stress, delays were identified in 10/264 (3.8%) segments in the control group compared to 215/564 (39.4%) in the NQRS (p<0.001) and 163/360 (45.28%) in the WQRS (p<0.001) (p=0.08 comparing patient QRS groups). In response to stress, the Tscor lengthened in 44/264 (16.7%) segments in the control group compared to 262/564 (46.5%) in the NQRS (p<0.001) and 172/360 (47.8%) in the WQRS (p<0.001) (p=0.69 comparing patient QRS groups).

Standard Deviation of the Time to Peak Systolic Velocity (Ts-SD)

Ts-SD uncorrected for heart rate was markedly greater in patients compared to control subjects but changed little with stress (Figure 2). However, marked differences with stress were observed after correction for heart rate. In the controls,

Ts-SD and Tscor-SD were 20.3±8.8 and 23.9±11.4 at rest and 22.3±6.7 and 28.4±7.3 at peak stress. At rest, a Tscor-SD > 46.7 ms (mean+2SD of controls) was seen in one control subject and 46 (60%) patients with heart failure ($p<0.001$), 21(45%) in NQRS ($p=0.004$ v controls) and 25(83%) in WQRS ($p<0.001$ v controls) groups ($p=0.003$ for the difference between NQRS and WQRS groups). At peak stress, a Tscor-SD of > 43.0 ms (mean+2SD of controls) was seen in none of the controls but 65 (83%) ($p<0.0001$) patients with heart failure, 36(77%) in NQRS ($p<0.001$ v controls) and 29(97%) in WQRS ($p<0.001$ v controls) groups ($p=0.061$ for the difference between patient QRS groups) (Figure 3).

Maximum Difference Between Segmental Peak Velocities (Ts-diff)

Ts-diff uncorrected for heart rate was markedly greater in patients compared to control subjects and increased with stress especially in patients with WQRS (Figure 2). After correction for heart rate, the effects of stress were even more marked in patients but not in control subjects. In the controls, Ts-diff and Tscor-diff were 62.7±24.4 and 73.6±30.5 at rest and 70.9±22.4 and 88.3±21.8 at peak stress. At rest, no (0%) control subject but 47 (61%) patients ($p<0.001$) had Tscor-diff >134.5 ms (mean+2SD of controls). Twenty-three (49%) patients in NQRS group ($p<0.001$ v controls) and 24(80%) in WQRS group ($p<0.001$ v controls) ($p= 0.024$ for the difference between patient QRS groups) had Tscor-diff > 134.5 ms. At peak stress, 38 (81%) patients in NQRS group ($p<0.001$ v controls), 30 (100%) patients in the WQRS group ($p<0.001$ v controls and $p= 0.038$ comparing patient QRS groups) and none of the control subjects had Tscor-diff > 131.8 ms (mean+2SD of controls) (Figure 3).

Depending on the TD variable, 95-100% of controls were normal at rest and all remained that way at peak stress compared to 8-13% in the NQRS group and none in the WQRS group (Figure 4). In 43% of NQRS patients, the TD variables were normal at rest and became abnormal at peak stress compared to 20% in the WQRS group and none of the controls. 80% of the WQRS patients were dyssynchronous at rest and continued to be abnormal at stress compared to 38-40% in the NQRS and none of the controls. Depending on the variable, 6-8% of patients in the NQRS group and none of the WQRS group improved with stress.

DISCUSSION

Cardiac dyssynchrony has rarely been studied during stress. This study corroborates the reported high prevalence of intraventricular dyssynchrony at rest in patients with LVSD irrespective of QRS duration.(93-96) However, during pharmacological stress both the prevalence and severity of dyssynchrony increase. Since the prevalence of dyssynchrony at rest is lower in patients with QRSd <120 ms the increase is most evident in this population. The prevalence of stress-induced dyssynchrony in these patients approached that observed in patients with QRSd >120 ms during pharmacological stress. Indeed, most patients with LVSD had dyssynchrony during stress regardless of QRS duration. Stress rarely improved dyssynchrony in this study.

Compared to control subjects, the time to peak systolic velocity was greater in most myocardial segments at rest and in all segments at peak stress in patients with LVSD regardless of QRS duration. Stress shortened the time to peak systolic velocity in all segments in healthy subjects and in most segments of patients with LSVD. Indeed, when corrected for heart rate, stress shortened the time to peak velocity in control subjects but not in patients with LSVD regardless of QRS duration. Additional delays in some segments were observed in the latter. The lateral and posterior wall segments were particularly prone to delay both at rest and during stress in patients regardless of QRSd, as previously reported in patients at rest. (272;355) The greater vulnerability of the LV free-wall to dyssynchrony presumably reflects an exaggeration of the usual pattern of ventricular activation in the presence of a dilated ventricle, greater myocardial mass, slowed intra-myocardial conduction and areas of fibrosis and scar. (356)

Studies, investigating the effects of pacing-induced tachycardia, exercise or pharmacological stress on ventricular dyssynchrony, have yielded conflicting results.(97-100;357) Indices of dyssynchrony did not change in subjects without heart disease in these studies whether the stressor was exercise or dobutamine. Pacing induced tachycardia augmented LV mechanical dyssynchrony in one study of patients with non-ischaemic LVSD. In 65 patients with heart failure studied by

Lafitte et al (97) , only 22 of whom had QRS <120 ms, the mean values of the dyssynchrony indices did not change with exercise stress. Dyssynchrony increased in 37% and diminished in 20%. The changes may partly have reflected measurement error given the technical difficulties of exercise echocardiography. Valzania et al (99) reported a lack of increase in dyssynchrony indices, derived from timings not corrected for heart rate, with dobutamine-stress in patients with QRSd ≥ 130 ms undergoing CRT. This is consistent with our findings. Neither Hummel et al (98) nor Da Costa et al (100) reported the effects of stress on dyssynchrony in heart failure patients with wide QRS. Differences in the proportion of patients with QRSd <120 ms, the proportion with dyssynchrony at rest, the magnitude of change in heart rate, the stressor and the criteria by which dyssynchrony is judged to be present may account for some of the differences observed. Importantly, CRT appears to maintain its synchronising effect during exercise stress. (195)

Pharmacological stress permitted us to investigate patients who were elderly with poor exercise capacity and mobility and those with severe heart failure; patients that are difficult or impossible to study using exercise stress. (97) Higher heart rates may be reached during exercise than with peak dose dobutamine but the rapid decline in heart rate after exercise and delays in acquisition are common (262) as are the difficulties in obtaining adequate images due to the increased rate and depth of breathing.

Patients with LVSD are prone to subendocardial ischaemia whether or not they have epicardial coronary disease (324;358) and treatments that decrease ischaemia may improve dyssynchrony. (324;359) Stress induced dyssynchrony could reflect induction of ischaemia and this could not be discounted as a contributing factor. However, in the absence of substantial deterioration of WMSI and mitral annular velocity at peak stress, it is unlikely that clinically overt ischaemia played a significant role in inducing dyssynchrony in our patients. The chronotropic effect of dobutamine may at least partly be responsible. Pacing induced tachycardia augments LV mechanical dyssynchrony in patients with non-ischaemic LVSD. (357)

LIMITATION

The mechanism of stress-induced dyssynchrony or its ability to predict the response to CRT was not studied. The absence of recent coronary angiograms or segmental strain data precludes exclusion of ischaemia as a mechanism. In the absence of data on the sequence of electrical activation through the LV at rest and stress, we are unable to say whether the stress induced worsening of dyssynchrony is due to alteration in the electrical activity as a result of changes in the conduction properties or impaired mechanical coupling. The dyssynchrony was assessed at heart rates that are unlikely to be reached in elderly patients with relatively sedentary life styles and optimally treated with beta-blockers. It is uncertain what effects would be produced by a lesser degree of stress. The relationship of post-systolic motion induced by stress to dyssynchrony was not studied. Segments that developed extreme delay in attaining their highest positive velocity were excluded from analysis (36/924, 3.9 %). These would have contributed even further to the severity of dyssynchrony on stress.

CLINICAL IMPLICATION

It is far from clear how patients should be selected for CRT. QRS duration thresholds and echo dyssynchrony criteria were chosen rather arbitrarily as entry criteria for clinical trials based on pathophysiological concepts and observed associations in small series of patients. Widened QRS is a marker of more severe left ventricular dilatation and dysfunction (12) and may be a marker of dyssynchrony mainly because it indicates a sicker ventricle. There is remarkably little evidence that echo dyssynchrony is associated with a worse prognosis and indeed some evidence that inter-ventricular dyssynchrony is associated with better outcome. (348) If QRS duration and dyssynchrony are being used as markers of risk rather than of dyssynchrony then NT-proBNP is better than either. (360;361) Now that it is known that CRT works for some patients, it is important to find out whether current guidelines are appropriate or too restrictive.

Observational studies suggest that CRT may be effective in patients with narrower QRS (362;363) whether or not they have mechanical dyssynchrony at rest. Recent

reports have failed to identify a strong-link between echo dyssynchrony at rest and outcome of CRT. (364) One of the many potential explanations for the lack of this relationship may be that dyssynchrony is dynamic and changes with stress. If stress-dyssynchrony is an appropriate target for therapy stress-echocardiography might be considered necessary in order to select patients for CRT. However, if stress dyssynchrony is as common as this study suggests, then a strategy of CRT implantation in all patients who have persistent major LVSD could be considered a more pragmatic approach. These concepts need to be tested in randomised controlled trials. This data also suggests that measuring dyssynchrony only at rest underestimates its prevalence and fixed setting of the biventricular pacemakers may not be physiological in the presence of such dynamicity.

CONCLUSION

Dobutamine-stress induces and exacerbates dyssynchrony in patients with LVSD. LV dyssynchrony, unmasked by stress in patients with narrow QRS, could be a target for therapy. If so, then most patients with LVSD, regardless of QRS duration or evidence of dyssynchrony at rest might benefit from CRT. This hypothesis remains to be tested.

TABLE 7.1. Comparison of Baseline Clinical Characteristics of the Controls and Study Groups.

	Control (n=22)	N QRS (n=47)	W QRS (n=30)	p value*	p value ANOVA
Age (years)	69 ± 12	68 ± 9	69 ± 9	0.89	0.86
Males n (%)	14 (64)	37 (79)	23 (77)	0.83	0.39
BMI	26.5 ± 5.0	26.4 ± 3.5	26.1 ± 4.0	0.72	0.78
QRSd (ms)	93 ± 21	98 ± 12	146 ± 20	<0.001	0.023
Aetiology					
IHD n(%)	0	36 (77)	20 (67)	0.34	-
DCM n(%)	0	9 (19)	7 (23)	0.66	-
Hypertension n(%)	0	2 (4)	3 (10)	0.32	-
MI n (%)	0	20 (43)	11 (37)	0.61	-
Prior revascularisation n (%)	0	14 (30)	11 (37)	0.53	
Diabetes n (%)	0	8 (17)	9 (30)	0.18	-
Hypertension n (%)	0	13 (28)	11 (33)	0.41	-
Drugs					
Diuretics n (%)	0	47 (100)	30 (100)	1.00	-
ACEI n (%)	0	42 (89)	25 (83)	0.44	-
ARB n (%)	0	5 (11)	5 (17)	0.44	-
Beta-blockers n (%)	0	42 (89)	24 (80)	0.25	-
Spironolactone n (%)	0	8 (17)	4 (13)	0.66	-
Digoxin n (%)	0	2 (4)	2 (7)	0.64	-
Echocardiography					
LVIDd (cm)	4.5±1.0	6.3±0.91	6.6±1.0	0.08	<0.001
LVIDs (cm)	2.9±1.0	5.2±1.0	5.7±0.9	0.09	<0.001
LVEDvol (ml)	71±27	129±53	161±56	0.02	<0.001
LVESvol (ml)	25±14	89±44	114±43	0.02	<0.001
EF (%)	65±9	33±9	29±8	0.12	<0.001
WMSI	1.0±0	2.3±0.4	2.6±0.3	0.00	<0.001
Sm	5.7±1.6	3.3±1.4	2.9±0.9	0.14	<0.001
DSE End-point reached at					

40 µg/kg/min+atropine n (%)	2 (9)	7 (15)	1(3)	0.11	0.26
40 µg/kg/min n (%)	16 (73)	16 (34)	8(27)	0.50	0.00
30 µg/kg/min n (%)	4 (18)	17(36)	10(33)	0.80	0.31
20 µg/kg/min n (%)	0 (0)	6(13)	11(37)	0.01	0.00
10 µg/kg/min n (%)	0 (0)	1(2)	0(0)	0.42	0.57

IHD, ischaemic heart disease; DCM, dilated cardiomyopathy; BMI, body mass index; QRSd, QRS duration; MI, myocardial infarction; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; LVIDd, left ventricular internal diameter in diastole; LVIDs, left ventricular internal diameter in systole; LVEDvol, left ventricular end-diastolic volume; LVESvol, left ventricular end-systolic volume; EF, ejection fraction; WMSI, wall motion score index; Sm, mitral annular myocardial velocity; DSE, DSE. Values are mean±2SD unless stated otherwise. * p value for comparison of NQRS versus WQRS

TABLE 7.2. Comparison of Response to Stress in the Controls and Study Groups.

	REST			p	STRESS			p	CONT	NQRS	WQRS
	CONT	NQRS	WQRS	ANOVA	CONT	NQRS	WQRS	ANOVA	R v S	R v S	R v S
SBP	132.3±18.9	135.7±26.4	125.5±17.9	0.247	161.9±22.1	176.4±25.5	160.8±24.7	0.011	<0.001	<0.001	<0.001
DBP	75.2±12.2	80.0±11.6	78.1±14.3	0.385	89.0±7.6	96.7±7.0	92.0±7.5	<0.001	<0.001	<0.001	<0.001
HR	79.5±10.9	75.0±13.2	79.6±17.6	0.360	128.6±9.9	125.4±13.6	123.7±12.7	0.424	<0.001	<0.001	<0.001
RPP	10532±2229	10159±2587	10011±2749	0.763	20891±3845	22099±3807	19849±3447	0.036	<0.001	<0.001	<0.001
WMSI	1.00±0.0	2.27±0.39	2.59±0.32	<0.001	1.02±0.07	2.10±0.47	2.36±0.5	<0.001	0.13	0.07	0.04
Sm	5.72±1.57	3.28±1.39	2.88±0.96	<0.001	8.35±1.93	5.45±2.17	5.02±1.87	<0.001	<0.001	<0.001	<0.001

SBP, systolic blood pressure; DBP, diastolic blood pressure, HR, heart rate; RPP, rate pressure product; WMSI, wall motion score index; Sm, mitral annular myocardial velocity.

Table 7.3. Intraobserver variability in the Ts measured in the 12 non-apical segments at rest and peak stress in a random sample of 10 patients.

	REST			STRESS		
Segment	Diff in Ts (Mean±SD)	95% CI	%	Diff in Ts (Mean±SD)	95% CI	%
LB	13.3±19.5	±12.1	5.1	2.5±2.2	±1.3	1.0
LM	10.7±10.3	±6.4	3.0	7.2±6.7	±4.2	3.1
SB	7.6±8.3	±5.1	2.4	8.8±19.1	±11.8	9.6
SM	7.3±8.2	±5.1	2.3	3.4±3.2	±2.0	1.6
AB	8.0±6.8	±4.2	1.9	7.5±7.6	±4.7	3.7
AM	7.4±6.6	±4.1	1.5	5.0±4.8	±3.0	2.4
IB	7.9±12.6	±7.8	3.3	8.6±10.9	±6.7	5.1
IM	6.8±5.6	±3.5	1.5	7.4±7.6	±4.7	3.4
PB	8.2±13.8	±8.6	3.3	8.3±8.9	±5.5	4.0
PM	8.8±7.5	±4.6	1.9	6.1±6.6	±4.1	3.1
ASB	9.3±18.3	±12.0	5.9	8.0±6.8	±4.2	3.2
ASM	4.3±3.7	±2.4	1.2	5.2±5.6	±3.5	2.6

B, basal; M, middle; L, lateral; S, septal; A, anterior, I, inferior; P, posterior; AS, anteroseptal

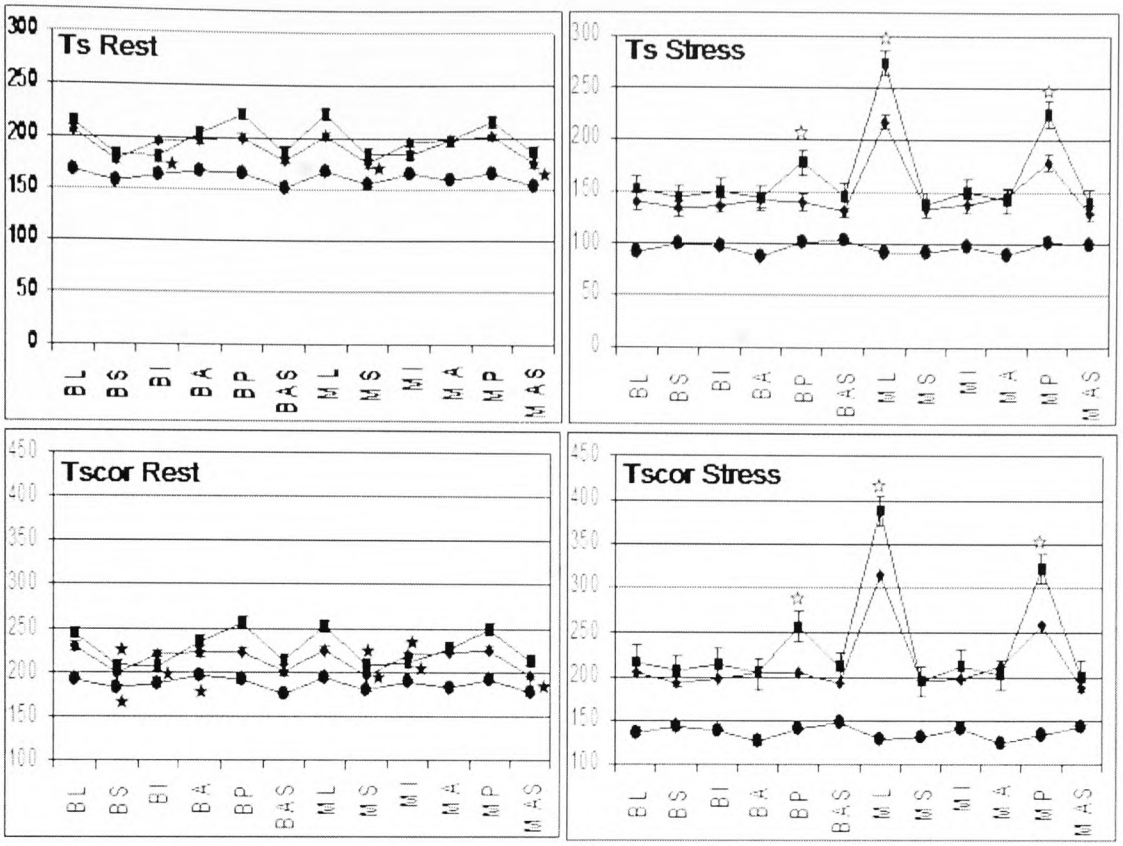


Figure 7.1. Segmental time to peak velocity (mean±SE), uncorrected and corrected for heart rate, at rest and stress across the groups. Unmarked values, $p<0.05$ NQRS and WQRS v controls; p=ns, ★QRS and WQRS v controls; $p<0.05$ ☆QRS v WQRS.

●Controls◆ NQRS■ WQRS. B=basal, M=mid, L=lateral, S=septal, I=inferior, A=anterior, P=posterior, AS=anteroseptal.

