



Copyright Statement

The digital copy of this thesis is protected by the Copyright Act 1994 (New Zealand). This thesis may be consulted by you, provided you comply with the provisions of the Act and the following conditions of use:

- Any use you make of these documents or images must be for research or private study purposes only, and you may not make them available to any other person.
- Authors control the copyright of their thesis. You will recognise the author's right to be identified as the author of this thesis, and due acknowledgement will be made to the author where appropriate.
- You will obtain the author's permission before publishing any material from their thesis.

To request permissions please use the Feedback form on our webpage.
<http://researchspace.auckland.ac.nz/feedback>

General copyright and disclaimer

In addition to the above conditions, authors give their consent for the digital copy of their work to be used subject to the conditions specified on the Library [Thesis Consent Form](#)

**The Role of Contemporary
Echocardiography in the Management of
Heart Failure**

Gillian A Whalley, BAppSc, MHSc, DMU

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

The University of Auckland

Thesis Consent Form

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

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

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

Signed:

Date: 21 January 2006

Abstract

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

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

Acknowledgements

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

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

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

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

With heartfelt appreciation to you all.

Table of Contents

Chapter 1 - The Role of Echocardiography in the Contemporary Management of Chronic Heart Failure	xiv
The role of echocardiography in heart failure management	1
The role of echocardiography in heart failure diagnosis	5
Anatomy	5
Ventricular size and hypertrophy	5
The left atrium	6
Assessment of LV systolic function	7
The role of stress echocardiography	10
Assessment of diastolic function	10
Relationship of diastolic echocardiography parameters measures with left atrial and ventricular pressure	14
Systolic versus diastolic heart failure	17
The role of echocardiography for diagnosis of HF in primary care	17
Prognostic Value of Echocardiography in Heart Failure	18
Heart size and systolic function	19
Diastolic measurements	20
Beyond left ventricular function	23
The Role of Echocardiography in Heart Failure Management	23
Ejection fraction is not the diagnosis	23
Echocardiography guidance for device implantation	24
Summary	25
Objectives	25
Chapter 2 - Quantification of Left Ventricular Function in Heart Failure - Effects of Measurement Variability	27
Part A - Systolic Function	29
Background	29
Aims	31
Methods	31
Subjects	31
Study Imaging Protocol	32
Contrast protocol	34
Contrast performance – degree of opacification	34
Endocardial visualisation	34
Left ventricular volume measurements	34
Left ventricular wall motion scoring	35
Statistics	36
Results	37

Subjects	37
Left ventricular opacification	39
Endocardial Visualisation	40
Regional differences in endocardial visualisation	43
Left ventricular volume measurements	46
Wall motion score index	47
Discussion	53
Enhancement of endocardial borders	53
Regional differences in endocardial visualisation	53
Comparison of modalities for determination of LV volumes and ejection fraction	55
Wall motion score index	56
Intra-observer, inter-observer and test-retest variability of EF measurements	56
Expert versus non-expert readers	58
Performance of contrast in patients with heart failure	58
Limitations	59
Part B - Diastolic Function.....	61
Background	61
Aims.....	62
Methods.....	62
Subjects	62
Mitral valve inflow Doppler	62
Contrast enhancement of pulmonary venous Doppler recordings	63
Non-standardised Valsalva	63
Diastolic echocardiographic measurements.....	65
Differentiation between diastolic filling patterns	65
Evaluation of preload reduction methods	67
Statistics	68
Results.....	69
Diastolic echocardiography parameters.....	69
Diastolic filling classification	70
Test-retest of diastolic filling grade classification	71
Sensitivity, specificity and predictive values.....	73
Comparison of different preload reduction manoeuvres	74
Discussion	75
Limitations	77
Conclusions	78
Summary	78
Key Findings:.....	80
Chapter 3 - Predicting Future Hospitalisations and Mortality in HF Patients After Hospital Discharge	81

Methods.....	83
Subjects	83
Echocardiographic methods.....	84
Echocardiographic measurements.....	85
Differentiation between diastolic filling patterns	85
Patients exclusions and final mitral filling class.....	85
Statistical Analysis.....	86
Results.....	87
Patients.....	87
Mitral filling pattern	87
Time to first admission.....	89
Time to first hospitalisation	91
All-cause mortality and readmission.....	95
All-cause mortality and heart failure readmission	97
Discussion	102
Early readmissions	103
Restrictive versus non-restrictive filling in heart failure	102
Comparison with previous studies.....	103
Generalisability of results	104
Limitations	104
Conclusions	105
Chapter 4 - The prognostic significance of restrictive diastolic filling associated with HF or MI: A meta-analysis.	107
Methods.....	108
Identification of studies.....	108
Criteria for study inclusion	109
Definition of a prospective study	109
Criteria for heart failure or myocardial infarction	110
Data collection	110
Differentiation of restrictive filling.....	110
Statistical methods	110
Results.....	111
Heart failure	113
Restrictive filling and mortality.....	115
Restrictive filling and death and/or transplantation	117
Criteria for detection of restrictive filling	119
Development of heart failure	119
Post Myocardial Infarction	121
Restrictive filling versus non-restrictive filling and death.....	123
Criteria for detection of restrictive filling	125

Development of HF	125
Other Filling Patterns.....	127
Reversible restrictive filling versus non-reversible restrictive filling and mortality.....	127
Non-restrictive filling patterns	127
Summary of survival according to filling pattern.....	132
Discussion	132
Heart failure	133
Post myocardial infarction	135
Limitations	138
Conclusions	139
Key Findings:.....	139
Chapter 5 - Complementary role of echocardiography and brain natriuretic peptide for diagnosis of HF and determining prognosis in symptomatic breathless patients in the community.	141
Prognosis of symptomatic patients in the community	143
Methods.....	144
Subjects	144
Panel standard diagnosis of heart failure	144
BNP assay	144
Echocardiography methods.....	145
Pulsed wave tissue Doppler	145
Echocardiographic measurements.....	145
Differentiation between diastolic filling patterns	145
Statistical analysis	146
Results.....	148
Baseline characteristics.....	148
Echocardiographic measurements.....	149
Diagnostic Accuracy	152
Time to first hospitalisation.....	155
Brain Natriuretic Peptide.....	156
Ejection Fraction	159
Restrictive Filling Pattern.....	161
E/Ea ratio	164
Multi-variate predictors of hospitalisation	168
Discussion	169
The role of echocardiography for diagnosis of HF in primary care	169
Echocardiography in general practice	171
Conclusions	172
Key Findings:.....	173
Chapter 6 – Conclusions	174
Key findings from this research	175

Assessment of systolic function	177
Assessment of diastolic function	178
Echocardiography predicts outcome in patients with heart failure	179
Meta-analyses of diastolic filling and prognosis	179
The role of contemporary echocardiography for diagnosis of heart failure	180
The role of contemporary echocardiography in heart failure management	181
Future directions.....	183
Assessment of systolic function	183
Three-dimensional echocardiography	184
Assessment of diastolic function	184
Handheld Echo	185
Natriuretic hormones	185
Left atrial volume	185
Repeat Echocardiography	186
Summary	186
References	187

List of Tables

Table 1 - Non-invasive echocardiography surrogates of LV filling pressure.....	15
Table 2 - Echocardiographic assessment of diastolic function and prognosis.....	22
Table 3 - Baseline clinical characteristics and medications in patients with heart failure	38
Table 4 - Baseline demographics and echocardiography measurements in HF patients and healthy controls	39
Table 5 - Contrast performance in heart failure patients and healthy controls	40
Table 6 - Endocardial visualisation in HF patients and healthy controls.....	42
Table 7 - Left ventricular volume measurements (Simpson's biplane method) obtained with four different imaging modalities in patients with heart failure and control subjects	46
Table 8 - Wall motion score index by the three real time echo methods in heart failure patients and healthy controls.....	47
Table 9 - Intra-observer, inter-observer and between days reproducibility for ejection fraction, by four different echo methods.....	49
Table 10 - Doppler measurements of diastolic filling	69
Table 11 - Classification of diastolic filling grade.....	70
Table 12 – Classification of diastolic filling grade	71
Table 13 - Sensitivity, specificity, positive and negative predictive values of the different methods: Detection of any abnormal diastolic filling grade	73
Table 14 - Effect of preload reduction method upon mitral inflow pulsed wave Doppler	74
Table 15 - Classification of diastolic filling grade by five methods.....	74
Table 16 - Clinical and echocardiographic parameters at the time of discharge from hospital, after stabilisation with medication.....	88
Table 17 - Study review questionnaire	109
Table 18 - Excluded Studies	112
Table 19 - Prospective prognosis studies using restrictive filling pattern classification in HF.....	114
Table 20 - Prognosis studies using or restrictive filling pattern classification post myocardial infarction.....	122
Table 21 - Summary of meta-analysis odds ratios for all-cause mortality associated with different diastolic filling patterns.	132
Table 22 - Baseline demographics and clinical characteristics of patients	148
Table 23 - Characteristics of patients excluded from and included in the diastolic analyses.....	149
Table 24 - Echocardiographic parameters in patients with and without heart failure.....	151
Table 25 - Characteristics of patients according to NT-proBNP level.....	157
Table 26 - Characteristics of patients with depressed systolic function (< 45 %) compared to those with normal function (EF > 45 %).	159
Table 27 - Characteristics of patients with restrictive mitral filling pattern compared to patients with non- restrictive pattern.....	161
Table 28 - Characteristics of three groups of E/Ea ratio.....	164
Table 29 - Characteristics of patients with E/Ea < 11 and those with E/Ea ratio > 11	166
Table 30 - Stepwise multivariate predictors of hospitalization	168
Table 31 - Key findings from each chapter.....	176