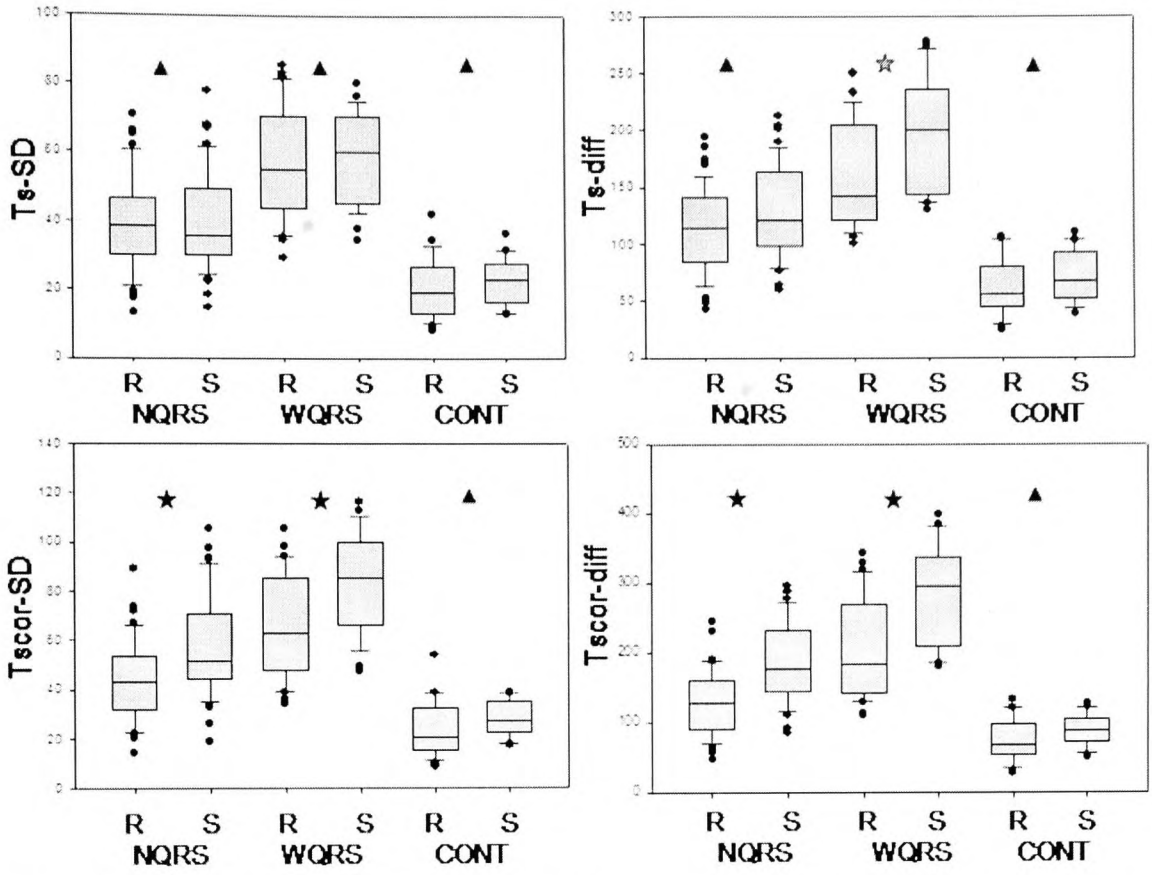


Figure 7.2. Median, interquartile range, 95% confidence and outlying results for Ts-SD, Ts-diff, Tscor-SD and Tscor-diff at rest (R) and stress (S) in the NQRS, WQRS and control groups. ★p<0.001, ☆p<0.05, ▲p=ns

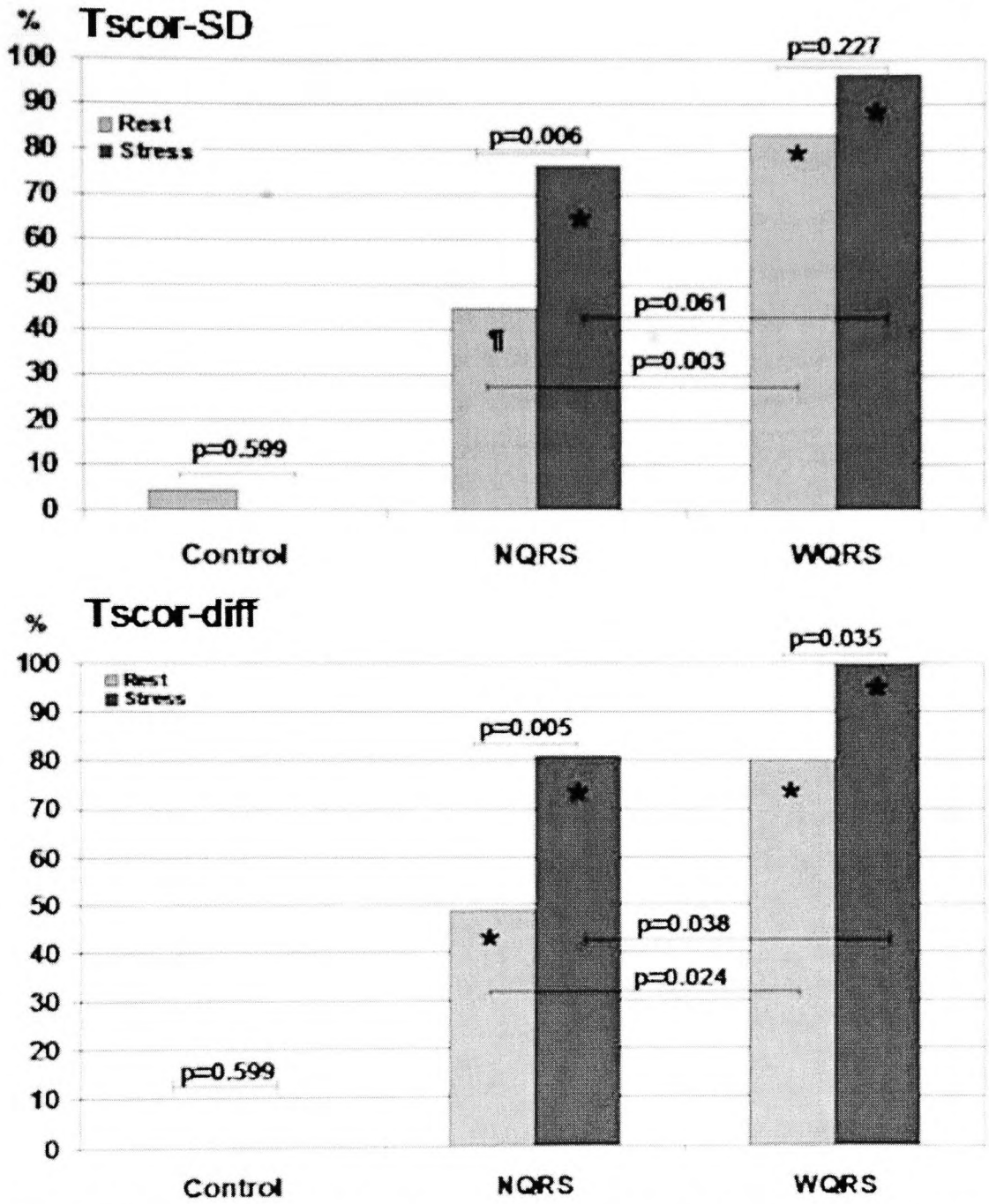


Figure 7.3. Percentage of patients with Tscor-SD and Tscordiff of > mean+2SD of controls at rest and stress within and across the groups.★ p=0.000 and ‖ p=0.004 compared to controls.

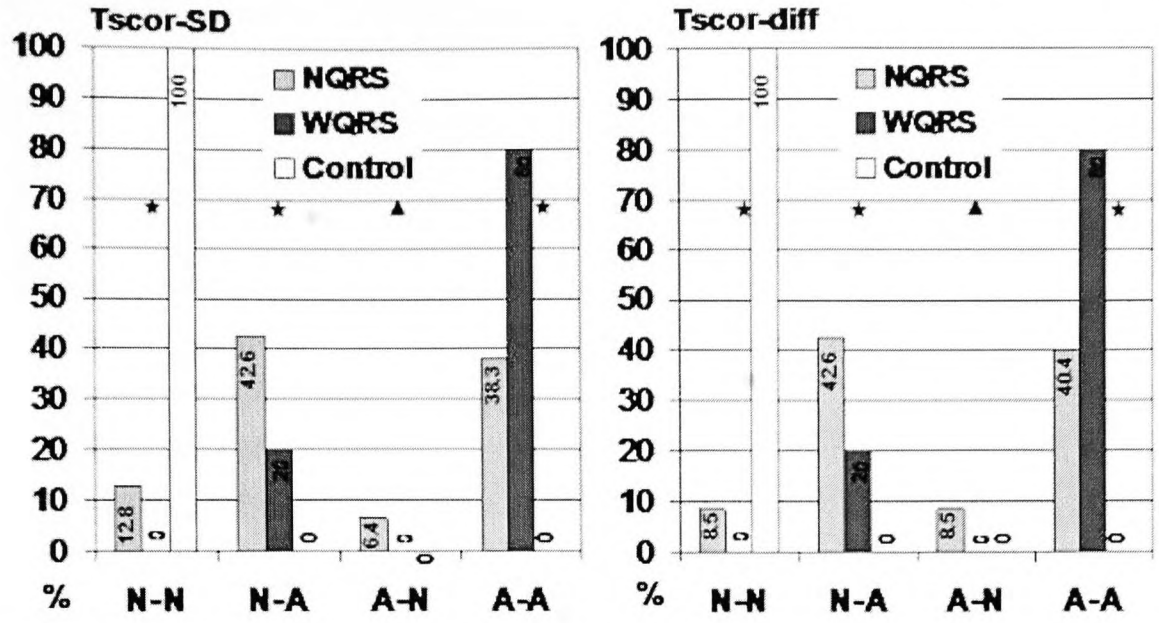


Figure 7.4. Percentage of patients in whom the dyssynchrony indices either improved or worsened under stress grouped according to whether they were normal or abnormal at rest. ★ $p<0.05$, ▲ p= ns. N-N, normal at rest and stress; N-A, normal at rest and abnormal at stress; A-N, abnormal at rest and normal at stress; A-A, abnormal at rest and stress.

Chapter 8: Summary

To the best of our knowledge this is the only report on the feasibility of DSE with cTDI in the assessment of an unselected population of patients with suspected heart failure in an ambulatory setting. All previous reports on feasibility of DSE are based on retrospective analysis of data obtained on patients who underwent the test for established clinical indications, and selected in terms of their echocardiographic image quality, suitability to tolerate the procedure and the absence of contraindications. Thus the applicability of this technique in a truly unselected population of patients who attend a heart failure clinic with multiple cardiovascular and non-cardiovascular co-morbidities was hitherto unknown. The screened subjects were elderly (median age of those not recruited 78 years and those recruited 72 years) and reflected the population expected in a heart failure clinic. About 20% of the patients screened were ineligible for DSE. High mortality at index admission amongst patients admitted with heart failure, inability to consent, contraindications to DSE and non-cardiac co-morbidities that would constrain acquisition of images resulted in ineligibility. About 20% of the eligible patients refused to consent. The discomfort of the test described, inconvenience of attending for the test that may not be clinically relevant, general reluctance to join a research study, travel and travel costs may all have dissuaded the elderly subjects from consenting. Obtaining consent for clinically indicated DSE may be less of a problem. Of those recruited, 21% were excluded due to poor acoustic windows detected during resting echocardiography and a further 6% had uninterpretable studies due to deterioration in image quality during DSE. This conforms to published data. About a quarter of the referred patients could not undergo the test. Withdrawal of beta-blockers resulted in a higher incidence of exclusion due to loss of control over heart failure symptoms, ventricular response in patients with persistent atrial fibrillation and blood pressure. This finding is clinically relevant as a substantial proportion of patients with suspected heart failure are likely to suffer with the latter conditions. Intolerance to subjective symptoms may not lead to early termination of clinically indicated test. The test was feasible in 88% of the patients who underwent DSE. This compares favourably with published data suggesting that DSE is highly feasible in patients appropriately selected for the test.

The major complication rate (3%) was higher than previously reported. This was expected in absence of rigorous selection for the procedure and discontinuation of beta-blockers before the test. Safety of DSE would not be an issue if patients are appropriately selected. Minor complication rates leading to termination of the test conform to published data.

Similar to previous reports, 92-98% of the segments could be visually scored depending on the group of subjects and the level of stress. The feasibility of longitudinal systolic and diastolic and regional systolic quantitative analysis of the left ventricle was higher than some of the previous reports due to methodological differences. The apical segments were excluded from analysis. The anteroseptal and posterior walls were analysed in the apical rather than the parasternal view. Intraobserver variability was low. Segments could be evaluated quantitatively more frequently than visually at all levels of stress. 5% of the attempts at visual assessment of a segment were unsuccessful, most frequently in the HF-LVSD group. TDI could assess segments on 73% of these attempts. The levels of stress did not affect regional quantitative assessment in the HFNEF and NoHF group. Visual and quantitative analysis was least successful in subjects with LVSD especially at peak stress. Despite this limitation, success rate for quantitative evaluation of segments was consistently higher compared to visual assessment in this group. Both visual and quantitative analysis were equally successful in the other subjects. The three segments of the anterior wall were the most difficult to score visually. Quantitative analysis was least successfully at all levels of stress at the middle segment of the anterior wall due to inadequate visualisation and the basal and middle segments of the anteroseptal wall due to misalignment. About three fourths of the segments that could not be assessed visually could be analysed quantitatively. Mitral annular velocities were measured in 99%, 97% and 100% of the instances in the HF-LVSD, HFNEF and NoHF groups respectively. Fewer observations could be made at peak stress compared to rest and low dose in the HF-LVSD group but not in the others.

The feasibility of the analysis of the diastolic waveforms (conventional and TDI) was higher than previously reported. This resulted from the analysis of these waveforms at the highest heart rates where they could be separately measured. This prevented the problems associated with fusion. Analysis of diastolic velocities at sub-maximal stress seemed reasonable for diagnosis of stress-induced diastolic dysfunction firstly because ischaemia induces diastolic dysfunction occurs earlier than systolic and secondly because heart failure patients with exercise intolerance are unlikely to achieve maximal heart rates during day-to-day physical activity that make them breathless. Resting variables e.g. age, hypertension, LV hypertrophy, ischaemia etc. may alter resting diastolic functions in a way that may conceal the effect of stress induced ischaemia on these variables or at least make interpretation difficult. The high prevalence of these conditions in patients with suspected heart failure could adversely affect the evaluation of diastolic function under stress in these patients. The reproducibility of these measurements was acceptable.

Depending on the cut-offs used, 32-50% patients of the HF-LVSD, 17-23% in the HNEF and 29-48% in NoHF groups had prognostically significant volumes of myocardium in ventricles with systolic dysfunction. The systolic annular velocity at each wall increased by >1cm/sec in 61%, 65% ad 59% of the walls with low resting velocities in the three groups respectively suggesting viability in these walls. On visual assessment, 13%, 82%, 75% of the segments responded normally to stress, 42%, 10%, 18% were ischaemic and 30%, 4%, 0.3% were scars in the three groups respectively. On quantitative assessment, 29%, 56%, 55% of the segments responded normally to stress, 26%, 26%, 27% were ischaemic and 4%, 0.6%, 1% were scars.

E/A became abnormal with stress in 65%, 25% and 36% of the patients who were normal at rest and remained abnormal in 81%, 67% and 73% patients who were abnormal at rest in the HF-LVSD, HFNEF and NoHF groups respectively. EDT failed to shorten in 34%, 44% and 30% and EDTc increased with stress in 52%, 59% and 54% patients in the HF-LVSD, HF-PLVF and NoHF groups respectively.

IVRT failed to shorten in 21%, 46% and 35% and IVRTc increased with stress in 55%, 67% and 58% patients in the three groups respectively.

Amongst the patients with normal Ea at rest, it decreased with stress in 21%, 69% and 43% in the HF-LVSD, HFNEF and NoHF group respectively. It decreased by ≥20% in 11%, 32% and 21% and increased by ≥ 20% in 61%, 10% and 30% in the three groups. The mean Ea in the HF-LVSD group was lower than HFNEF group that was similar to the normal group at rest. At peak stress, Ea in the HFNEF group was lower compared to the normal group but was similar to the HF-LVSD group. In the HF-LVSD group, Ea and Aa increased with stress and their ratio remain unchanged. In the HFNEF group, Ea decreased, Aa increased but their ratio does not change. In the normal group, Aa increases but there are no changes in the Ea or Ea/Aa.

Among the patients who had normal resting E/Ea, 5%, 52% and 25% had high E/Ea at peak stress in the HF-LVSD, HFNEF and NoHF groups. Among the patients with high E/Ea ratio at rest, it remained high at peak stress in 43%, 92% and 88% patients in the three groups. At rest, E/Ea HF-LVSD>HFNEF=NoHF. With stress, E/Ea decreased in HF-LVSD, increased in HFNEF and remained unchanged in NoHF group.

The genesis of the symptoms of HF in the absence of reduced global LV systolic function was explored in this study. The changes in the LV global systolic and diastolic, and regional systolic function in response to stress were assessed. Pharmacological stress did not induce LV global (as assessed by WMSI), regional (as assessed by WMS and Sm) and long axis (as assessed by averaged peri-annular Sa) systolic dysfunction excluding this as a common cause of symptoms in patients with HFNEF. Obesity and obstructive airways disease also did not account for these symptoms. Stress impaired diastolic relaxation as evidenced by a reduction in the Ea as compared to controls. It also increased E/Ea ratio (an echocardiographic surrogate for left atrial and LV end-diastolic pressure). The E/Ea ratio at rest and stress correlated negatively with the 6-minute walk distance in the

HFNEF but not in the control group. On multiple regression analysis, the Ea and E at peak stress were found be predictive of the 6-minute walk distance.

This study was undertaken to assess the effect of pharmacological stress on intraventricular dyssynchrony in patients with heart failure with and without wide QRS duration (defined as 120 msec). Ts could be measured in 97% and 99% of segments being assessed at rest and 98% and 98% at peak stress in the HF-LVSD group and controls respectively. Ts was delayed in most myocardial segments at rest and in all myocardial segments at peak stress in the patients. The Tscor shortened in all segments with stress in controls. It failed to shorten in any segment and increased in the mid-segments of the lateral and posterior walls in patients with and without wide QRS.

The study confirmed the previously reported high prevalence of intraventricular dyssynchrony at rest in patients with LVSD irrespective of QRS duration. Depending on the parameter used, the prevalence of dyssynchrony increased from 45-49% at rest to 77-81% at peak stress in the NQRS and 80-83% at rest to 97-100% at peak stress in the WQRS patients. The prevalence of dyssynchrony in patients with QRSd <120 ms approached that observed in patients with QRSd >120 ms during pharmacological stress. Indeed, most patients with LVSD had dyssynchrony during stress regardless of QRS duration. Stress rarely improved dyssynchrony in this study. The severity of dyssynchrony increased during pharmacological stress irrespective of the QRS duration.

Chapter 9: Conclusions

DSE is feasible in patients with suspected heart failure only when they are appropriately selected for the test. About 46% of patients attending the heart failure clinic with suspected heart failure are likely to be excluded from undergoing DSE due to several reasons. Inadequate imaging windows and contraindications to DSE are the commonest causes for exclusion. The proportion of eligible patients who refused to or could not consent for the procedure or requested early test termination due to subjective symptoms are likely to be lower in a real-world situation where more patients are likely to undergo a clinically indicated DSE. The safety of DSE in an unselected group of patients may be a concern. This is unlikely to be an issue in selected patients. In a selected group of patients with suspected heart failure, both global and regional systolic and diastolic assessment is feasible during DSE. cTDI both at rest and stress may supplement visual interpretation of wall motion.

DSE identified prognostic volumes of hibernating and ischaemic myocardium in patients with suspected heart failure who had LVSD. It also unmasked stress induced diastolic impairment in patients with normal ejection fraction. The therapeutic and prognostic implications of this data were not tested in this thesis and needs to be tested larger outcome studies.

It is unlikely that exercise intolerance in patients with HFNEF is due to global, regional or long axis systolic dysfunction at rest or other non-cardiac causes. Stress does not commonly induce systolic dysfunction in these patients. Abnormalities in diastolic function are often induced or exacerbated by stress in these patients. Stress-induced impairment of early diastolic relaxation with consequent rise in the LVEDP is the likely cause of exercise intolerance. This study suggests that routine stress echocardiography may be useful in fully evaluating these patients. However, utility of the test is uncertain till it is shown to predict symptoms, morbidity, mortality and effects of treatment.

High prevalence of resting dyssynchrony was detected in patients with LVSD irrespective of the QRS duration. Dobutamine-stress induced and exacerbated dyssynchrony in these patients. It unmasked dyssynchrony especially in patients with LVSD and narrow QRS complexes. The prevalence and severity of dyssynchrony detected in patients with LVSD and narrow QRS duration under stress approaches that of patients with LVSD and wide QRS duration. LV dyssynchrony, unmasked by stress in patients with narrow QRS, could be a target for therapy. This hypothesis remains to be tested.

Thus, DSE identified left ventricular dysfunction not apparent at rest that could be therapeutic targets e.g. the hibernating and/or ischemic myocardium and dyssynchrony. It could be a useful diagnostic tool in evaluating patients with HFNEF both to detect stress-induced ischemia masquerading as breathlessness and/or impairment of diastolic relaxation. It may allow selection of patients for cardiac resynchronisation therapy. The diagnostic, therapeutic and prognostic implication of these findings will only be evident when tested in larger outcome studies.

Reference List

(1) Swedberg K, Cleland J, Dargie H, Drexler H, Follath F, Komajda M et al. Guidelines for the diagnosis and treatment of chronic heart failure: executive summary (update 2005): The Task Force for the Diagnosis and Treatment of Chronic Heart Failure of the European Society of Cardiology. Eur Heart J 2005; 26(11):1115-1140.

(2) Ho KK, Pinsky JL, Kannel WB, Levy D. The epidemiology of heart failure: the Framingham Study. J Am Coll Cardiol 1993; 22(4 Suppl A):6A-13A.

(3) Rodeheffer RJ, Jacobsen SJ, Gersh BJ, Kottke TE, McCann HA, Bailey KR et al. The incidence and prevalence of congestive heart failure in Rochester, Minnesota. Mayo Clin Proc 1993; 68(12):1143-1150.

(4) Cowie MR, Mosterd A, Wood DA, Deckers JW, Poole-Wilson PA, Sutton GC et al. The epidemiology of heart failure. Eur Heart J 1997; 18(2):208-225.

(5) Remes J, Reunanen A, Aromaa A, Pyorala K. Incidence of heart failure in eastern Finland: a population-based surveillance study. Eur Heart J 1992; 13(5):588-593.

(6) Cowie MR, Wood DA, Coats AJ, Thompson SG, Poole-Wilson PA, Suresh V et al. Incidence and aetiology of heart failure; a population-based study. Eur Heart J 1999; 20(6):421-428.

(7) Phillips SJ, Whisnant JP, O'Fallon WM, Frye RL. Prevalence of cardiovascular disease and diabetes mellitus in residents of Rochester, Minnesota. Mayo Clin Proc 1990; 65(3):344-359.

(8) Mittelmark MB, Psaty BM, Rautaharju PM, Fried LP, Borhani NO, Tracy RP et al. Prevalence of cardiovascular diseases among older adults. The Cardiovascular Health Study. Am J Epidemiol 1993; 137(3):311-317.

(9) Schocken DD, Arrieta MI, Leaverton PE, Ross EA. Prevalence and mortality rate of congestive heart failure in the United States. J Am Coll Cardiol 1992; 20(2):301-306.

(10) Landahl S, Svanborg A, Astrand K. Heart volume and the prevalence of certain common cardiovascular disorders at 70 and 75 years of age. Eur Heart J 1984; 5(4):326-331.

(11) Ambrosio GB, Riva LM, Zamboni S, Nogara A, Zanchi P, Parisi R et al. [Heart failure in the population: prevalence data]. Cardiologia 1992; 37(10):685-691.

(12) Khan NK, Goode KM, Cleland JG, Rigby AS, Freemantle N, Eastaugh J et al. Prevalence of ECG abnormalities in an international survey of patients

with suspected or confirmed heart failure at death or discharge. Eur J Heart Fail 2007; 9(5):491-501.

(13) Cleland JG, Cohen-Solal A, Aguilar JC, Dietz R, Eastaugh J, Follath F et al. Management of heart failure in primary care (the IMPROVEMENT of Heart Failure Programme): an international survey. Lancet 2002; 360(9346):1631-1639.

(14) 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(360):287-289.

(15) Cleland JG, Khand A, Clark A. The heart failure epidemic: exactly how big is it? Eur Heart J 2001; 22(8):623-626.

(16) Wolinsky FD, Smith DM, Stump TE, Overhage JM, Lubitz RM. The sequelae of hospitalization for congestive heart failure among older adults. J Am Geriatr Soc 1997; 45(5):558-563.

(17) 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(11):1292-1297.

(18) Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. The SOLVD Investigattors. N Engl J Med 1992; 327(10):685-691.

(19) Cleland JG, Massie BM, Packer M. Sudden death in heart failure: vascular or electrical? Eur J Heart Fail 1999; 1(1):41-45.

(20) Cleland JG, Swedberg K, Follath F, Komajda M, Cohen-Solal A, Aguilar JC et al. The EuroHeart Failure survey programme-- a survey on the quality of care among patients with heart failure in Europe. Part 1: patient characteristics and diagnosis. Eur Heart J 2003; 24(5):442-463.

(21) Cleland JG, Tendera M, Adamus J, Freemantle N, Polonski L, Taylor J. The perindopril in elderly people with chronic heart failure (PEP-CHF) study. Eur Heart J 2006; 27(19):2338-2345.

(22) Bhatia RS, Tu JV, Lee DS, Austin PC, Fang J, Haouzi A et al. Outcome of heart failure with preserved ejection fraction in a population-based study. N Engl J Med 2006; %20;355(3):260-269.

(23) Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. N Engl J Med 2006; %20;355(3):251-259.

(24) Yusuf S, Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJ et al. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. Lancet 2003; 362(9386):777-781.

(25) Parameshwar J, Poole-Wilson PA, Sutton GC. Heart failure in a district general hospital. J R Coll Physicians Lond 1992; 26(2):139-142.

(26) McMurray J, McDonagh T, Morrison CE, Dargie HJ. Trends in hospitalization for heart failure in Scotland 1980-1990. Eur Heart J 1993; 14(9):1158-1162.

(27) Cowie MR, Fox KF, Wood DA, Metcalfe C, Thompson SG, Coats AJ et al. Hospitalization of patients with heart failure: a population-based study. Eur Heart J 2002; 23(11):877-885.

(28) Cowie MR, Wood DA, Coats AJ, Thompson SG, Suresh V, Poole-Wilson PA et al. Survival of patients with a new diagnosis of heart failure: a population based study. Heart 2000; 83(5):505-510.

(29) Senni M, Tribouilloy CM, Rodeheffer RJ, Jacobsen SJ, Evans JM, Bailey KR et al. Congestive heart failure in the community: a study of all incident cases in Olmsted County, Minnesota, in 1991. Circulation 1998; 98(21):2282-2289.

(30) Khand A, Gemmel I, Clark AL, Cleland JG. Is the prognosis of heart failure improving? J Am Coll Cardiol 2000; 36(7):2284-2286.

(31) Stewart S, MacIntyre K, Hole DJ, Capewell S, McMurray JJ. More 'malignant' than cancer? Five-year survival following a first admission for heart failure. Eur J Heart Fail 2001; 3(3):315-322.

(32) Hallstrom AP, Anderson JL, Carlson M, Davies R, Greene HL, Kammerling JM et al. Time to arrhythmic, ischemic, and heart failure events: exploratory analyses to elucidate mechanisms of adverse drug effects in the Cardiac Arrhythmia Suppression Trial. Am Heart J 1995; 130(1):71-79.

(33) Khand AU, Shaw M, Gemmel I, Cleland JG. Do discharge codes underestimate hospitalisation due to heart failure? Validation study of hospital discharge coding for heart failure. Eur J Heart Fail 2005; 7(5):792-797.

(34) Remes J, Miettinen H, Reunanen A, Pyorala K. Validity of clinical diagnosis of heart failure in primary health care. Eur Heart J 1991; 12(3):315-321.

(35) Wheeldon NM, MacDonald TM, Flucker CJ, McKendrick AD, McDevitt DG, Struthers AD. Echocardiography in chronic heart failure in the community. Q J Med 1993; 86(1):17-23.

(36) Hlatky MA, Fleg JL, Hinton PC, Lakatta EG, Marcus FI, Smith TW et al. Physician practice in the management of congestive heart failure. J Am Coll Cardiol 1986; 8(4):966-970.

(37) Shah S, Davies MK, Cartwright D, Nightingale P. Management of chronic heart failure in the community: role of a hospital based open access heart failure service. Heart 2004; 90(7):755-759.

(38) Spiteri MA, Cook DG, Clarke SW. Reliability of eliciting physical signs in examination of the chest. Lancet 1988; 1(8590):873-875.

(39) Stevenson LW, Perloff JK. The limited reliability of physical signs for estimating hemodynamics in chronic heart failure. JAMA 1989; 261(6):884-888.

(40) Gadsboll N, Hoilund-Carlsen PF, Nielsen GG, Berning J, Brunn NE, Stage P et al. Symptoms and signs of heart failure in patients with myocardial infarction: reproducibility and relationship to chest X-ray, radionuclide ventriculography and right heart catheterization. Eur Heart J 1989; 10(11):1017-1028.

(41) Butman SM, Ewy GA, Standen JR, Kern KB, Hahn E. Bedside cardiovascular examination in patients with severe chronic heart failure: importance of rest or inducible jugular venous distension. J Am Coll Cardiol 1993; 22(4):968-974.

(42) Ishmail AA, Wing S, Ferguson J, Hutchinson TA, Magder S, Flegel KM. Interobserver agreement by auscultation in the presence of a third heart sound in patients with congestive heart failure. Chest 1987; 91(6):870-873.

(43) Marantz PR, Tobin JN, Wassertheil-Smoller S, Steingart RM, Wexler JP, Budner N et al. The relationship between left ventricular systolic function and congestive heart failure diagnosed by clinical criteria. Circulation 1988; 77(3):607-612.

(44) McMurray J, Ostergren J, Pfeffer M, Swedberg K, Granger C, Yusuf S et al. Clinical features and contemporary management of patients with low and preserved ejection fraction heart failure: baseline characteristics of patients in the Candesartan in Heart failure-Assessment of Reduction in Mortality and morbidity (CHARM) programme. Eur J Heart Fail 2003; 5(3):261-270.

(45) Cohn JN, Johnson GR, Shabetai R, Loeb H, Tristani F, Rector T et al. Ejection fraction, peak exercise oxygen consumption, cardiothoracic ratio, ventricular arrhythmias, and plasma norepinephrine as determinants of prognosis in heart failure. The V-HeFT VA Cooperative Studies Group. Circulation 1993; 87(6 Suppl):VI5-16.

(46) Chakko S, Woska D, Martinez H, de Marchena E, Futterman L, Kessler KM et al. Clinical, radiographic, and hemodynamic correlations in chronic

congestive heart failure: conflicting results may lead to inappropriate care. Am J Med 1991; 90(3):353-359.

(47) Rocker GM, Rose DH, Manhire AR, Pearson D, Shale DJ. The radiographic differentiation of pulmonary oedema. Br J Radiol 1989; 62(739):582-586.

(48) Bellenger NG, Burgess MI, Ray SG, Lahiri A, Coats AJ, Cleland JG et al. Comparison of left ventricular ejection fraction and volumes in heart failure by echocardiography, radionuclide ventriculography and cardiovascular magnetic resonance; are they interchangeable? Eur Heart J 2000; 21(16):1387-1396.

(49) Jensen-Urstad K, Bouvier F, Hojer J, Ruiz H, Hulting J, Samad B et al. Comparison of different echocardiographic methods with radionuclide imaging for measuring left ventricular ejection fraction during acute myocardial infarction treated by thrombolytic therapy. Am J Cardiol 1998; 81(5):538-544.

(50) Hedberg P, Jonason T, Henriksen E, Lonnberg I, Nilsson G, Pehrsson K et al. Mitral annulus motion compared with wall motion scoring index in the assessment of left ventricular ejection fraction. J Am Soc Echocardiogr 2003; 16(6):622-629.

(51) 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(7):1948-1955.

(52) Vasan RS, Benjamin EJ, Levy D. Prevalence, clinical features and prognosis of diastolic heart failure: an epidemiologic perspective. J Am Coll Cardiol 1995; 26(7):1565-1574.

(53) Mosterd A, Hoes AW, de Bruyne MC, Deckers JW, Linker DT, Hofman A et al. Prevalence of heart failure and left ventricular dysfunction in the general population; The Rotterdam Study. Eur Heart J 1999; 20(6):447-455.

(54) Hogg K, Swedberg K, McMurray J. Heart failure with preserved left ventricular systolic function; epidemiology, clinical characteristics, and prognosis. J Am Coll Cardiol 2004; 43(3):317-327.

(55) Caruana L, Petrie MC, Davie AP, McMurray JJ. Do patients with suspected heart failure and preserved left ventricular systolic function suffer from "diastolic heart failure" or from misdiagnosis? A prospective descriptive study. BMJ 2000; 321(7255):215-218.

(56) Grossman W. Defining diastolic dysfunction. Circulation 2000; 101(17):2020-2021.

(57) Nikitin NP, Witte KK, Clark AL, Cleland JG. Color tissue Doppler-derived long-axis left ventricular function in heart failure with preserved global systolic function. Am J Cardiol 2002; 90(10):1174-1177.

(58) Yip G, Wang M, Zhang Y, Fung JW, Ho PY, Sanderson JE. Left ventricular long axis function in diastolic heart failure is reduced in both diastole and systole: time for a redefinition? Heart 2002; 87(2):121-125.

(59) Yu CM, Lin H, Yang H, Kong SL, Zhang Q, Lee SW. Progression of systolic abnormalities in patients with "isolated" diastolic heart failure and diastolic dysfunction. Circulation 2002; 105(10):1195-1201.

(60) Petrie MC, Caruana L, Berry C, McMurray JJ. "Diastolic heart failure" or heart failure caused by subtle left ventricular systolic dysfunction? Heart 2002; 87(1):29-31.

(61) 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(10):1031-1036.

(62) Vinereanu D, Nicolaides E, Tweddel AC, Fraser AG. "Pure" diastolic dysfunction is associated with long-axis systolic dysfunction. Implications for the diagnosis and classification of heart failure. Eur J Heart Fail 2005; 7(5):820-828.

(63) Gandhi SK, Powers JC, Nomeir AM, Fowle K, Kitzman DW, Rankin KM et al. The pathogenesis of acute pulmonary edema associated with hypertension. N Engl J Med 2001; 344(1):17-22.

(64) Zile MR, Gaasch WH, Carroll JD, Feldman MD, Aurigemma GP, Schaer GL et al. Heart failure with a normal ejection fraction: is measurement of diastolic function necessary to make the diagnosis of diastolic heart failure? Circulation 2001; 104(7):779-782.

(65) Henein MY, O'Sullivan C, Sutton GC, Gibson DG, Coats AJ. Stress-induced left ventricular outflow tract obstruction: a potential cause of dyspnea in the elderly. J Am Coll Cardiol 1997; 30(5):1301-1307.

(66) How to diagnose diastolic heart failure. European Study Group on Diastolic Heart Failure. Eur Heart J 1998; 19(7):990-1003.

(67) Cahill JM, Horan M, Quigley P, Maurer B, McDonald K. Doppler-echocardiographic indices of diastolic function in heart failure admissions with preserved left ventricular systolic function. Eur J Heart Fail 2002; 4(4):473-478.

(68) Palmieri V, Innocenti F, Pini R, Celentano A. Reproducibility of Doppler echocardiographic assessment of left ventricular diastolic function in multicenter setting. J Am Soc Echocardiogr 2005; 18(2):99-106.

(69) Thomas MD, Fox KF, Wood DA, Gibbs JS, Coats AJ, Henein MY et al. Echocardiographic features and brain natriuretic peptides in patients presenting with heart failure and preserved systolic function. Heart 2006; 92(5):603-608.

(70) Petrie MC, Hogg K, Caruana L, McMurray JJ. Poor concordance of commonly used echocardiographic measures of left ventricular diastolic function in patients with suspected heart failure but preserved systolic function: is there a reliable echocardiographic measure of diastolic dysfunction? Heart 2004; 90(5):511-517.

(71) Lim TK, Ashrafian H, Dwivedi G, Collinson PO, Senior R. Increased left atrial volume index is an independent predictor of raised serum natriuretic peptide in patients with suspected heart failure but normal left ventricular ejection fraction: Implication for diagnosis of diastolic heart failure. Eur J Heart Fail 2006; 8(1):38-45.

(72) Mottram PM, Leano R, Marwick TH. Usefulness of B-type natriuretic peptide in hypertensive patients with exertional dyspnea and normal left ventricular ejection fraction and correlation with new echocardiographic indexes of systolic and diastolic function. Am J Cardiol 2003; 92(12):1434-1438.

(73) Ambrosio G, Betocchi S, Pace L, Losi MA, Perrone-Filardi P, Soricelli A et al. Prolonged impairment of regional contractile function after resolution of exercise-induced angina. Evidence of myocardial stunning in patients with coronary artery disease. Circulation 1996; 94(10):2455-2464.

(74) Aroesty JM, McKay RG, Heller GV, Royal HD, Als AV, Grossman W. Simultaneous assessment of left ventricular systolic and diastolic dysfunction during pacing-induced ischemia. Circulation 1985; 71(5):889-900.

(75) Presti CF, Walling AD, Montemayor I, Campbell JM, Crawford MH. Influence of exercise-induced myocardial ischemia on the pattern of left ventricular diastolic filling: a Doppler echocardiographic study. J Am Coll Cardiol 1991; 18(1):75-82.

(76) Mazeika PK, Nadazdin A, Oakley CM. Influence of haemodynamics and myocardial ischaemia on Doppler transmitral flow in patients undergoing dobutamine echocardiography. Eur Heart J 1994; 15(1):17-25.

(77) Labovitz AJ, Pearson AC, Chaitman BR. Doppler and two-dimensional echocardiographic assessment of left ventricular function before and after intravenous dipyridamole stress testing for detection of coronary artery disease. Am J Cardiol 1988; 62(17):1180-1185.

(78) Iliceto S, Amico A, Marangelli V, D'Ambrosio G, Rizzon P. Doppler echocardiographic evaluation of the effect of atrial pacing-induced ischemia on left ventricular filling in patients with coronary artery disease. J Am Coll Cardiol 1988; 11(5):953-961.

(79) Garcia-Fernandez MA, Azevedo J, Moreno M, Bermejo J, Perez-Castellano N, Puerta P et al. Regional diastolic function in ischaemic heart disease using pulsed wave Doppler tissue imaging. Eur Heart J 1999; 20(7):496-505.

(80) el Said ES, Roelandt JR, Fioretti PM, McNeill AJ, Forster T, Boersma H et al. Abnormal left ventricular early diastolic filling during dobutamine stress Doppler echocardiography is a sensitive indicator of significant coronary artery disease. J Am Coll Cardiol 1994; 24(7):1618-1624.

(81) Derumeaux G, Ovize M, Loufoua J, Pontier G, Andre-Fouet X, Cribier A. Assessment of nonuniformity of transmural myocardial velocities by color-coded tissue Doppler imaging: characterization of normal, ischemic, and stunned myocardium. Circulation 2000; 101(12):1390-1395.

(82) Little WC, Kitzman DW, Cheng CP. Diastolic dysfunction as a cause of exercise intolerance. Heart Fail Rev 2000; 5(4):301-306.

(83) Warner JG, Jr., Metzger DC, Kitzman DW, Wesley DJ, Little WC. Losartan improves exercise tolerance in patients with diastolic dysfunction and a hypertensive response to exercise. J Am Coll Cardiol 1999; 33(6):1567-1572.

(84) Kawaguchi M, Hay I, Fetics B, Kass DA. Combined ventricular systolic and arterial stiffening in patients with heart failure and preserved ejection fraction: implications for systolic and diastolic reserve limitations. Circulation 2003; 107(5):714-720.

(85) Liu CP, Ting CT, Lawrence W, Maughan WL, Chang MS, Kass DA. Diminished contractile response to increased heart rate in intact human left ventricular hypertrophy. Systolic versus diastolic determinants. Circulation 1993; 88(4 Pt 1):1893-1906.

(86) Pellikka PA, Oh JK, Bailey KR, Nichols BA, Monahan KH, Tajik AJ. Dynamic intraventricular obstruction during dobutamine stress echocardiography. A new observation. Circulation 1992; 86(5):1429-1432.