List of Figures

Figure 1 - Apical four chamber view in diastole and systole in systolic and diastolic heart failure.....	4
Figure 2 - Diastolic filling grades based upon mitral, pulmonary venous and mitral annular pulsed wave Doppler.....	13
Figure 3 - Apical four chamber view at end-diastole by four methods.....	33
Figure 4 - American Society of Echocardiography twelve segment model for analysis of regional wall motion and calculation of wall motion score index	36
Figure 5 - Endocardial visualisation by four echocardiographic methods in heart failure patients and healthy controls.....	41
Figure 6 - Regional endocardial visualisation by four echo methods in heart failure patients	44
Figure 7 - Regional endocardial visualisation by four echo methods in control subjects.....	45
Figure 8 - Correlation of wall motion score index with ejection fraction by different echo methods.....	48
Figure 9 - Inter-observer variability associated with ejection fraction measurements by four different echo modalities	50
Figure 10 - Intra-observer variability associated with ejection fraction measurements by four different echo modalities	51
Figure 11 - Test-retest variability associated with ejection fraction measurements by four different echo modalities	52
Figure 12 - Effect of preload reduction on mitral inflow	64
Figure 13 - Diastolic Doppler measurements - mitral inflow and pulmonary veins	64
Figure 14 - Diastolic filling grades by pulsed wave mitral inflow Doppler	66
Figure 15 - Mitral valve inflow Doppler - Effect of three different preload manipulations.....	68
Figure 16 - Movement of subjects within diastolic categories on each visit.....	72
Figure 17 - Recruitment and final group classification of patients.	86
Figure 18- All-cause hospital admissions by non-restrictive versus restrictive filling (A) and abnormal relaxation, pseudonormal and restrictive filling (B)	90
Figure 19 - Hospital readmissions by non-restrictive versus restrictive filling (A) and abnormal, pseudonormal and restrictive filling (B)	92
Figure 20 - All-cause death by non-restrictive versus restrictive filling (A) and abnormal, pseudonormal and restrictive filling (B)	94
Figure 21 - All-cause death/hospital readmission by non-restrictive versus restrictive filling (A) and abnormal, pseudonormal and restrictive filling (B)	96
Figure 22 - All-cause death/HF hospital readmission by non-restrictive versus restrictive filling (A) and abnormal, pseudonormal and restrictive filling (B).....	98
Figure 23 – Three month survival plots for all-cause death, HF hospital readmission and combined mortality + readmissions (time to first event analysis) by non-restrictive versus restrictive filling.....	100
Figure 24 - Three month survival plots for hospital readmission (time to first event analysis) by mitral filling pattern	101
Figure 25 - Meta-analysis of all-cause mortality associated with restrictive filling in HF.....	116
Figure 26 - Meta-analysis of all-cause mortality and/or transplantation associated with restrictive filling in heart failure	118
Figure 27 - Odds ratio according to different deceleration time criteria	119
Figure 28 - Meta-analysis of hospitalisation in patients with heart failure.....	120

Figure 29 - Metanalysis of the restrictive filling pattern post myocardial infarction	124
Figure 30 - Odds ratio according to different deceleration time criteria	125
Figure 31 - Meta-analysis of development of HF in post MI patients.....	126
Figure 32 - Meta-analysis of reversible restrictive filling pattern in heart failure	128
Figure 33 - Meta-analysis of pseudonormal compared to restrictive filling	129
Figure 34 - Meta-analysis of pseudonormal filling compared abnormal relaxation or normal filling.....	130
Figure 35 - Meta-analysis of restrictive filling compared to abnormal relaxation or normal filling	131
Figure 36 - Time to first hospitalisation in those patients with diastolic data and those without	150
Figure 37 - Receiver operating characteristic curves for NT-proBNP, systolic and diastolic echocardiographic variables (all patients, N=305)	153
Figure 38 - Receiver operating characteristic curves for NT-proBNP, systolic and diastolic echocardiographic variables (Patients with NT-proBNP > 50 pmol/l, N=161).....	154
Figure 39 - Receiver operating characteristic curves for NT-proBNP, systolic and diastolic echocardiographic variables (Patients with NT-proBNP 50 - 150 pmol/l, N=98).....	155
Figure 40 - Time to first hospitalisation by NT-proBNP level	158
Figure 41 - Time to first hospitalisation by ejection fraction.....	160
Figure 42 - Time to first hospitalisation by restrictive and non-restrictive filling pattern	162
Figure 43 - Time to first hospitalisation by diastolic filling pattern.....	163
Figure 44 - Time to first readmission by E/Ea ratio.....	165
Figure 45 - Time to first readmission by E/Ea ratio > 11	167

Publications

Chapter 1

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

Chapter 2

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

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

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

Chapter 3

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

Chapter 4

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

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

Chapter 5

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

Abbreviations

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

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