(87) Luria D, Klutstein MW, Rosenmann D, Shaheen J, Sergey S, Tzivoni D. Prevalence and significance of left ventricular outflow gradient during dobutamine echocardiography. Eur Heart J 1999; 20(5):386-392.

(88) Setaro JF, Zaret BL, Schulman DS, Black HR, Soufer R. Usefulness of verapamil for congestive heart failure associated with abnormal left ventricular diastolic filling and normal left ventricular systolic performance. Am J Cardiol 1990; 66(12):981-986.

(89) Choudhury L, Gheorghiade M, Bonow RO. Coronary artery disease in patients with heart failure and preserved systolic function. Am J Cardiol 2002; 89(6):719-722.

(90) Zile MR, Baicu CF, Gaasch WH. Diastolic heart failure--abnormalities in active relaxation and passive stiffness of the left ventricle. N Engl J Med 2004; 350(19):1953-1959.

(91) Baicu CF, Zile MR, Aurigemma GP, Gaasch WH. Left ventricular systolic performance, function, and contractility in patients with diastolic heart failure. Circulation 2005; 111(18):2306-2312.

(92) Gheorghiade M, Bonow RO. Chronic heart failure in the United States: a manifestation of coronary artery disease. Circulation 1998; 97(3):282-289.

(93) Fauchier L, Marie O, Casset-Senon D, Babuty D, Cosnay P, Fauchier JP. Reliability of QRS duration and morphology on surface electrocardiogram to identify ventricular dyssynchrony in patients with idiopathic dilated cardiomyopathy. Am J Cardiol 2003; 92(3):341-344.

(94) Yu CM, Lin H, Zhang Q, Sanderson JE. High prevalence of left ventricular systolic and diastolic asynchrony in patients with congestive heart failure and normal QRS duration. Heart 2003; 89(1):54-60.

(95) Ghio S, Constantin C, Klersy C, Serio A, Fontana A, Campana C et al. Interventricular and intraventricular dyssynchrony are common in heart failure patients, regardless of QRS duration. Eur Heart J 2004; 25(7):571-578.

(96) Yu CM, Yang H, Lau CP, Wang Q, Wang S, Lam L et al. Regional left ventricle mechanical asynchrony in patients with heart disease and normal QRS duration: implication for biventricular pacing therapy. Pacing Clin Electrophysiol 2003; 26(2 Pt 1):562-570.

(97) Lafitte S, Bordachar P, Lafitte M, Garrigue S, Reuter S, Reant P et al. Dynamic ventricular dyssynchrony: an exercise-echocardiography study. J Am Coll Cardiol 2006; 47(11):2253-2259.

(98) Hummel JP, Lindner JR, Belcik JT, Ferguson JD, Mangrum JM, Bergin JD et al. Extent of myocardial viability predicts response to biventricular pacing in ischemic cardiomyopathy. Heart Rhythm 2005; 2(11):1211-1217.

(99) Valzania C, Gadler F, Eriksson MJ, Olsson A, Boriani G, Braunschweig F. Electromechanical effects of cardiac resynchronization therapy during rest and stress in patients with heart failure. Eur J Heart Fail 2007; 9(6-7):644-650.

(100) Da Costa A, Thevenin J, Roche F, Faure E, Romeyer-Bouchard C, Messier M et al. Prospective validation of stress echocardiography as an identifier of cardiac resynchronization therapy responders. Heart Rhythm 2006; 3(4):406-413.

(101) Detrano R, Gianrossi R, Froelicher V. The diagnostic accuracy of the exercise electrocardiogram: a meta-analysis of 22 years of research. Prog Cardiovasc Dis 1989; 32(3):173-206.

(102) Marwick TH. Current status of non-invasive techniques for the diagnosis of myocardial ischemia. Acta Clin Belg 1992; 47(1):1-5.

(103) Becher H, Chambers J, Fox K, Jones R, Leech GJ, Masani N et al. BSE procedure guidelines for the clinical application of stress echocardiography, recommendations for performance and interpretation of stress echocardiography: a report of the British Society of Echocardiography Policy Committee. Heart 2004; 90 Suppl 6:vi23-30.:vi23-vi30.

(104) Nesto RW, Kowalchuk GJ. The ischemic cascade: temporal sequence of hemodynamic, electrocardiographic and symptomatic expressions of ischemia. Am J Cardiol 1987; 59(7):23C-30C.

(105) Presti CF, Armstrong WF, Feigenbaum H. Comparison of echocardiography at peak exercise and after bicycle exercise in evaluation of patients with known or suspected coronary artery disease. J Am Soc Echocardiogr 1988; 1(2):119-126.

(106) Peteiro J, Fabregas R, Montserrat L, Alvarez N, Castro-Beiras A. Comparison of treadmill exercise echocardiography before and after exercise in the evaluation of patients with known or suspected coronary artery disease. J Am Soc Echocardiogr 1999; 12(12):1073-1079.

(107) Rallidis L, Cokkinos P, Tousoulis D, Nihoyannopoulos P. Comparison of dobutamine and treadmill exercise echocardiography in inducing ischemia in patients with coronary artery disease. J Am Coll Cardiol 1997; 30(7):1660-1668.

(108) Cohen JL, Ottenweller JE, George AK, Duvvuri S. Comparison of dobutamine and exercise echocardiography for detecting coronary artery disease. Am J Cardiol 1993; 72(17):1226-1231.

(109) Attenhofer CH, Pellikka PA, Oh JK, Roger VL, Sohn DW, Seward JB. Comparison of ischemic response during exercise and dobutamine echocardiography in patients with left main coronary artery disease. J Am Coll Cardiol 1996; 27(5):1171-1177.

(110) Wann LS, Faris JV, Childress RH, Dillon JC, Weyman AE, Feigenbaum H. Exercise cross-sectional echocardiography in ischemic heart disease. Circulation 1979; 60(6):1300-1308.

(111) Gallagher KP, Matsuzaki M, Osakada G, Kemper WS, Ross J, Jr. Effect of exercise on the relationship between myocardial blood flow and systolic wall thickening in dogs with acute coronary stenosis. Circ Res 1983; 52(6):716-729.

(112) Ross J, Jr. Mechanisms of regional ischemia and antianginal drug action during exercise. Prog Cardiovasc Dis 1989; 31(6):455-466.

(113) Nahar T, Croft L, Shapiro R, Fruchtman S, Diamond J, Henzlova M et al. Comparison of four echocardiographic techniques for measuring left ventricular ejection fraction. Am J Cardiol 2000; 86(12):1358-1362.

(114) Shehata AR, Gillam LD, Mascitelli VA, Herman SD, Ahlberg AW, White MP et al. Impact of acute propranolol administration on dobutamine-induced myocardial ischemia as evaluated by myocardial perfusion imaging and echocardiography. Am J Cardiol 1997; 80(3):268-272.

(115) Allman KC, Shaw LJ, Hachamovitch R, Udelson JE. Myocardial viability testing and impact of revascularization on prognosis in patients with coronary artery disease and left ventricular dysfunction: a meta-analysis. J Am Coll Cardiol 2002; 39(7):1151-1158.

(116) Schiller NB, Shah PM, Crawford M, DeMaria A, Devereux R, Feigenbaum H et al. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. J Am Soc Echocardiogr 1989; 2(5):358-367.

(117) Cerqueira MD, Weissman NJ, Dilsizian V, Jacobs AK, Kaul S, Laskey WK et al. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart: a statement for healthcare professionals from the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association. Circulation 2002; 105(4):539-542.

(118) Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr 2005; 18(12):1440-1463.

(119) Berning J, Rokkedal NJ, Launbjerg J, Fogh J, Mickley H, Andersen PE. Rapid estimation of left ventricular ejection fraction in acute myocardial infarction by echocardiographic wall motion analysis. Cardiology 1992; 80(3-4):257-266.

(120) Berning J, Steensgaard-Hansen F. Early estimation of risk by echocardiographic determination of wall motion index in an unselected population with acute myocardial infarction. Am J Cardiol 1990; 65(9):567-576.

(121) Diamond GA, Forrester JS, deLuz PL, Wyatt HL, Swan HJ. Post-extrasystolic potentiation of ischemic myocardium by atrial stimulation. Am Heart J 1978; 95(2):204-209.

(122) Rahimtoola SH. The hibernating myocardium. Am Heart J 1989; 117(1):211-221.

(123) Rahimtoola SH. A perspective on the three large multicenter randomized clinical trials of coronary bypass surgery for chronic stable angina. Circulation 1985; 72(6 Pt 2):V123-V135.

(124) Bonow RO. The hibernating myocardium: implications for management of congestive heart failure. Am J Cardiol 1995; %19;75(3):17A-25A.

(125) Rahimtoola SH. From coronary artery disease to heart failure: role of the hibernating myocardium. Am J Cardiol 1995; 75(13):16E-22E.

(126) Rahimtoola SH. Hibernating myocardium has reduced blood flow at rest that increases with low-dose dobutamine. Circulation 1996; 94(12):3055-3061.

(127) Gerber BL, Vanoverschelde JL, Bol A, Michel C, Labar D, Wijns W et al. Myocardial blood flow, glucose uptake, and recruitment of inotropic reserve in chronic left ventricular ischemic dysfunction. Implications for the pathophysiology of chronic myocardial hibernation. Circulation 1996; 94(4):651-659.

(128) Marinho NV, Keogh BE, Costa DC, Lammerstma AA, Ell PJ, Camici PG. Pathophysiology of chronic left ventricular dysfunction. New insights from the measurement of absolute myocardial blood flow and glucose utilization. Circulation 1996; 93(4):737-744.

(129) Sun KT, Czernin J, Krivokapich J, Lau YK, Bottcher M, Maurer G et al. Effects of dobutamine stimulation on myocardial blood flow, glucose metabolism, and wall motion in normal and dysfunctional myocardium. Circulation 1996; 94(12):3146-3154.

(130) Lee HH, Davila-Roman VG, Ludbrook PA, Courtois M, Walsh JF, Delano DA et al. Dependency of contractile reserve on myocardial blood flow: implications for the assessment of myocardial viability with dobutamine stress echocardiography. Circulation 1997; 96(9):2884-2891.

(131) Heyndrickx GR, Millard RW, McRitchie RJ, Maroko PR, Vatner SF. Regional myocardial functional and electrophysiological alterations after brief coronary artery occlusion in conscious dogs. J Clin Invest 1975; 56(4):978-985.

(132) Braunwald E, Kloner RA. The stunned myocardium: prolonged, postischemic ventricular dysfunction. Circulation 1982; 66(6):1146-1149.

(133) Bolli R. Mechanism of myocardial "stunning". Circulation 1990; 82(3):723-738.

(134) Matsuzaki M, Gallagher KP, Kemper WS, White F, Ross J, Jr. Sustained regional dysfunction produced by prolonged coronary stenosis: gradual recovery after reperfusion. Circulation 1983; 68(1):170-182.

(135) Homans DC, Sublett E, Dai XZ, Bache RJ. Persistence of regional left ventricular dysfunction after exercise-induced myocardial ischemia. J Clin Invest 1986; 77(1):66-73.

(136) Homans DC, Laxson DD, Sublett E, Lindstrom P, Bache RJ. Cumulative deterioration of myocardial function after repeated episodes of exercise-induced ischemia. Am J Physiol 1989; 256(5 Pt 2):H1462-H1471.

(137) Scognamiglio R, Ponchia A, Fasoli G, Miraglia G, Dalla-Volta S. Exercise-induced left ventricular dysfunction in coronary heart disease. A model for studying the stunned myocardium in man. Eur Heart J 1991; 12 Suppl G:16-9.:16-19.

(138) Kloner RA, Allen J, Cox TA, Zheng Y, Ruiz CE. Stunned left ventricular myocardium after exercise treadmill testing in coronary artery disease. Am J Cardiol 1991; 68(4):329-334.

(139) Hittinger L, Shannon RP, Kohin S, Manders WT, Kelly P, Vatner SF. Exercise-induced subendocardial dysfunction in dogs with left ventricular hypertrophy. Circ Res 1990; 66(2):329-343.

(140) Vanoverschelde JL, Wijns W, Depre C, Essamri B, Heyndrickx GR, Borgers M et al. Mechanisms of chronic regional postischemic dysfunction in humans. New insights from the study of noninfarcted collateral-dependent myocardium. Circulation 1993; 87(5):1513-1523.

(141) Shen YT, Vatner SF. Mechanism of impaired myocardial function during progressive coronary stenosis in conscious pigs. Hibernation versus stunning? Circ Res 1995; 76(3):479-488.

(142) Senior R, Lahiri A. Dobutamine echocardiography predicts functional outcome after revascularisation in patients with dysfunctional myocardium irrespective of the perfusion pattern on resting thallium-201 imaging. Heart 1999; 82(6):668-673.

(143) Bonow RO. Identification of viable myocardium. Circulation 1996; 94(11):2674-2680.

(144) Beanlands RS, Hendry PJ, Masters RG, deKemp RA, Woodend K, Ruddy TD. Delay in revascularization is associated with increased mortality rate in patients with severe left ventricular dysfunction and viable myocardium on fluorine 18-fluorodeoxyglucose positron emission tomography imaging. Circulation 1998; 98(19 Suppl):II51-II56.

(145) Atkinson JB, Virmani R. Congestive heart failure due to coronary artery disease without myocardial infarction: clinicopathologic description of an unusual cardiomyopathy. Hum Pathol 1989; 20(12):1155-1162.

(146) Elsasser A, Muller KD, Skwara W, Bode C, Kubler W, Vogt AM. Severe energy deprivation of human hibernating myocardium as possible common pathomechanism of contractile dysfunction, structural degeneration and cell death. J Am Coll Cardiol 2002; 39(7):1189-1198.

(147) Elsasser A, Schlepper M, Klovekorn WP, Cai WJ, Zimmermann R, Muller KD et al. Hibernating myocardium: an incomplete adaptation to ischemia. Circulation 1997; 96(9):2920-2931.

(148) Frangogiannis NG, Shimoni S, Chang SM, Ren G, Dewald O, Gersch C et al. Active interstitial remodeling: an important process in the hibernating human myocardium. J Am Coll Cardiol 2002; 39(9):1468-1474.

(149) Depre C, Vanoverschelde JL, Gerber B, Borgers M, Melin JA, Dion R. Correlation of functional recovery with myocardial blood flow, glucose uptake, and morphologic features in patients with chronic left ventricular ischemic dysfunction undergoing coronary artery bypass grafting. J Thorac Cardiovasc Surg 1997; 113(2):371-378.

(150) Colucci WS. Myocardial endothelin. Does it play a role in myocardial failure? Circulation 1996; 93(6):1069-1072.

(151) Shivalkar B, Maes A, Borgers M, Ausma J, Scheys I, Nuyts J et al. Only hibernating myocardium invariably shows early recovery after coronary revascularization. Circulation 1996; 94(3):308-315.

(152) Horn HR, Teichholz LE, Cohn PF, Herman MV, Gorlin R. Augmentation of left ventricular contraction pattern in coronary artery disease by an inotropic catecholamine. The epinephrine ventriculogram. Circulation 1974; 49(6):1063-1071.

(153) Popio KA, Gorlin R, Bechtel D, Levine JA. Postextrasystolic potentiation as a predictor of potential myocardial viability: preoperative analyses compared with studies after coronary bypass surgery. Am J Cardiol 1977; 39(7):944-953.

(154) Dyke SH, Cohn PF, Gorlin R, Sonnenblick EH. Detection of residual myocardial function in coronary artery disease using post-extra systolic potentiation. Circulation 1974; 50(4):694-699.

(155) Cohn PF, Gorlin R, Herman MV, Sonnenblick EH, Horn HR, Cohn LH et al. Relation between contractile reserve and prognosis in patients with coronary artery disease and a depressed ejection fraction. Circulation 1975; 51(3):414-420.

(156) Krivokapich J, Czernin J, Schelbert HR. Dobutamine positron emission tomography: absolute quantitation of rest and dobutamine myocardial blood flow and correlation with cardiac work and percent diameter stenosis in patients with and without coronary artery disease. J Am Coll Cardiol 1996; 28(3):565-572.

(157) Schulz R, Rose J, Martin C, Brodde OE, Heusch G. Development of short-term myocardial hibernation. Its limitation by the severity of ischemia and inotropic stimulation. Circulation 1993; 88(2):684-695.

(158) La Canna G, Alfieri O, Giubbini R, Gargano M, Ferrari R, Visioli O. Echocardiography during infusion of dobutamine for identification of reversibly dysfunction in patients with chronic coronary artery disease. J Am Coll Cardiol 1994; 23(3):617-626.

(159) Geleijnse ML, Fioretti PM, Roelandt JR. Methodology, feasibility, safety and diagnostic accuracy of dobutamine stress echocardiography. J Am Coll Cardiol 1997; 30(3):595-606.

(160) Hoffmann R, Lethen H, Kleinhans E, Weiss M, Flachskampf FA, Hanrath P. Comparative evaluation of bicycle and dobutamine stress echocardiography with perfusion scintigraphy and bicycle electrocardiogram for identification of coronary artery disease. Am J Cardiol 1993; 72(7):555-559.

(161) Dagianti A, Penco M, Agati L, Sciomer S, Dagianti A, Rosanio S et al. Stress echocardiography: comparison of exercise, dipyridamole and dobutamine in detecting and predicting the extent of coronary artery disease. J Am Coll Cardiol 1995; 26(1):18-25.

(162) Beleslin BD, Ostojic M, Djordjevic-Dikic A, Babic R, Nedeljkovic M, Stankovic G et al. Integrated evaluation of relation between coronary lesion features and stress echocardiography results: the importance of coronary lesion morphology. J Am Coll Cardiol 1999; 33(3):717-726.

(163) Oguzhan A, Kisacik HL, Ozdemir K, Altunkeser BB, Durmaz T, Altinyay E et al. Comparison of exercise stress testing with dobutamine stress echocardiography and exercise technetium-99m isonitrile single photon emission computerized tomography for diagnosis of coronary artery disease. Jpn Heart J 1997; 38(3):333-344.

(164) Yuda S, Fang ZY, Leano R, Marwick TH. Is quantitative interpretation likely to increase sensitivity of dobutamine stress echocardiography? A study of false-negative results. J Am Soc Echocardiogr 2004; 17(5):448-453.

(165) Smart SC, Knickelbine T, Malik F, Sagar KB. Dobutamine-atropine stress echocardiography for the detection of coronary artery disease in patients with left ventricular hypertrophy. Importance of chamber size and systolic wall stress. Circulation 2000; 101(3):258-263.

(166) Sadler DB, Aurigemma GP, Williams DW, Reda DJ, Materson BJ, Gottdiener JS. Systolic function in hypertensive men with concentric remodeling. Hypertension 1997; 30(4):777-781.

(167) Yuda S, Khoury V, Marwick TH. Influence of wall stress and left ventricular geometry on the accuracy of dobutamine stress echocardiography. J Am Coll Cardiol 2002; 40(7):1311-1319.

(168) Milano CA, White WD, Smith LR, Jones RH, Lowe JE, Smith PK et al. Coronary artery bypass in patients with severely depressed ventricular function. Ann Thorac Surg 1993; 56(3):487-493.

(169) Williams MJ, Odabashian J, Lauer MS, Thomas JD, Marwick TH. Prognostic value of dobutamine echocardiography in patients with left ventricular dysfunction. J Am Coll Cardiol 1996; 27(1):132-139.

(170) Afridi I, Grayburn PA, Panza JA, Oh JK, Zoghbi WA, Marwick TH. Myocardial viability during dobutamine echocardiography predicts survival in patients with coronary artery disease and severe left ventricular systolic dysfunction. J Am Coll Cardiol 1998; 32(4):921-926.

(171) Anselmi M, Golia G, Cicoira M, Tinto M, Nitti MT, Trappolin R et al. Prognostic value of detection of myocardial viability using low-dose dobutamine echocardiography in infarcted patients. Am J Cardiol 1998; 81(12A):21G-28G.

(172) Meluzin J, Cerny J, Frelich M, Stetka F, Spinarova L, Popelova J et al. Prognostic value of the amount of dysfunctional but viable myocardium in revascularized patients with coronary artery disease and left ventricular dysfunction. Investigators of this Multicenter Study. J Am Coll Cardiol 1998; 32(4):912-920.

(173) Bax JJ, Poldermans D, Elhendy A, Cornel JH, Boersma E, Rambaldi R et al. Improvement of left ventricular ejection fraction, heart failure symptoms and prognosis after revascularization in patients with chronic coronary artery disease and viable myocardium detected by dobutamine stress echocardiography. J Am Coll Cardiol 1999; 34(1):163-169.

(174) Senior R, Kaul S, Lahiri A. Myocardial viability on echocardiography predicts long-term survival after revascularization in patients with ischemic congestive heart failure. J Am Coll Cardiol 1999; 33(7):1848-1854.

(175) Smart SC, Dionisopoulos PN, Knickelbine TA, Schuchard T, Sagar KB. Dobutamine-atropine stress echocardiography for risk stratification in patients with chronic left ventricular dysfunction. J Am Coll Cardiol 1999; 33(2):512-521.

(176) Sicari R, Picano E, Cortigiani L, Borges AC, Varga A, Palagi C et al. Prognostic value of myocardial viability recognized by low-dose dobutamine

echocardiography in chronic ischemic left ventricular dysfunction. Am J Cardiol 2003; 92(11):1263-1266.

(177) Bax JJ, Poldermans D, Elhendy A, Boersma E, Rahimtoola SH. Sensitivity, specificity, and predictive accuracies of various noninvasive techniques for detecting hibernating myocardium. Curr Probl Cardiol 2001; 26(2):147-186.

(178) Baer FM, Voth E, Deutsch HJ, Schneider CA, Schicha H, Sechtem U. Assessment of viable myocardium by dobutamine transesophageal echocardiography and comparison with fluorine-18 fluorodeoxyglucose positron emission tomography. J Am Coll Cardiol 1994; 24(2):343-353.

(179) Meluzin J, Cigarroa CG, Brickner ME, Cerny J, Spinarova L, Frelich M et al. Dobutamine echocardiography in predicting improvement in global left ventricular systolic function after coronary bypass or angioplasty in patients with healed myocardial infarcts. Am J Cardiol 1995; 76(12):877-880.

(180) Auerbach MA, Schoder H, Hoh C, Gambhir SS, Yaghoubi S, Sayre JW et al. Prevalence of myocardial viability as detected by positron emission tomography in patients with ischemic cardiomyopathy. Circulation 1999; 99(22):2921-2926.

(181) Picano E, Lattanzi F, Orlandini A, Marini C, L'Abbate A. Stress echocardiography and the human factor: the importance of being expert. J Am Coll Cardiol 1991; 17(3):666-669.

(182) Hoffmann R, Lethen H, Marwick T, Arnese M, Fioretti P, Pingitore A et al. Analysis of interinstitutional observer agreement in interpretation of dobutamine stress echocardiograms. J Am Coll Cardiol 1996; 27(2):330-336.

(183) Kitzman DW, Higginbotham MB, Cobb FR, Sheikh KH, Sullivan MJ. Exercise intolerance in patients with heart failure and preserved left ventricular systolic function: failure of the Frank-Starling mechanism. J Am Coll Cardiol 1991; 17(5):1065-1072.

(184) Burgess MI, Jenkins C, Sharman JE, Marwick TH. Diastolic stress echocardiography: hemodynamic validation and clinical significance of estimation of ventricular filling pressure with exercise. J Am Coll Cardiol 2006; 47(9):1891-1900.

(185) von Bibra H, Tuchnitz A, Klein A, Schneider-Eicke J, Schomig A, Schwaiger M. Regional diastolic function by pulsed Doppler myocardial mapping for the detection of left ventricular ischemia during pharmacologic stress testing: a comparison with stress echocardiography and perfusion scintigraphy. J Am Coll Cardiol 2000; 36(2):444-452.

(186) Najos-Valencia O, Cain P, Case C, Wahi S, Marwick TH. Determinants of tissue Doppler measures of regional diastolic function during dobutamine stress echocardiography. Am Heart J 2002; 144(3):516-523.

(187) Visner MS, Arentzen CE, Parrish DG, Larson EV, O'Connor MJ, Crumbley AJ, III et al. Effects of global ischemia on the diastolic properties of the left ventricle in the conscious dog. Circulation 1985; 71(3):610-619.

(188) Yamada E, Garcia M, Thomas JD, Marwick TH. Myocardial Doppler velocity imaging--a quantitative technique for interpretation of dobutamine echocardiography. Am J Cardiol 1998; 82(6):806-810.

(189) Zile MR, Brutsaert DL. New concepts in diastolic dysfunction and diastolic heart failure: Part II: causal mechanisms and treatment. Circulation 2002; 105(12):1503-1508.

(190) Dabrowska-Kugacka A, Claeys MJ, Rademakers FE. Diastolic indexes during dobutamine stress echocardiography in patients early after myocardial infarction. J Am Soc Echocardiogr 1998; 11(1):26-35.

(191) Stoylen A, Wisloff U, Slordahl S. Left ventricular mechanics during exercise: a Doppler and tissue Doppler study. Eur J Echocardiogr 2003; 4(4):286-291.

(192) Ommen SR, Nishimura RA, Appleton CP, Miller FA, Oh JK, Redfield MM et al. Clinical utility of Doppler echocardiography and tissue Doppler imaging in the estimation of left ventricular filling pressures: A comparative simultaneous Doppler-catheterization study. Circulation 2000; 102(15):1788-1794.

(193) 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; %20;98(16):1644-1650.

(194) Ha JW, Lulic F, Bailey KR, Pellikka PA, Seward JB, Tajik AJ et al. Effects of treadmill exercise on mitral inflow and annular velocities in healthy adults. Am J Cardiol 2003; 91(1):114-115.

(195) Bordachar P, Lafitte S, Reuter S, Serri K, Garrigue S, Laborderie J et al. Echocardiographic assessment during exercise of heart failure patients with cardiac resynchronization therapy. Am J Cardiol 2006; 97(11):1622-1625.

(196) Kukulski T, Voigt JU, Wilkenshoff UM, Strotmann JM, Wranne B, Hatle L et al. A comparison of regional myocardial velocity information derived by pulsed and color Doppler techniques: an in vitro and in vivo study. Echocardiography 2000; 17(7):639-651.

(197) Cain P, Baglin T, Case C, Spicer D, Short L, Marwick TH. Application of tissue Doppler to interpretation of dobutamine echocardiography and comparison with quantitative coronary angiography. Am J Cardiol 2001; 87(5):525-531.

(198) Fathi R, Cain P, Nakatani S, Yu HC, Marwick TH. Effect of tissue Doppler on the accuracy of novice and expert interpreters of dobutamine echocardiography. Am J Cardiol 2001; 88(4):400-405.

(199) Henein MY, Gibson DG. Normal long axis function. Heart 1999; 81(2):111-113.

(200) Vinereanu D, Khokhar A, Fraser AG. Reproducibility of pulsed wave tissue Doppler echocardiography. J Am Soc Echocardiogr 1999; 12(6):492-499.

(201) Bess RL, Khan S, Rosman HS, Cohen GI, Allebban Z, Gardin JM. Technical aspects of diastology: why mitral inflow and tissue Doppler imaging are the preferred parameters? Echocardiography 2006; 23(4):332-339.

(202) Sohn DW, Chai IH, Lee DJ, Kim HC, Kim HS, Oh BH et al. Assessment of mitral annulus velocity by Doppler tissue imaging in the evaluation of left ventricular diastolic function. J Am Coll Cardiol 1997; 30(2):474-480.

(203) Rodriguez L, Garcia M, Ares M, Griffin BP, Nakatani S, Thomas JD. Assessment of mitral annular dynamics during diastole by Doppler tissue imaging: comparison with mitral Doppler inflow in subjects without heart disease and in patients with left ventricular hypertrophy. Am Heart J 1996; 131(5):982-987.

(204) Nagueh SF, Middleton KJ, Kopelen HA, Zoghbi WA, Quinones MA. Doppler tissue imaging: a noninvasive technique for evaluation of left ventricular relaxation and estimation of filling pressures. J Am Coll Cardiol 1997; 30(6):1527-1533.

(205) Sundereswaran L, Nagueh SF, Vardan S, Middleton KJ, Zoghbi WA, Quinones MA et al. Estimation of left and right ventricular filling pressures after heart transplantation by tissue Doppler imaging. Am J Cardiol 1998; 82(3):352-357.

(206) Garcia MJ, Rodriguez L, Ares M, Griffin BP, Thomas JD, Klein AL. Differentiation of constrictive pericarditis from restrictive cardiomyopathy: assessment of left ventricular diastolic velocities in longitudinal axis by Doppler tissue imaging. J Am Coll Cardiol 1996; 27(1):108-114.

(207) Firstenberg MS, Levine BD, Garcia MJ, Greenberg NL, Cardon L, Morehead AJ et al. Relationship of echocardiographic indices to pulmonary capillary wedge pressures in healthy volunteers. J Am Coll Cardiol 2000; 36(5):1664-1669.

(208) Agmon Y, Oh JK, McCarthy JT, Khandheria BK, Bailey KR, Seward JB. Effect of volume reduction on mitral annular diastolic velocities in hemodialysis patients. Am J Cardiol 2000; 85(5):665-8, A11.

(209) Yalcin F, Kaftan A, Muderrisoglu H, Korkmaz ME, Flachskampf F, Garcia M et al. Is Doppler tissue velocity during early left ventricular filling preload independent? Heart 2002; 87(4):336-339.

(210) Yip GW, Zhang Y, Tan PY, Wang M, Ho PY, Brodin LA et al. Left ventricular long-axis changes in early diastole and systole: impact of systolic function on diastole. Clin Sci (Lond) 2002; 102(5):515-522.

(211) Edvardsen T, Gerber BL, Garot J, Bluemke DA, Lima JA, Smiseth OA. Quantitative assessment of intrinsic regional myocardial deformation by Doppler strain rate echocardiography in humans: validation against three-dimensional tagged magnetic resonance imaging. Circulation 2002; 106(1):50-56.

(212) Nikitin NP, Witte KK, Thackray SD, de Silva R, Clark AL, Cleland JG. Longitudinal ventricular function: normal values of atrioventricular annular and myocardial velocities measured with quantitative two-dimensional color Doppler tissue imaging. J Am Soc Echocardiogr 2003; 16(9):906-921.

(213) Yamada H, Oki T, Tabata T, Iuchi A, Ito S. Assessment of left ventricular systolic wall motion velocity with pulsed tissue Doppler imaging: comparison with peak dP/dt of the left ventricular pressure curve. J Am Soc Echocardiogr 1998; 11(5):442-449.

(214) Wilkenshoff UM, Sovany A, Wigstrom L, Olstad B, Lindstrom L, Engvall J et al. Regional mean systolic myocardial velocity estimation by real-time color Doppler myocardial imaging: a new technique for quantifying regional systolic function. J Am Soc Echocardiogr 1998; 11(7):683-692.

(215) Nikitin NP, Witte KK, Ingle L, Clark AL, Farnsworth TA, Cleland JG. Longitudinal myocardial dysfunction in healthy older subjects as a manifestation of cardiac ageing. Age Ageing 2005; 34(4):343-349.

(216) Wandt B, Bojo L, Hatle L, Wranne B. Left ventricular contraction pattern changes with age in normal adults. J Am Soc Echocardiogr 1998; 11(9):857-863.

(217) Alam M, Wardell J, Andersson E, Samad BA, Nordlander R. Characteristics of mitral and tricuspid annular velocities determined by pulsed wave Doppler tissue imaging in healthy subjects. J Am Soc Echocardiogr 1999; 12(8):618-628.

(218) Madler CF, Payne N, Wilkenshoff U, Cohen A, Derumeaux GA, Pierard LA et al. Non-invasive diagnosis of coronary artery disease by quantitative stress echocardiography: optimal diagnostic models using off-line tissue Doppler in the MYDISE study. Eur Heart J 2003; 24(17):1584-1594.

(219) Henein M, Lindqvist P, Francis D, Morner S, Waldenstrom A, Kazzam E. Tissue Doppler analysis of age-dependency in diastolic ventricular

behaviour and filling: a cross-sectional study of healthy hearts (the Umea General Population Heart Study). Eur Heart J 2002; 23(2):162-171.

(220) Yamada H, Oki T, Mishiro Y, Tabata T, Abe M, Onose Y et al. Effect of aging on diastolic left ventricular myocardial velocities measured by pulsed tissue Doppler imaging in healthy subjects. J Am Soc Echocardiogr 1999; 12(7):574-581.

(221) Tighe DA, Vinch CS, Hill JC, Meyer TE, Goldberg RJ, Aurigemma GP. Influence of age on assessment of diastolic function by Doppler tissue imaging. Am J Cardiol 2003; 91(2):254-257.

(222) De Sutter J, De Backer J, Van d, V, Velghe A, De Buyzere M, Gillebert TC. Effects of age, gender, and left ventricular mass on septal mitral annulus velocity (E') and the ratio of transmitral early peak velocity to E' (E/E'). Am J Cardiol 2005; 95(8):1020-1023.

(223) Garcia EH, Perna ER, Farias EF, Obregon RO, Macin SM, Parras JI et al. Reduced systolic performance by tissue Doppler in patients with preserved and abnormal ejection fraction: new insights in chronic heart failure. Int J Cardiol 2006; 108(2):181-188.

(224) Brucks S, Little WC, Chao T, Kitzman DW, Wesley-Farrington D, Gandhi S et al. Contribution of left ventricular diastolic dysfunction to heart failure regardless of ejection fraction. Am J Cardiol 2005; 95(5):603-606.

(225) Kasner M, Westermann D, Steendijk P, Gaub R, Wilkenshoff U, Weitmann K et al. Utility of Doppler echocardiography and tissue Doppler imaging in the estimation of diastolic function in heart failure with normal ejection fraction: a comparative Doppler-conductance catheterization study. Circulation 2007; 116(6):637-647.

(226) Nagueh SF, Lakkis NM, Middleton KJ, Spencer WH, III, Zoghbi WA, Quinones MA. Doppler estimation of left ventricular filling pressures in patients with hypertrophic cardiomyopathy. Circulation 1999; %19;99(2):254-261.

(227) Sohn DW, Song JM, Zo JH, Chai IH, Kim HS, Chun HG et al. Mitral annulus velocity in the evaluation of left ventricular diastolic function in atrial fibrillation. J Am Soc Echocardiogr 1999; 12(11):927-931.

(228) Ishida Y, Meisner JS, Tsujioka K, Gallo JI, Yoran C, Frater RW et al. Left ventricular filling dynamics: influence of left ventricular relaxation and left atrial pressure. Circulation 1986; 74(1):187-196.

(229) Rivas-Gotz C, Manolios M, Thohan V, Nagueh SF. Impact of left ventricular ejection fraction on estimation of left ventricular filling pressures using tissue Doppler and flow propagation velocity. Am J Cardiol 2003; 91(6):780-784.

(230) Bruch C, Grude M, Muller J, Breithardt G, Wichter T. Usefulness of tissue Doppler imaging for estimation of left ventricular filling pressures in patients with systolic and diastolic heart failure. Am J Cardiol 2005; 95(7):892-895.

(231) Bruch C, Stypmann J, Grude M, Gradaus R, Breithardt G, Wichter T. Tissue Doppler imaging in patients with moderate to severe aortic valve stenosis: clinical usefulness and diagnostic accuracy. Am Heart J 2004; 148(4):696-702.

(232) Hadano Y, Murata K, Liu J, Oyama R, Harada N, Okuda S et al. Can transthoracic Doppler echocardiography predict the discrepancy between left ventricular end-diastolic pressure and mean pulmonary capillary wedge pressure in patients with heart failure? Circ J 2005; 69(4):432-438.

(233) Talreja DR, Nishimura RA, Oh JK. Estimation of left ventricular filling pressure with exercise by Doppler echocardiography in patients with normal systolic function: a simultaneous echocardiographic-cardiac catheterization study. J Am Soc Echocardiogr 2007; 20(5):477-479.

(234) Ha JW, Oh JK, Pellikka PA, Ommen SR, Stussy VL, Bailey KR et al. Diastolic stress echocardiography: a novel noninvasive diagnostic test for diastolic dysfunction using supine bicycle exercise Doppler echocardiography. J Am Soc Echocardiogr 2005; 18(1):63-68.

(235) Smart N, Haluska B, Leano R, Case C, Mottram PM, Marwick TH. Determinants of functional capacity in patients with chronic heart failure: role of filling pressure and systolic and diastolic function. Am Heart J 2005; 149(1):152-158.

(236) Lee SH, Jung JH, Choi SH, Lee N, Oh DJ, Ryu KH et al. Exercise intolerance in patients with atrial fibrillation: clinical and echocardiographic determinants of exercise capacity. J Am Soc Echocardiogr 2005; 18(12):1349-1354.

(237) Hadano Y, Murata K, Yamamoto T, Kunichika H, Matsumoto T, Akagawa E et al. Usefulness of mitral annular velocity in predicting exercise tolerance in patients with impaired left ventricular systolic function. Am J Cardiol 2006; 97(7):1025-1028.

(238) Van de Veire NR, De Winter O, Philippe J, De Buyzere M, Bernard D, Langlois M et al. Maximum oxygen uptake at peak exercise in elderly patients with coronary artery disease and preserved left ventricular function: the role of inflammation on top of tissue Doppler-derived systolic and diastolic function. Am Heart J 2006; 152(2):297.

(239) Skaluba SJ, Litwin SE. Mechanisms of exercise intolerance: insights from tissue Doppler imaging. Circulation 2004; 109(8):972-977.

(240) Dokainish H, Zoghbi WA, Lakkis NM, Quinones MA, Nagueh SF. Comparative accuracy of B-type natriuretic peptide and tissue Doppler

echocardiography in the diagnosis of congestive heart failure. Am J Cardiol 2004; 93(9):1130-1135.

(241) Arques S, Roux E, Sbragia P, Ambrosi P, Taieb L, Pieri B et al. Accuracy of tissue Doppler echocardiography in the emergency diagnosis of decompensated heart failure with preserved left ventricular systolic function: comparison with B-type natriuretic peptide measurement. Echocardiography 2005; 22(8):657-664.

(242) Arques S, Roux E, Sbragia P, Pieri B, Gelisse R, Ambrosi P et al. Accuracy of tissue Doppler echocardiography in the diagnosis of new-onset congestive heart failure in patients with levels of B-type natriuretic peptide in the midrange and normal left ventricular ejection fraction. Echocardiography 2006; 23(8):627-634.

(243) Arques S, Roux E, Sbragia P, Gelisse R, Ambrosi P, Pieri B et al. Comparative accuracy of color M-mode and tissue Doppler echocardiography in the emergency diagnosis of congestive heart failure in chronic hypertensive patients with normal left ventricular ejection fraction. Am J Cardiol 2005; 96(10):1456-1459.

(244) McCulloch M, Zoghbi WA, Davis R, Thomas C, Dokainish H. Color tissue Doppler myocardial velocities consistently underestimate spectral tissue Doppler velocities: impact on calculation peak transmitral pulsed Doppler velocity/early diastolic tissue Doppler velocity (E/Ea). J Am Soc Echocardiogr 2006; 19(6):744-748.

(245) D'Souza KA, Mooney DJ, Russell AE, MacIsaac AI, Aylward PE, Prior DL. Abnormal septal motion affects early diastolic velocities at the septal and lateral mitral annulus, and impacts on estimation of the pulmonary capillary wedge pressure. J Am Soc Echocardiogr 2005; 18(5):445-453.

(246) Fukuda K, Oki T, Tabata T, Iuchi A, Ito S. Regional left ventricular wall motion abnormalities in myocardial infarction and mitral annular descent velocities studied with pulsed tissue Doppler imaging. J Am Soc Echocardiogr 1998; 11(9):841-848.

(247) Alam M, Hoglund C, Thorstrand C, Hellekant C. Haemodynamic significance of the atrioventricular plane displacement in patients with coronary artery disease. Eur Heart J 1992; 13(2):194-200.

(248) Gorcsan J, III, Strum DP, Mandarino WA, Pinsky MR. Color-coded tissue Doppler assessment of the effects of acute ischemia on regional left ventricular function: comparison with sonomicrometry. J Am Soc Echocardiogr 2001; 14(5):335-342.

(249) Derumeaux G, Ovize M, Loufoua J, Andre-Fouet X, Minaire Y, Cribier A et al. Doppler tissue imaging quantitates regional wall motion during myocardial ischemia and reperfusion. Circulation 1998; %19;97(19):1970-1977.

(250) Edvardsen T, Aakhus S, Endresen K, Bjomerheim R, Smiseth OA, Ihlen H. Acute regional myocardial ischemia identified by 2-dimensional multiregion tissue Doppler imaging technique. J Am Soc Echocardiogr 2000; 13(11):986-994.

(251) Bach DS, Armstrong WF, Donovan CL, Muller DW. Quantitative Doppler tissue imaging for assessment of regional myocardial velocities during transient ischemia and reperfusion. Am Heart J 1996; 132(4):721-725.

(252) Kukulski T, Jamal F, D'Hooge J, Bijnens B, De S, I, Sutherland GR. Acute changes in systolic and diastolic events during clinical coronary angioplasty: a comparison of regional velocity, strain rate, and strain measurement. J Am Soc Echocardiogr 2002; 15(1):1-12.

(253) Gorcsan J, III, Strum DP, Mandarino WA, Gulati VK, Pinsky MR. Quantitative assessment of alterations in regional left ventricular contractility with color-coded tissue Doppler echocardiography. Comparison with sonomicrometry and pressure-volume relations. Circulation 1997; %20;95(10):2423-2433.

(254) Gorcsan J, III, Deswal A, Mankad S, Mandarino WA, Mahler CM, Yamazaki N et al. Quantification of the myocardial response to low-dose dobutamine using tissue Doppler echocardiographic measures of velocity and velocity gradient. Am J Cardiol 1998; 81(5):615-623.

(255) Katz WE, Gulati VK, Mahler CM, Gorcsan J, III. Quantitative evaluation of the segmental left ventricular response to dobutamine stress by tissue Doppler echocardiography. Am J Cardiol 1997; 79(8):1036-1042.

(256) Gorcsan J, III, Gulati VK, Mandarino WA, Katz WE. Color-coded measures of myocardial velocity throughout the cardiac cycle by tissue Doppler imaging to quantify regional left ventricular function. Am Heart J 1996; 131(6):1203-1213.

(257) Rambaldi R, Poldermans D, Fioretti PM, ten Cate FJ, Vletter WB, Bax JJ et al. Usefulness of pulse-wave Doppler tissue sampling and dobutamine stress echocardiography for the diagnosis of right coronary artery narrowing. Am J Cardiol 1998; 81(12):1411-1415.

(258) Tsutsui H, Uematsu M, Shimizu H, Yamagishi M, Tanaka N, Matsuda H et al. Comparative usefulness of myocardial velocity gradient in detecting ischemic myocardium by a dobutamine challenge. J Am Coll Cardiol 1998; 31(1):89-93.

(259) Pasquet A, Armstrong G, Beachler L, Lauer MS, Marwick TH. Use of segmental tissue Doppler velocity to quantitate exercise echocardiography. J Am Soc Echocardiogr 1999; 12(11):901-912.

(260) Pasquet A, Armstrong G, Rimmerman C, Marwick TH. Correlation of myocardial Doppler velocity response to exercise with independent

evidence of myocardial ischemia by dual-isotope single-photon emission computed tomography. Am J Cardiol 2000; 85(5):536-542.

(261) Dagianti A, Vitarelli A, Conde Y, Penco M, Fedele F, Dagianti A. Assessment of regional left ventricular function during exercise test with pulsed tissue Doppler imaging. Am J Cardiol 2000; 86(4A):30G-32G.

(262) Pasquet A, Yamada E, Armstrong G, Beachler L, Marwick TH. Influence of dobutamine or exercise stress on the results of pulsed-wave Doppler assessment of myocardial velocity. Am Heart J 1999; 138(4 Pt 1):753-758.

(263) Cain P, Napier S, Haluska B, Short L, Marwick TH. Influence of left ventricular size and hemodynamics on the systolic longitudinal myocardial Doppler velocity response to stress. Am Heart J 2002; 143(1):169-175.

(264) Edvardsen T, Urheim S, Skulstad H, Steine K, Ihlen H, Smiseth OA. Quantification of left ventricular systolic function by tissue Doppler echocardiography: added value of measuring pre- and postejection velocities in ischemic myocardium. Circulation 2002; 105(17):2071-2077.

(265) Cain P, Marwick TH, Case C, Baglin T, Dart J, Short L et al. Assessment of regional long-axis function during dobutamine echocardiography. Clin Sci (Lond) 2001; 100(4):423-432.

(266) Altinmakas S, Dagdeviren B, Uyan C, Keser N, Gumus V, Pektas O. Prediction of viability by pulsed-wave Doppler tissue sampling of asynergic myocardium during low-dose dobutamine challenge. Int J Cardiol 2000; 74(2-3):107-113.

(267) Larrazet F, Pellerin D, Daou D, Witchitz S, Fournier C, Prigent A et al. Concordance between dobutamine Doppler tissue imaging echocardiography and rest reinjection thallium-201 tomography in dysfunctional hypoperfused myocardium. Heart 1999; 82(4):432-437.

(268) Rambaldi R, Poldermans D, Bax JJ, Boersma E, Elhendy A, Vletter W et al. Doppler tissue velocity sampling improves diagnostic accuracy during dobutamine stress echocardiography for the assessment of viable myocardium in patients with severe left ventricular dysfunction. Eur Heart J 2000; 21(13):1091-1098.

(269) Palmes PP, Masuyama T, Yamamoto K, Kondo H, Sakata Y, Takiuchi S et al. Myocardial longitudinal motion by tissue velocity imaging in the evaluation of patients with myocardial infarction. J Am Soc Echocardiogr 2000; 13(9):818-826.

(270) Bax JJ, Marwick TH, Molhoek SG, Bleeker GB, van Erven L, Boersma E et al. Left ventricular dyssynchrony predicts benefit of cardiac resynchronization therapy in patients with end-stage heart failure before pacemaker implantation. Am J Cardiol 2003; 92(10):1238-1240.

(271) Yu CM, Fung WH, Lin H, Zhang Q, Sanderson JE, Lau CP. Predictors of left ventricular reverse remodeling after cardiac resynchronization therapy for heart failure secondary to idiopathic dilated or ischemic cardiomyopathy. Am J Cardiol 2003; 91(6):684-688.

(272) Yu CM, Fung JW, Zhang Q, Chan CK, Chan YS, Lin H et al. Tissue Doppler imaging is superior to strain rate imaging and postsystolic shortening on the prediction of reverse remodeling in both ischemic and nonischemic heart failure after cardiac resynchronization therapy. Circulation 2004; 110(1):66-73.

(273) Chung ES, Leon AR, Tavazzi L, Sun JP, Nihoyannopoulos P, Merlino J et al. Results of the Predictors of Response to CRT (PROSPECT) trial. Circulation 2008; %20;117(20):2608-2616.

(274) Notabartolo D, Merlino JD, Smith AL, DeLurgio DB, Vera FV, Easley KA et al. Usefulness of the peak velocity difference by tissue Doppler imaging technique as an effective predictor of response to cardiac resynchronization therapy. Am J Cardiol 2004; 94(6):817-820.

(275) Penicka M, Bartunek J, De Bruyne B, Vanderheyden M, Goethals M, De Zutter M et al. Improvement of left ventricular function after cardiac resynchronization therapy is predicted by tissue Doppler imaging echocardiography. Circulation 2004; 109(8):978-983.

(276) Bax JJ, Bleeker GB, Marwick TH, Molhoek SG, Boersma E, Steendijk P et al. Left ventricular dyssynchrony predicts response and prognosis after cardiac resynchronization therapy. J Am Coll Cardiol 2004; 44(9):1834-1840.

(277) Cazeau S, Bordachar P, Jauvert G, Lazarus A, Alonso C, Vandrell MC et al. Echocardiographic modeling of cardiac dyssynchrony before and during multisite stimulation: a prospective study. Pacing Clin Electrophysiol 2003; 26(1 Pt 2):137-143.

(278) Sogaard P, Egeblad H, Pedersen AK, Kim WY, Kristensen BO, Hansen PS et al. Sequential versus simultaneous biventricular resynchronization for severe heart failure: evaluation by tissue Doppler imaging. Circulation 2002; 106(16):2078-2084.

(279) Sogaard P, Egeblad H, Kim WY, Jensen HK, Pedersen AK, Kristensen BO et al. Tissue Doppler imaging predicts improved systolic performance and reversed left ventricular remodeling during long-term cardiac resynchronization therapy. J Am Coll Cardiol 2002; 40(4):723-730.

(280) Beshai JF, Grimm RA, Nagueh SF, Baker JH, Beau SL, Greenberg SM et al. Cardiac-resynchronization therapy in heart failure with narrow QRS complexes. N Engl J Med 2007; 357(24):2461-2471.

(281) Cortigiani L, Picano E, Coletta C, Chiarella F, Mathias W, Gandolfo N et al. Safety, feasibility, and prognostic implications of pharmacologic stress

echocardiography in 1482 patients evaluated in an ambulatory setting. Am Heart J 2001; 141(4):621-629.

(282) Mathias W, Jr., Arruda A, Santos FC, Arruda AL, Mattos E, Osorio A et al. Safety of dobutamine-atropine stress echocardiography: A prospective experience of 4,033 consecutive studies. J Am Soc Echocardiogr 1999; 12(10):785-791.

(283) Poldermans D, Fioretti PM, Boersma E, Bax JJ, Thomson IR, Roelandt JR et al. Long-term prognostic value of dobutamine-atropine stress echocardiography in 1737 patients with known or suspected coronary artery disease: A single-center experience. Circulation 1999; 99(6):757-762.

(284) Secknus MA, Marwick TH. Evolution of dobutamine echocardiography protocols and indications: safety and side effects in 3,011 studies over 5 years. J Am Coll Cardiol 1997; 29(6):1234-1240.

(285) Hennessy TG, Codd MB, Kane G, McCarthy C, McCann HA, Sugrue DD. Safety of dobutamine stress echocardiography in 474 consecutive studies. Coron Artery Dis 1997; 8(3-4):175-178.

(286) Gordon BM, Mohan V, Chapekis AT, Kander NH, Elwell J, Antalis G et al. An analysis of the safety of performing dobutamine stress echocardiography in an ambulatory setting. J Am Soc Echocardiogr 1995; 8(1):15-20.

(287) Picano E, Mathias W, Jr., Pingitore A, Bigi R, Previtali M. Safety and tolerability of dobutamine-atropine stress echocardiography: a prospective, multicentre study. Echo Dobutamine International Cooperative Study Group. Lancet 1994; 344(8931):1190-1192.

(288) Poldermans D, Fioretti PM, Boersma E, Forster T, van Urk H, Cornel JH et al. Safety of dobutamine-atropine stress echocardiography in patients with suspected or proven coronary artery disease. Am J Cardiol 1994; 73(7):456-459.

(289) Mertes H, Sawada SG, Ryan T, Segar DS, Kovacs R, Foltz J et al. Symptoms, adverse effects, and complications associated with dobutamine stress echocardiography. Experience in 1118 patients. Circulation 1993; 88(1):15-19.

(290) Poldermans D, Rambaldi R, Bax JJ, Cornel JH, Thomson IR, Valkema R et al. Safety and utility of atropine addition during dobutamine stress echocardiography for the assessment of viable myocardium in patients with severe left ventricular dysfunction. Eur Heart J 1998; 19(11):1712-1718.

(291) Cornel JH, Balk AH, Boersma E, Maat AP, Elhendy A, Arnese M et al. Safety and feasibility of dobutamine-atropine stress echocardiography in patients with ischemic left ventricular dysfunction. J Am Soc Echocardiogr 1996; 9(1):27-32.

(292) Cortigiani L, Zanetti L, Bigi R, Desideri A, Fiorentini C, Nannini E. Safety and feasibility of dobutamine and dipyridamole stress echocardiography in hypertensive patients. J Hypertens 2002; 20(7):1423-1429.

(293) Elhendy A, van Domburg RT, Roelandt JR, Geleijnse ML, Ibrahim MM, Fioretti PM. Safety and feasibility of dobutamine-atropine stress testing in hypertensive patients. Hypertension 1997; 29(6):1232-1239.

(294) Baudhuin T, Marwick T, Melin J, Wijns W, D'Hondt AM, Detry JM. Diagnosis of coronary artery disease in elderly patients: safety and efficacy of dobutamine echocardiography. Eur Heart J 1993; 14(6):799-803.

(295) Previtali M, Scelsi L, Sebastiani R, Lanzarini L, Raisaro A, Klersy C. Feasibility, safety, and prognostic value of dobutamine stress echocardiography in patients > or = 70 years of age early after acute myocardial infarction. Am J Cardiol 2002; 90(7):792-795.

(296) Hiro J, Hiro T, Reid CL, Ebrahimi R, Matsuzaki M, Gardin JM. Safety and results of dobutamine stress echocardiography in women versus men and in patients older and younger than 75 years of age. Am J Cardiol 1997; 80(8):1014-1020.

(297) Anthopoulos LP, Bonou MS, Kardaras FG, Sioras EP, Kardara DN, Sideris AM et al. Stress echocardiography in elderly patients with coronary artery disease: applicability, safety and prognostic value of dobutamine and adenosine echocardiography in elderly patients. J Am Coll Cardiol 1996; 28(1):52-59.

(298) Poldermans D, Fioretti PM, Boersma E, Thomson IR, Cornel JH, ten Cate FJ et al. Dobutamine-atropine stress echocardiography in elderly patients unable to perform an exercise test. Hemodynamic characteristics, safety, and prognostic value. Arch Intern Med 1994; 154(23):2681-2686.

(299) Fraser AG, Payne N, Madler CF, Janerot-Sjoberg B, Lind B, Grocott-Mason RM et al. Feasibility and reproducibility of off-line tissue Doppler measurement of regional myocardial function during dobutamine stress echocardiography. Eur J Echocardiogr 2003; 4(1):43-53.

(300) Cortigiani L, Lombardi M, Landi P, Paolini EA, Nannini E. Risk stratification by pharmacological stress echocardiography in a primary care cardiology centre. Experience in 1082 patients. Eur Heart J 1998; 19(11):1673-1680.

(301) Reitsma JB, Mosterd A, Koster RW, van Capelle FJ, Grobbee DE, Tijssen JG. [Increase in the number of admissions due to heart failure in Dutch hospitals in the period 1980-1992]. Ned Tijdschr Geneeskd 1994; 138(17):866-871.

(302) Davies M, Hobbs F, Davis R, Kenkre J, Roalfe AK, Hare R et al. Prevalence of left-ventricular systolic dysfunction and heart failure in the

Echocardiographic Heart of England Screening study: a population based study. Lancet 2001; 358(9280):439-444.

(303) Ross S, Grant A, Counsell C, Gillespie W, Russell I, Prescott R. Barriers to participation in randomised controlled trials: a systematic review. J Clin Epidemiol 1999; 52(12):1143-1156.

(304) Pellikka PA, Roger VL, Oh JK, Miller FA, Seward JB, Tajik AJ. Stress echocardiography. Part II. Dobutamine stress echocardiography: techniques, implementation, clinical applications, and correlations. Mayo Clin Proc 1995; 70(1):16-27.

(305) Mulvagh SL, DeMaria AN, Feinstein SB, Burns PN, Kaul S, Miller JG et al. Contrast echocardiography: current and future applications. J Am Soc Echocardiogr 2000; 13(4):331-342.

(306) Sitges M, Pare C, Azqueta M, Bosch X, Miranda-Guardiola F, Velamazan M et al. Feasibility and prognostic value of dobutamine-atropine stress echocardiography early in unstable angina. Eur Heart J 2000; 21(13):1063-1071.

(307) McNeill AJ, Fioretti PM, el Said SM, Salustri A, Forster T, Roelandt JR. Enhanced sensitivity for detection of coronary artery disease by addition of atropine to dobutamine stress echocardiography. Am J Cardiol 1992; 70(1):41-46.

(308) Coma-Canella I. Changes in plasma potassium during the dobutamine stress test. Int J Cardiol 1991; 33(1):55-59.

(309) Geleijnse ML, Elhendy A, van Domburg RT, Rambaldi R, Reijs AE, Roelandt JR et al. Prognostic significance of systolic blood pressure changes during dobutamine-atropine stress technetium-99m sestamibi perfusion scintigraphy in patients with chest pain and known or suspected coronary artery disease. Am J Cardiol 1997; 79(8):1031-1035.

(310) Marcovitz PA, Bach DS, Mathias W, Shayna V, Armstrong WF. Paradoxic hypotension during dobutamine stress echocardiography: clinical and diagnostic implications. J Am Coll Cardiol 1993; 21(5):1080-1086.

(311) Tanimoto M, Pai RG, Jintapakorn W, Shah PM. Mechanisms of hypotension during dobutamine stress echocardiography in patients with coronary artery disease. Am J Cardiol 1995; 76(1):26-30.

(312) Kowalski M, Herregods MC, Herbots L, Weidemann F, Simmons L, Strotmann J et al. The feasibility of ultrasonic regional strain and strain rate imaging in quantifying dobutamine stress echocardiography. Eur J Echocardiogr 2003; 4(2):81-91.

(313) Voigt JU, Nixdorff U, Bogdan R, Exner B, Schmiedehausen K, Platsch G et al. Comparison of deformation imaging and velocity imaging for detecting

regional inducible ischaemia during dobutamine stress echocardiography. Eur Heart J 2004; 25(17):1517-1525.

(314) Cain P, Short L, Baglin T, Case C, Bosch HG, Marwick TH. Development of a fully quantitative approach to the interpretation of stress echocardiography using radial and longitudinal myocardial velocities. J Am Soc Echocardiogr 2002; 15(8):759-767.

(315) Peteiro J, Monserrat L, Fabregas R, Manuel VJ, Calvino R, Castro-Beiras A. Comparison of two-dimensional echocardiography and pulsed Doppler tissue imaging during dobutamine-atropine stress testing to detect coronary artery disease. Echocardiography 2001; 18(4):275-284.

(316) Meluzin J, Cerny J, Groch L, Frelich M, Stetka F, Spinarova L et al. Prognostic importance of the quantification of myocardial viability in revascularized patients with coronary artery disease and moderate-to-severe left ventricular dysfunction. Int J Cardiol 2003; 90(1):23-31.

(317) Sicari R, Ripoli A, Picano E, Borges AC, Varga A, Mathias W et al. The prognostic value of myocardial viability recognized by low dose dipyridamole echocardiography in patients with chronic ischaemic left ventricular dysfunction. Eur Heart J 2001; 22(10):837-844.

(318) Sawada S, Bapat A, Vaz D, Weksler J, Fineberg N, Greene A et al. Incremental value of myocardial viability for prediction of long-term prognosis in surgically revascularized patients with left ventricular dysfunction. J Am Coll Cardiol 2003; 42(12):2099-2105.

(319) Nikitin NP, Loh PH, Silva R, Ghosh J, Khaleva OY, Goode K et al. Prognostic value of systolic mitral annular velocity measured with Doppler tissue imaging in patients with chronic heart failure caused by left ventricular systolic dysfunction. Heart 2006; 92(6):775-779.

(320) McDicken WN, Sutherland GR, Moran CM, Gordon LN. Colour Doppler velocity imaging of the myocardium. Ultrasound Med Biol 1992; 18(6-7):651-654.

(321) Cleland JG, Freemantle N, Ball SG, Bonser RS, Camici P, Chattopadhyay S et al. The heart failure revascularisation trial (HEART): rationale, design and methodology. Eur J Heart Fail 2003; 5(3):295-303.

(322) Schinkel AF, Bax JJ, Boersma E, Elhendy A, Roelandt JR, Poldermans D. How many patients with ischemic cardiomyopathy exhibit viable myocardium? Am J Cardiol 2001; 88(5):561-564.

(323) Picano E, Sicari R, Landi P, Cortigiani L, Bigi R, Coletta C et al. Prognostic value of myocardial viability in medically treated patients with global left ventricular dysfunction early after an acute uncomplicated myocardial infarction: a dobutamine stress echocardiographic study. Circulation 1998; 98(11):1078-1084.

(324) Cleland JG, Pennell DJ, Ray SG, Coats AJ, Macfarlane PW, Murray GD et al. Myocardial viability as a determinant of the ejection fraction response to carvedilol in patients with heart failure (CHRISTMAS trial): randomised controlled trial. Lancet 2003; 362(9377):14-21.

(325) Seghatol FF, Shah DJ, Diluzio S, Bello D, Johnson MR, Cotts WG et al. Relation between contractile reserve and improvement in left ventricular function with beta-blocker therapy in patients with heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. Am J Cardiol 2004; 93(7):854-859.

(326) Jourdain P, Funck F, Fulla Y, Hagege A, Bellorini M, Guillard N et al. Myocardial contractile reserve under low doses of dobutamine and improvement of left ventricular ejection fraction with treatment by carvedilol. Eur J Heart Fail 2002; 4(3):269-276.

(327) Eichhorn EJ, Grayburn PA, Mayer SA, St John SM, Appleton C, Plehn J et al. Myocardial contractile reserve by dobutamine stress echocardiography predicts improvement in ejection fraction with beta-blockade in patients with heart failure: the Beta-Blocker Evaluation of Survival Trial (BEST). Circulation 2003; 108(19):2336-2341.

(328) Elhendy A, Sozzi F, van Domburg RT, Bax JJ, Schinkel AF, Roelandt JR et al. Effect of myocardial ischemia during dobutamine stress echocardiography on cardiac mortality in patients with heart failure secondary to ischemic cardiomyopathy. Am J Cardiol 2005; 96(4):469-473.

(329) Rizzello V, Poldermans D, Schinkel AF, Biagini E, Boersma E, Elhendy A et al. Long term prognostic value of myocardial viability and ischaemia during dobutamine stress echocardiography in patients with ischaemic cardiomyopathy undergoing coronary revascularisation. Heart 2006; 92(2):239-244.

(330) Miyatake K, Yamagishi M, Tanaka N, Uematsu M, Yamazaki N, Mine Y et al. New method for evaluating left ventricular wall motion by color-coded tissue Doppler imaging: in vitro and in vivo studies. J Am Coll Cardiol 1995; 25(3):717-724.

(331) Gulati VK, Katz WE, Follansbee WP, Gorcsan J, III. Mitral annular descent velocity by tissue Doppler echocardiography as an index of global left ventricular function. Am J Cardiol 1996; 77(11):979-984.

(332) Marwick TH, Case C, Leano R, Short L, Baglin T, Cain P et al. Use of tissue Doppler imaging to facilitate the prediction of events in patients with abnormal left ventricular function by dobutamine echocardiography. Am J Cardiol 2004; 93(2):142-146.

(333) Matsuoka M, Oki T, Mishiro Y, Yamada H, Tabata T, Wakatsuki T et al. Early systolic mitral annular motion velocities responses to dobutamine

infusion predict myocardial viability in patients with previous myocardial infarction. Am Heart J 2002; 143(3):552-558.

(334) Bountioukos M, Schinkel AF, Bax JJ, Biagini E, Rizzello V, Krenning BJ et al. Pulsed-wave tissue Doppler quantification of systolic and diastolic function of viable and nonviable myocardium in patients with ischemic cardiomyopathy. Am Heart J 2004; 148(6):1079-1084.

(335) Farias CA, Rodriguez L, Garcia MJ, Sun JP, Klein AL, Thomas JD. Assessment of diastolic function by tissue Doppler echocardiography: comparison with standard transmitral and pulmonary venous flow. J Am Soc Echocardiogr 1999; 12(8):609-617.

(336) Oki T, Tabata T, Yamada H, Wakatsuki T, Shinohara H, Nishikado A et al. Clinical application of pulsed Doppler tissue imaging for assessing abnormal left ventricular relaxation. Am J Cardiol 1997; 79(7):921-928.

(337) van Heerebeek L, Borbely A, Niessen HW, Bronzwaer JG, van d, V, Stienen GJ et al. Myocardial structure and function differ in systolic and diastolic heart failure. Circulation 2006; 113(16):1966-1973.

(338) Borbely A, van d, V, Papp Z, Bronzwaer JG, Edes I, Stienen GJ et al. Cardiomyocyte stiffness in diastolic heart failure. Circulation 2005; 111(6):774-781.

(339) Yotti R, Bermejo J, Antoranz JC, Desco MM, Cortina C, Rojo-Alvarez JL et al. A noninvasive method for assessing impaired diastolic suction in patients with dilated cardiomyopathy. Circulation 2005; 112(19):2921-2929.

(340) Ahmed SH, Clark LL, Pennington WR, Webb CS, Bonnema DD, Leonardi AH et al. Matrix metalloproteinases/tissue inhibitors of metalloproteinases: relationship between changes in proteolytic determinants of matrix composition and structural, functional, and clinical manifestations of hypertensive heart disease. Circulation 2006; 113(17):2089-2096.

(341) Beuckelmann DJ, Nabauer M, Erdmann E. Intracellular calcium handling in isolated ventricular myocytes from patients with terminal heart failure. Circulation 1992; 85(3):1046-1055.

(342) Hasenfuss G, Pieske B. Calcium cycling in congestive heart failure. J Mol Cell Cardiol 2002; 34(8):951-969.

(343) Schmidt U, Hajjar RJ, Helm PA, Kim CS, Doye AA, Gwathmey JK. Contribution of abnormal sarcoplasmic reticulum ATPase activity to systolic and diastolic dysfunction in human heart failure. J Mol Cell Cardiol 1998; 30(10):1929-1937.

(344) Pieske B, Houser SR. [Na+]i handling in the failing human heart. Cardiovasc Res 2003; 57(4):874-886.

(345) Richardson P, McKenna W, Bristow M, Maisch B, Mautner B, O'Connell J et al. Report of the 1995 World Health Organization/International Society and Federation of Cardiology Task Force on the Definition and Classification of cardiomyopathies. Circulation 1996; 93(5):841-842.

(346) Cleland JG, Swedberg K, Cohen-Solal A, Cosin-Aguilar J, Dietz R, Follath F et al. The Euro Heart Failure Survey of the EUROHEART survey programme. A survey on the quality of care among patients with heart failure in Europe. The Study Group on Diagnosis of the Working Group on Heart Failure of the European Society of Cardiology. The Medicines Evaluation Group Centre for Health Economics University of York. Eur J Heart Fail 2000; 2(2):123-132.

(347) Freemantle N, Tharmanathan P, Calvert MJ, Abraham WT, Ghosh J, Cleland JG. Cardiac resynchronisation for patients with heart failure due to left ventricular systolic dysfunction -- a systematic review and meta-analysis. Eur J Heart Fail 2006; 8(4):433-440.

(348) Cleland JG, Nasir M, Tageldien A. Cardiac resynchronization therapy or atrio-biventricular pacing-what should it be called? Nat Clin Pract Cardiovasc Med 2007; 4(2):90-101.

(349) Kashani A, Barold SS. Significance of QRS complex duration in patients with heart failure. J Am Coll Cardiol 2005; %20;46(12):2183-2192.

(350) Breithardt OA, Stellbrink C, Kramer AP, Sinha AM, Franke A, Salo R et al. Echocardiographic quantification of left ventricular asynchrony predicts an acute hemodynamic benefit of cardiac resynchronization therapy. J Am Coll Cardiol 2002; 40(3):536-545.

(351) Ansalone G, Giannantoni P, Ricci R, Trambaiolo P, Laurenti A, Fedele F et al. Doppler myocardial imaging in patients with heart failure receiving biventricular pacing treatment. Am Heart J 2001; 142(5):881-896.

(352) Sogaard P, Kim WY, Jensen HK, Mortensen P, Pedersen AK, Kristensen BO et al. Impact of acute biventricular pacing on left ventricular performance and volumes in patients with severe heart failure. A tissue doppler and three-dimensional echocardiographic study. Cardiology 2001; 95(4):173-182.

(353) Nelson GS, Curry CW, Wyman BT, Kramer A, Declerck J, Talbot M et al. Predictors of systolic augmentation from left ventricular preexcitation in patients with dilated cardiomyopathy and intraventricular conduction delay. Circulation 2000; 101(23):2703-2709.

(354) Yu CM, Chau E, Sanderson JE, Fan K, Tang MO, Fung WH et al. 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(4):438-445.

(355) Zhang Y, Chan AK, Yu CM, Lam WW, Yip GW, Fung WH et al. Left ventricular systolic asynchrony after acute myocardial infarction in patients with narrow QRS complexes. Am Heart J 2005; 149(3):497-503.

(356) Akar FG, Spragg DD, Tunin RS, Kass DA, Tomaselli GF. Mechanisms underlying conduction slowing and arrhythmogenesis in nonischemic dilated cardiomyopathy. Circ Res 2004; 95(7):717-725.

(357) Kurita T, Onishi K, Dohi K, Tanabe M, Fujimoto N, Tanigawa T et al. Impact of heart rate on mechanical dyssynchrony and left ventricular contractility in patients with heart failure and normal QRS duration. Eur J Heart Fail 2007; 9(6-7):637-643.

(358) Skalidis EI, Parthenakis FI, Patrianakos AP, Hamilos MI, Vardas PE. Regional coronary flow and contractile reserve in patients with idiopathic dilated cardiomyopathy. J Am Coll Cardiol 2004; 44(10):2027-2032.

(359) Duncan A, Francis D, Gibson D, Pepper J, Henein M. Electromechanical left ventricular resynchronisation by coronary artery bypass surgery. Eur J Cardiothorac Surg 2004; 26(4):711-719.

(360) Olsson LG, Swedberg K, Cleland JG, Spark PA, Komajda M, Metra M et al. Prognostic importance of plasma NT-pro BNP in chronic heart failure in patients treated with a beta-blocker: results from the Carvedilol Or Metoprolol European Trial (COMET) trial. Eur J Heart Fail 2007; 9(8):795-801.

(361) Richardson M, Freemantle N, Calvert MJ, Cleland JG, Tavazzi L. Predictors and treatment response with cardiac resynchronization therapy in patients with heart failure characterized by dyssynchrony: a pre-defined analysis from the CARE-HF trial. Eur Heart J 2007; 28(15):1827-1834.

(362) Achilli A, Sassara M, Ficili S, Pontillo D, Achilli P, Alessi C et al. Long-term effectiveness of cardiac resynchronization therapy in patients with refractory heart failure and "narrow" QRS. J Am Coll Cardiol 2003; 42(12):2117-2124.

(363) Gasparini M, Mantica M, Galimberti P, Marconi M, Genovese L, Faletra F et al. Beneficial effects of biventricular pacing in patients with a "narrow" QRS. Pacing Clin Electrophysiol 2003; 26(1 Pt 2):169-174.

(364) Cleland JG, Abdellah AT, Khaleva O, Coletta AP, Clark AL. Clinical trials update from the European Society of Cardiology Congress 2007: 3CPO, ALOFT, PROSPECT and statins for heart failure. Eur J Heart Fail 2007; 9(10):1070-1073.

APPENDIX A
Additional figures

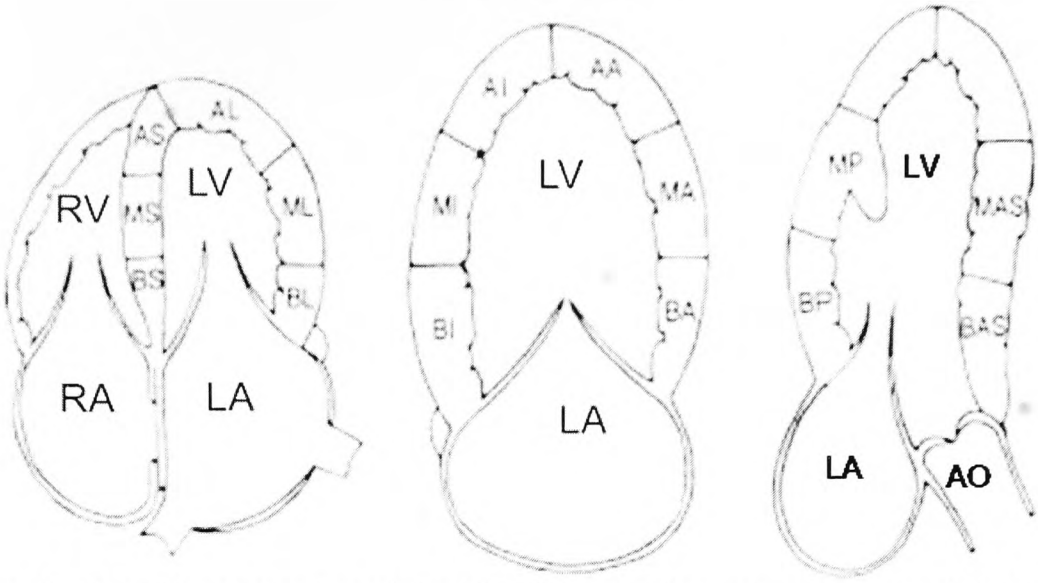


Figure 1. The 16-segment model of the left ventricle, as recommended by the American Society of Echocardiography for interpretation of regional wall motion. The lateral and septal (left: apical 4-chamber view), the anterior and inferior (middle: apical 2-chamber view) and antero-septal and posterior (right: apical 3-chamber view) walls of the left ventricle are divided into 3 segments each (basal, middle and apical). The apical segments of the anteroseptal and posterior walls are excluded from analysis.

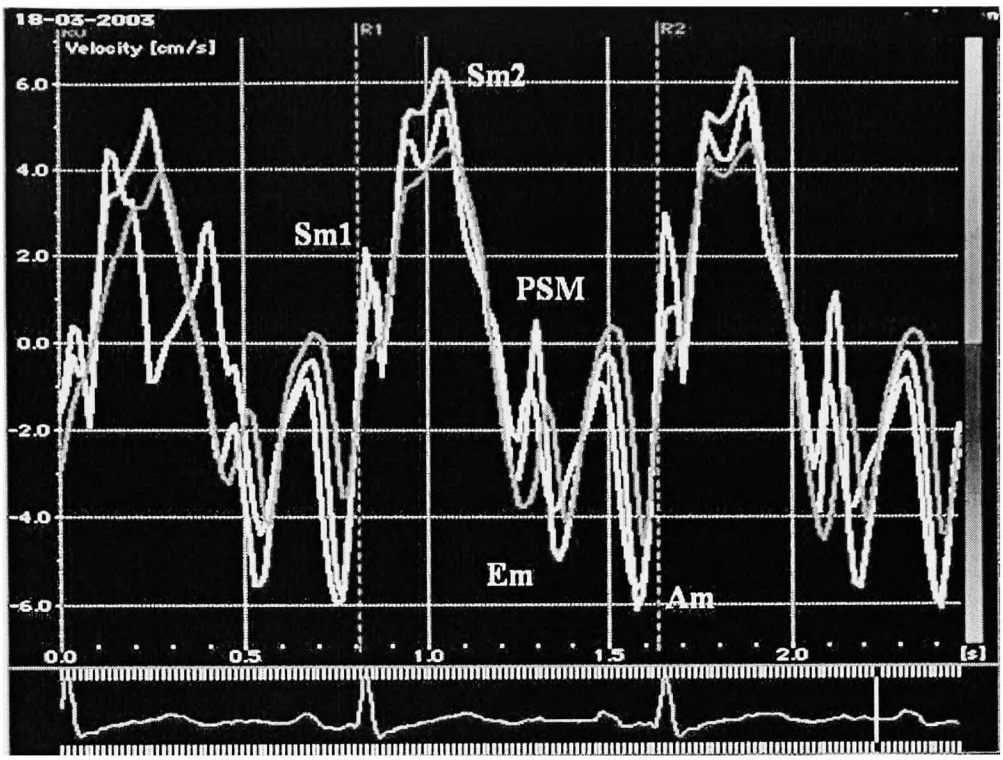


Figure 2. Typical myocardial and annular velocity pattern seen with cTDI. S_1: systolic velocity during isovolumetric contraction corresponding to the QRS complex; S_2: systolic velocity during ejection phase seen after the QRS complex; E: early diastolic velocity seen after the T-wave; A: late diastolic velocity seen after the P-wave. PSM: post systolic velocity.

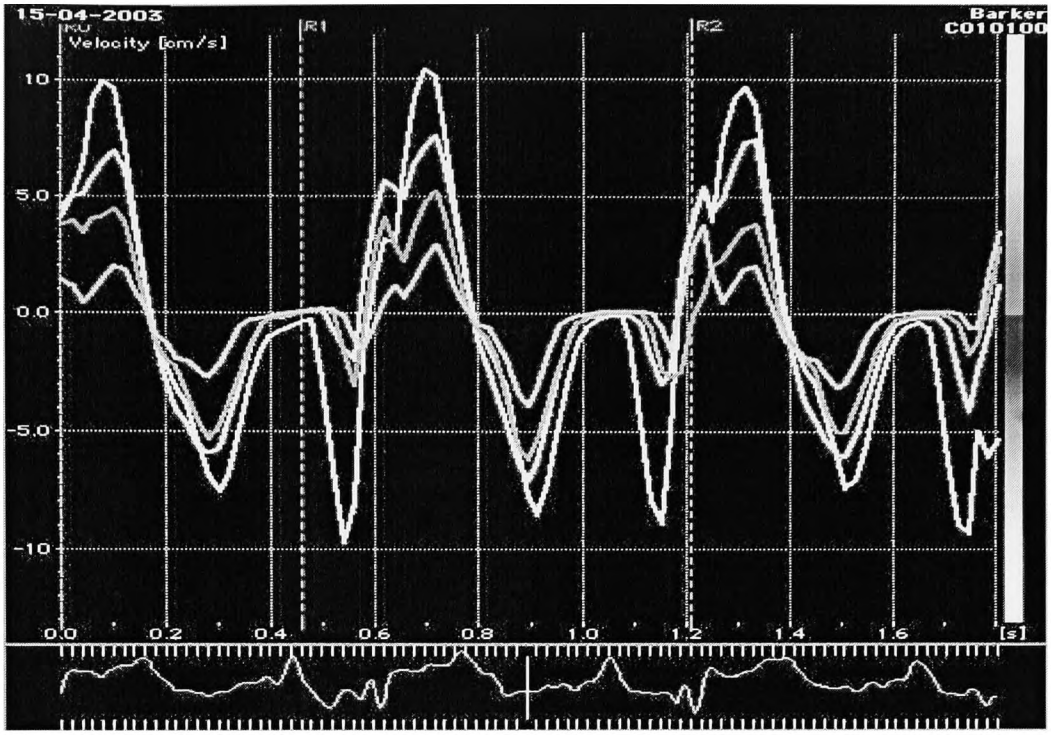


Figure 3: Apico-basal gradient in velocity from annulus to apex in the same wall. The systolic myocardial velocity increases and the diastolic velocities decrease from the annulus to the apex in a typical normal left ventricular wall. Annulus: yellow; basal segment: light green; middle segment: red; apical segment: deep green

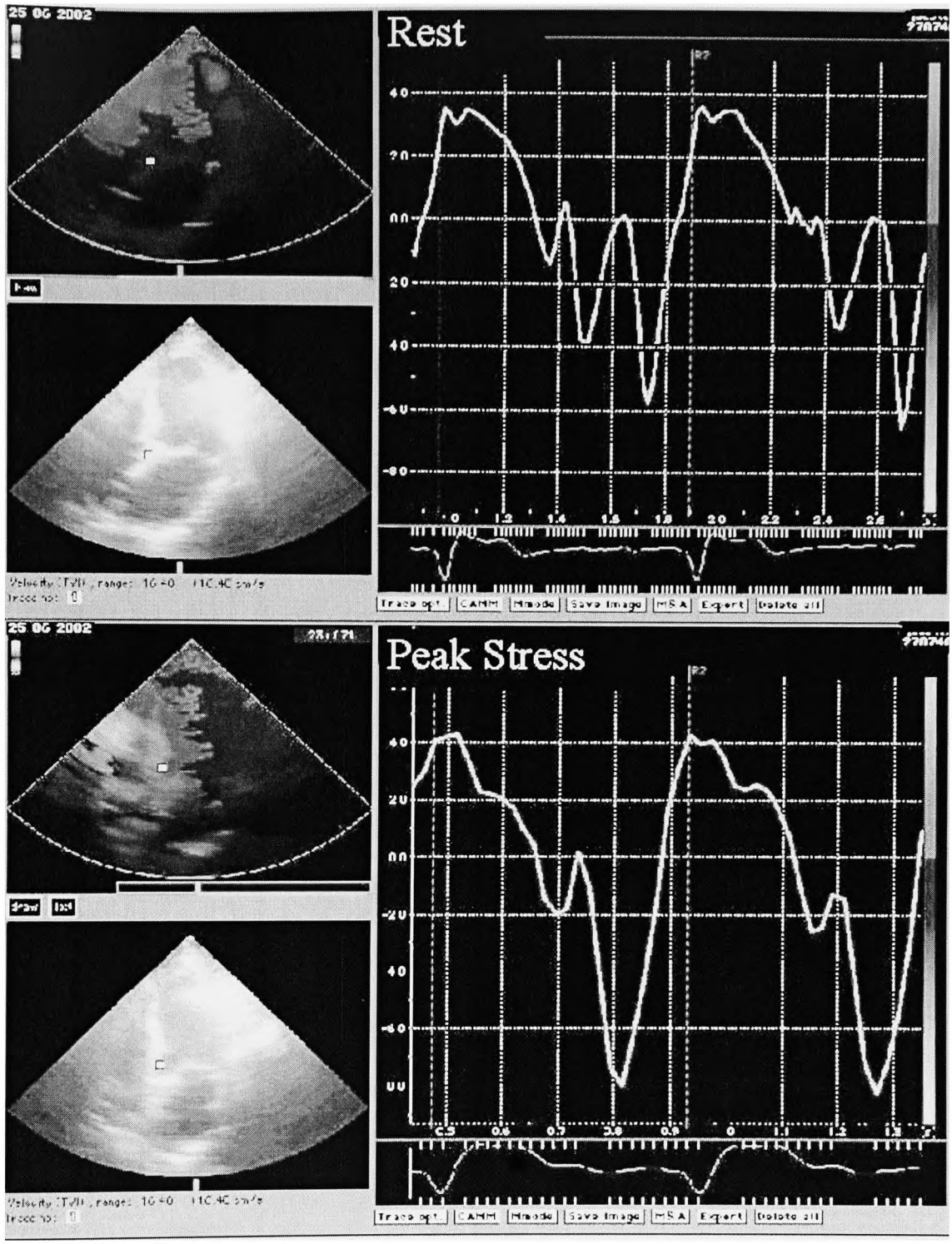


Figure 4. Stress-induced impairment in early diastolic myocardial relaxation as measured at the septal annulus in a patient with HFNEF.
cTDI at the septal annulus shows reversal of Ea/Aa ratio at rest (upper panel). The Sa_{sep} and Aa_{sep} increased but the Ea_{sep} halved at sub-maximal stress (lower panel) suggesting stress-induced abnormal myocardial relaxation without significant systolic impairment.

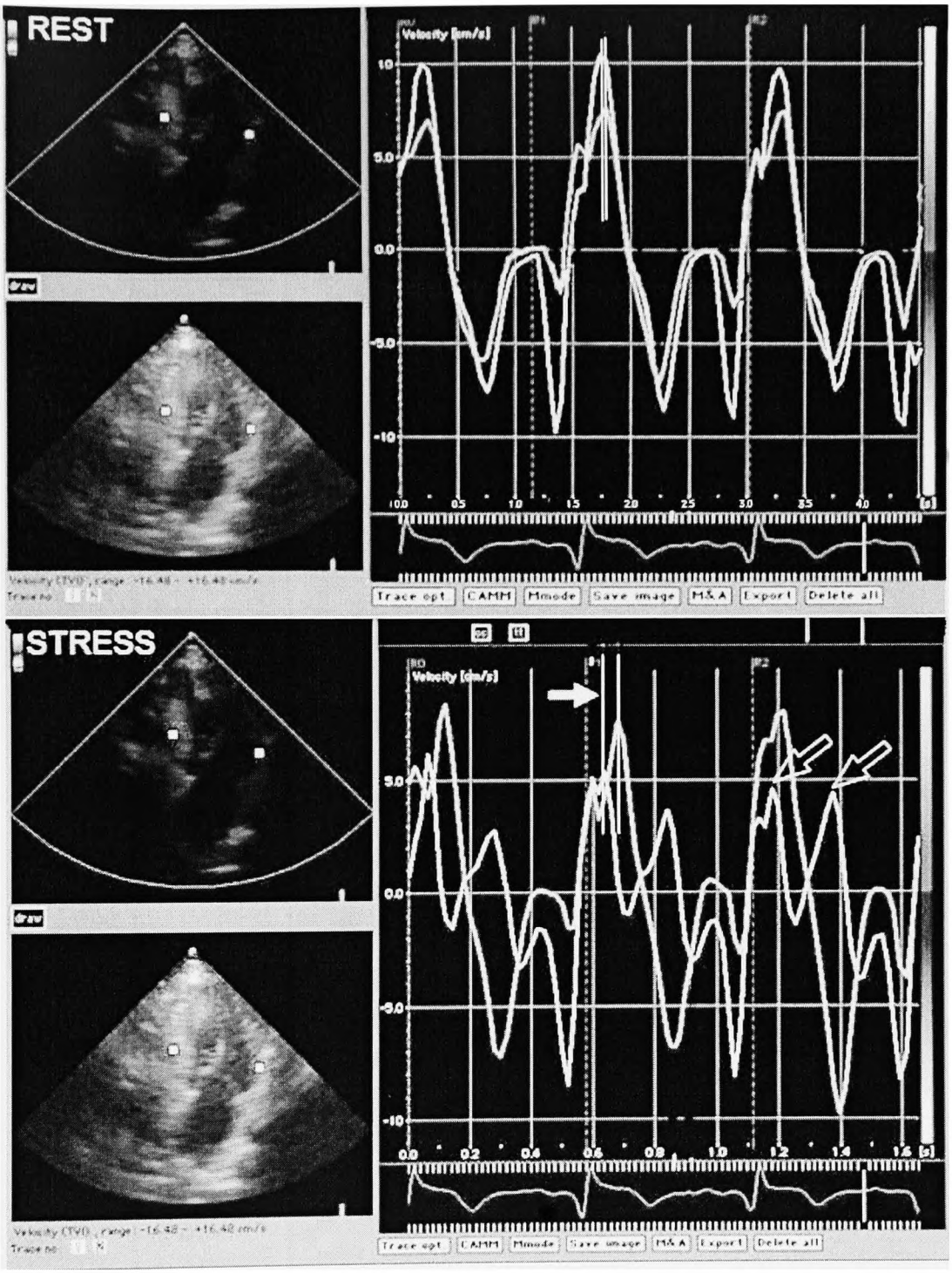


Figure 5. Appearance of LV Dyssynchrony with Stress in a patient HF with LVSD. At rest (upper panel), the Sm_{lat} (green) and Sm_{sep} (yellow) reach their peak nearly simultaneously i.e. there is almost no difference in the time from the onset of the QRS complex to the peak Sm in these two opposing segments. At peak stress (lower panel), the Sm_{lat} reaches the peak later than Sm_{sep} i.e. the difference between the times from the onset of the QRS complex to the peak systolic velocities in the two segments increase. Post-systolic velocity (open-arrow) becomes evident in the septal segment.

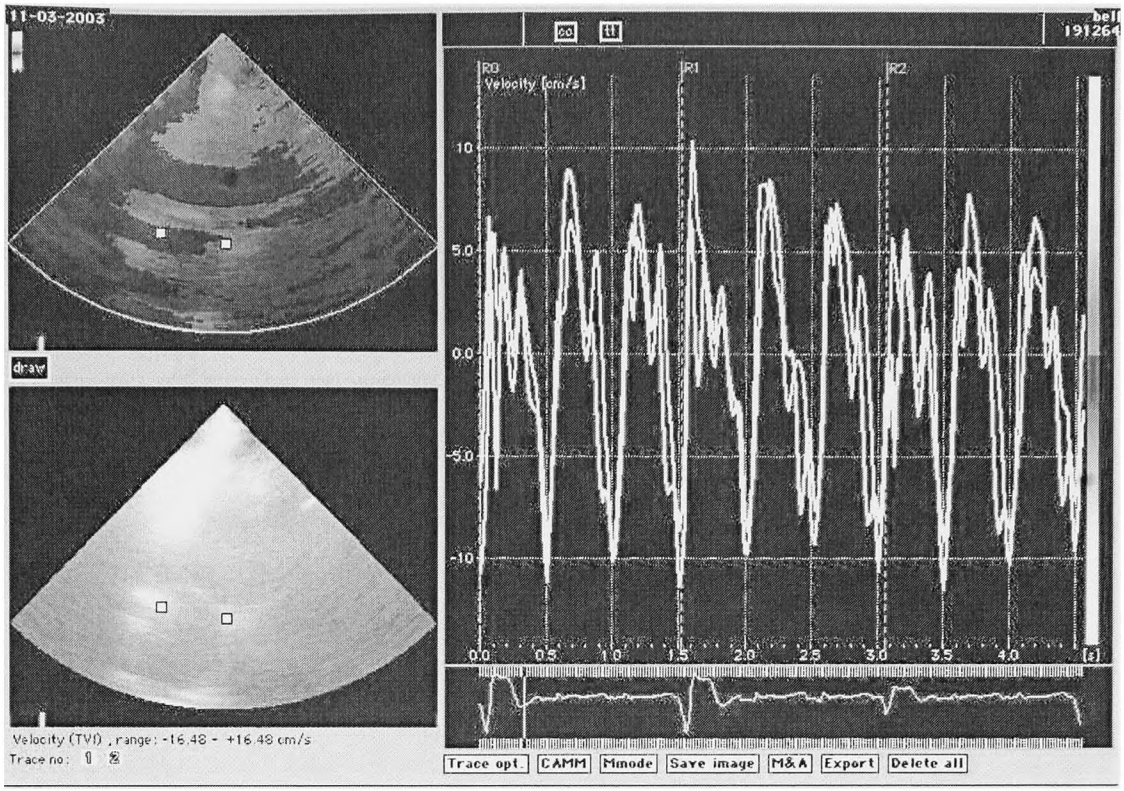


Figure 6. Uninterpretable cTDI curves at the anterior and inferior annuli in a patient with ventricular trigemminy. The auto-calibration of the ECG amplitude during acquisition resulted in very small sinus complexes. The three beats that were automatically captured were the 3 larger amplitude ectopic beats. In the process, the interim smaller sinus beats were also acquired leading to several uninterpretable waveforms.

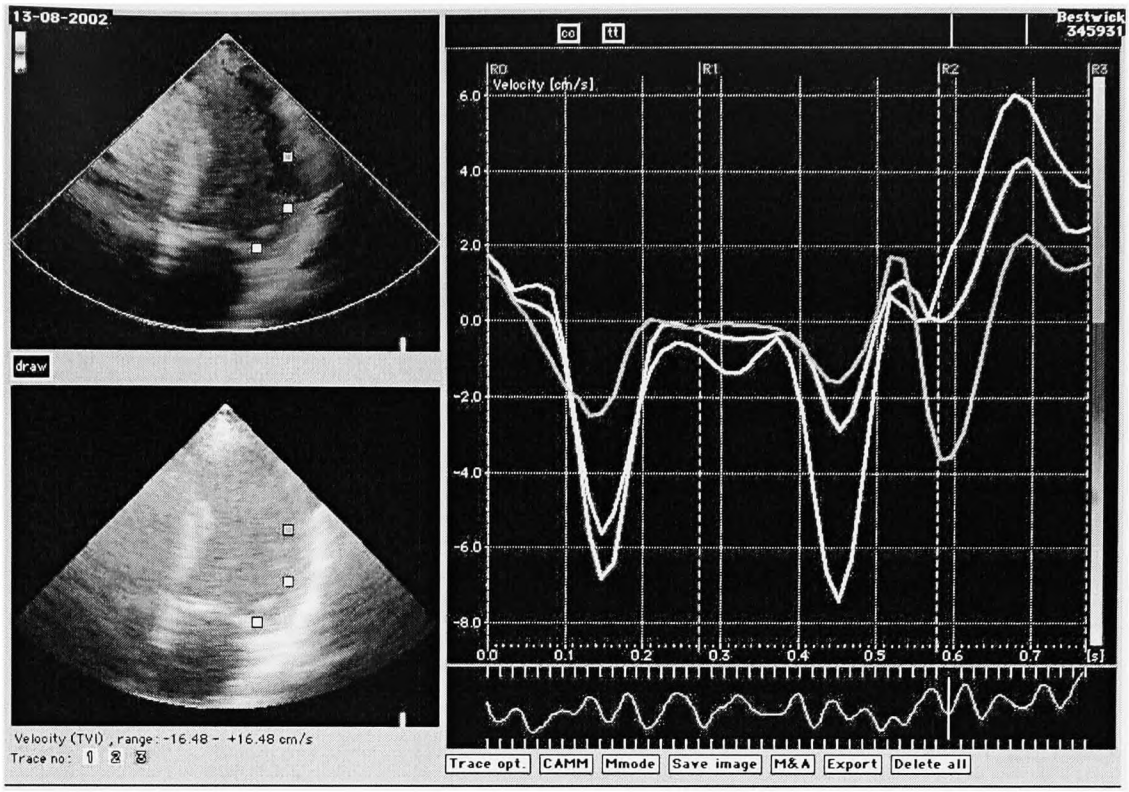


Figure 7. Uninterpretable cTDI curves at the lateral wall in a patient whose ECG electrode disconnected during acquisition.

APPENDIX B

Publications and Presentations

Publications

1. **Chattopadhyay S,** Alamgir MF, Nikitin NP, Fraser AG, Clark AL, Cleland JG. Lack of Diastolic Reserve In Patients With Heart Failure And Normal Ejection Fraction. ***Circ Heart Fail. 2009 Oct 30. [Epub ahead of print]***
2. **Chattopadhyay S,** Alamgir MF, Nikitin NP, Fraser AG, Clark AL, Cleland JG. The Effect of Pharmacological Stress on Intraventricular Dyssynchrony in Left Ventricular Systolic Dysfunction. ***Eur J Heart Fail. 2008 Jun;5(3):295-303***
3. Cleland JG, Freemantle N, Ball SG, Bonser RS, Camici P, **Chattopadhyay S,** Dutka D, Eastaugh J, Hampton J, Large S, Norell MS, Pennell DJ, Pepper J, Sanda S, Senior R, Smith D. The heart failure revascularisation trial (HEART-UK): rationale, design and methodology. ***Eur J Heart Fail. 2003 Jun;5(3):295-303.***

Presentations and Abstracts

1. **S. Chattopadhyay**, MF. Alamgir, NP. Nikitin, AL. Clark, JGF. Cleland. Temporal sequence of longitudinal systolic contraction in left ventricular systolic dysfunction. ***e-Poster, World Congress of Cardiology, ESC, 2006, Barcelona***.
2. **S. Chattopadhyay**, MF. Alamgir, NP. Nikitin, AL. Clark, JGF. Cleland. Apex-to-base dyssynchrony in left ventricular systolic dysfunction. ***e-Poster, World Congress of Cardiology, ESC, 2006, Barcelona***.
3. **S Chattopadhyay**, MF Alamgir, NP Nikitin, AL Clark, JGF Cleland. Exercise intolerance in patients with heart failure and preserved left ventricular systolic function: systolic or diastolic? ***Poster, EUROECHO 9 2005, Florence, Italy.*** *Eur J Echocardiography Vol 6, Sppl 1, Dec 2005, p S28.*
4. **S Chattopadhyay**, MF Alamgir, NP Nikitin, AL Clark, JGF Cleland. Stress Induced Left Ventricular Dyssynchrony In Left Ventricular Systolic Dysfunction: Does QRS Duration Matter? ***Oral Contribution, AHA Scientific Sessions 2005 in Dallas, Texas.*** *Circulation Vol 112, No 5, Suppl II, Oct 25, 2005, p402.*

5. **S Chattopadhyay**, MF Alamgir, NP Nikitin, AL Clark, JGF Cleland. Prevalence Of Intraventricular Dyssynchrony Increases With Stress. ***Oral Contribution, AHA Scientific Sessions 2005 in Dallas, Texas.*** *Circulation Vol 112, No 5, Suppl II, Oct 25, 2005, p403.*
6. **S Chattopadhyay**, MF Alamgir, NP Nikitin, AL Clark, JGF Cleland. Exercise Intolerance In Left Ventricular Systolic Dysfunction: Related To Dyssynchrony? ***Oral Contribution, AHA Scientific Sessions 2005 in Dallas, Texas.*** *Circulation Vol 112, No 5, Suppl II, Oct 25, 2005, p403.*
7. **S Chattopadhyay**, MF Alamgir, NP Nikitin, AL Clark, JGF Cleland. Does Intaventricular Dyssynchrony Worsen With Stress In Patients With Left Ventricular Systolic Dysfunction? ***Poster, ESC Congress 2005, Stockholm, Sweden.*** *Eur Heart J, Vol 26, Abstract Suppl, Sep 2005, p185.*
8. **S Chattopadhyay**, MF Alamgir, NP Nikitin, AL Clark, JGF Cleland. Intra-Ventricular Dyssynchrony Under Pharmacological Stress: Does QRS Duration Matter? ***Poster, Heart Rhythm 2005, New Orleans, Louisiana.*** *Heart Rhythm Vol 2(1S); May 2005, pS149.*
9. **S Chattopadhyay**, MF Alamgir, NP Nikitin, AL Clark, JGF Cleland. Stress-induced Left Ventricular Diastolic Impairment Causes Exercise Intolerance In Patients With Heart Failure And Preserved Left Ventricular Systolic Function. ***Poster, Annual Scientific Session, ACC 2005, Orlando***. *J Am Coll Cardiol Vol 45(3), (Suppl A); Feb 2005, p131A.*
10. **S Chattopadhyay**, MF Alamgir, NP Nikitin, AL Clark, JGF Cleland. Does Intaventricular Dyssynchrony Worsen With Stress In Patients With Left Ventricular Systolic Dysfunction? ***Oral Contribution, Annual Scientific Session, ACC 2005, Orlando*** *J Am Coll Cardiol Vol 45(3), (Suppl A); Feb 2005, p286A.*
11. **S Chattopadhyay**, MF Alamgir, NP Nikitin, AL Clark, JGF Cleland. Pharmacological stress unmasks impairment of left ventricular diastolic function in patients with heart failure and preserved left ventricular systolic function. ***Oral Contribution, Annual Scientific Conference, BCS 2004, Manchester.*** *Heart Vol 90 Suppl II, May 2004, p A7.*
12. **S Chattopadhyay**, MF Alamgir, NP Nikitin, AL Clark, JGF Cleland. Stress-induced left ventricular diastolic dysfunction is associated with an increase in the left atrial pressure and reduced exercise tolerance in patients with heart

failure and preserved left ventricular systolic function. ***Oral Contribution, Annual Scientific Conference, BCS 2004, Manchester.*** *Heart Vol 90 Suppl II, May 2004, p A8.*

13. **S Chattopadhyay**, MF Alamgir, NP Nikitin, AL Clark, JGF Cleland Impaired LV Diastolic Function under Pharmacological Stress in Patients with Heart Failure and Preserved LV Systolic Function as Assessed by Tissue Doppler Imaging. ***Poster, Annual Scientific Meeting, HFSA 2003, Las Vegas.*** *J Cardiac Fail, Vol 9, Issue 5, Suppl 1, October 2003, p S17. (Abstract).*
14. **S Chattopadhyay**, MF Alamgir, NP Nikitin, AL Clark, JGF Cleland. Assessment of left ventricular long axis function under pharmacological stress in patients with heart failure and preserved LV systolic function using tissue Doppler imaging. ***Poster, ESC Congress 2003, Vienna.*** *Eur Heart J, Vol 24, Issue 5, Suppl 1, Aug/Sep 2003, p110.*

Others Presentations

1. **S Chattopadhyay.** Should dyssynchrony be assessed under stress? **Invited speaker.** ***EUROECHO 9 2005, Florence, Italy.***
2. Pharmacological stress unmasks impairment of left ventricular diastolic function in patients with suspected heart failure and preserved left ventricular function. ***The Merseyside and North Wales Society of Physicians: Autumn meeting, 17 Nov. 03.***