

**EARLY CHANGES OF CORONARY ATHEROSCLEROSIS  
DETECTED WITH HIGH RESOLUTION  
TRANSTHORACIC ECHOCARDIOGRAPHY**

Student: Rebecca Perry BSc DMU (cardiac)  
School: Medicine  
Faculty: Department of Health Sciences  
Principal Supervisor: Professor Philip Aylward  
Co-supervisors: Dr Carmine De Pasquale  
Dr Majo Joseph  
Professor Derek Chew

# TABLE OF CONTENTS

Summary .....	ix
Declaration .....	xi
Acknowledgment .....	xii
Publications .....	xiv
Dedication .....	xix
Chapter 1 .....	1
General Introduction .....	1
1.1 Coronary artery disease.....	2
1.1.1 Prevalence of coronary artery disease.....	2
1.1.2 Pathology of coronary artery disease .....	2
1.1.3 The burden of coronary artery disease.....	3
1.2 Relevant coronary artery anatomy .....	3
1.2.1 Normal anatomy.....	3
1.2.2 The walls of the coronary arteries.....	4
1.2.3 Role of endothelial cells.....	4
1.3 Coronary artery remodelling.....	5
1.3.1 History of remodelling.....	6
1.3.2 Types of remodelling .....	7
1.3.3 Plaque vulnerability and remodelling .....	8
1.3.4 Location of remodelling.....	8
1.3.5 Failure of remodelling.....	9

1.3.6 Implications of remodelling on detection of coronary artery disease.....	9
1.4 Atherosclerosis .....	10
1.4.1 Components of atherosclerosis.....	10
1.4.2 Development of atherosclerosis.....	11
1.4.3 Evolution of atherosclerotic lesions .....	11
1.4.4 Thrombosis causing lesion progression.....	12
1.4.5 Endothelial dysfunction.....	13
1.5 Plaque vulnerability.....	14
1.5.1 Factors influencing plaque vulnerability .....	14
1.5.2 Endothelial erosion and plaque disruption .....	15
1.5.3 Fibrous cap stability.....	17
1.6 Invasive detection of coronary artery disease.....	18
1.6.1 Angiography .....	18
1.6.2 Intravascular ultrasound.....	20
1.6.3 Optical Coherence Tomography.....	22
1.7 Non-invasive detection of coronary artery disease.....	22
1.7.1 Electron beam computer tomographic imaging.....	22
1.7.2 Magnetic resonance imaging .....	24
1.7.3 Carotid intima-media thickness .....	25
1.7.4 Transthoracic echocardiography.....	26
1.7.5 High resolution transthoracic echocardiography .....	28
1.8 Risk factor analysis.....	29

1.9 Summary .....	30
Chapter 2 .....	32
Coronary artery wall thickness of the left anterior descending artery using high resolution transthoracic echocardiography – normal range of values .....	32
2.1 Introduction.....	33
2.1.1 Aims .....	33
2.2 Methods.....	35
2.2.1 Subjects .....	35
2.2.2 Procedures.....	35
2.2.3 Statistical analysis .....	40
2.3 Results.....	41
2.4 Discussion .....	53
2.4.1 Limitations: .....	54
2.5 Conclusion .....	55
Chapter 3 .....	56
Changes in Left Anterior Descending Coronary Artery Wall Thickness Detected by High Resolution Transthoracic Echocardiography.....	56
3.1 Introduction.....	57
3.1.1 Aims.....	57
3.2 Methods.....	58
3.2.1 Subjects .....	58
3.2.2 Procedures.....	58
3.2.3 Statistical analysis .....	58

3.3 Results .....	60
3.4 Discussion.....	67
3.4.1 Limitations:.....	69
3.5 Conclusion.....	70
Chapter 4.....	71
High Resolution Transthoracic Echocardiography of the Left Anterior Descending Coronary Artery: A novel non-invasive assessment of coronary vasoreactivity.....	71
4.1 Introduction.....	72
4.1.1 Aims.....	73
4.2 Methods .....	74
4.2.1 Subjects.....	74
4.2.2 Procedures.....	74
4.2.3 Statistical analysis.....	76
4.3 Results .....	77
4.4 Discussion.....	85
4.4.1 Limitations:.....	88
4.5 Conclusion.....	89
Chapter 5.....	90
Left Anterior Descending Coronary Artery Wall Thickness Detected by High Resolution Transthoracic Echocardiography Predicts Future Ischemic Events .....	90
5.1 Introduction.....	91

5.1.1 Aim .....	92
5.2 Methods.....	93
5.2.1 Subjects .....	93
5.2.2 .Procedures.....	93
5.2.3 Statistical analysis .....	95
5.3 Results.....	97
5.4 Discussion .....	113
5.4.1 Limitations: .....	115
5.5 Conclusion .....	116
Chapter 6.....	117
Echocardiographic Left Anterior Descending Coronary Artery Wall Thickness and Future Events: a Comparison with Exercise Stress Echocardiography ..	117
6.1 Introduction.....	118
6.1.1 Aims.....	119
6.2 Methods.....	120
6.2.1 Subjects .....	120
6.2.2 Procedures.....	120
6.2.3 Statistical analysis .....	121
6.3 Results.....	123
6.4 Discussion .....	134
6.4.1 Limitations: .....	135
6.5 Conclusion .....	135
Chapter 7.....	137

Predictors of Statin Induced Regression of Left Anterior Descending Coronary Artery Wall Thickness as Measured by High Resolution Transthoracic Echocardiography .....	137
7.1 Introduction.....	138
7.1.1 Aims.....	139
7.2 Methods .....	140
7.2.1 Subjects.....	140
7.2.2 Procedures.....	140
7.2.3 Statistical analysis.....	141
7.3 Results .....	142
7.4 Discussion.....	151
7.4.1 Limitations:.....	153
7.5 Conclusion .....	153
Chapter 8.....	154
Summary and conclusions .....	154
8.1 Summary of findings .....	155
8.2 Conclusions .....	157
8.3 Future Studies .....	157
Appendix A:.....	158
Appendix B:.....	160
Appendix C:.....	163
Appendix D:.....	165
Appendix E:.....	170

Appendix F: .....	175
Appendix G: .....	183
Bibliography .....	185



## Summary

Coronary artery disease (CAD) in its subclinical phase is a silent disease process accumulating over time until a catastrophic event such as myocardial infarction or death occurs often as the first presentation of the disease.

Conventional risk factors do not fully explain the incidence of CAD and many people considered as low or intermediate risk for development of CAD based on these risk factors are often overlooked for primary prevention measures.

However; it is often these people in which cardiovascular events occur as there is no pre existing urgency to modify important risk factors such as diet and exercise. Imaging plays an important role in this context as it may allow for targeted primary prevention measures despite a low or intermediate risk assessment using conventional methods. A novel imaging technique known as high resolution transthoracic echocardiography (HRTTE) was used to image the proximal left anterior descending coronary artery (LAD) to make measurements of the wall thickness and therefore the degree of subclinical atherosclerosis in varying cohorts of subjects.

HRTTE demonstrated that the LAD wall thickness and the external diameter of patients with CAD were significantly larger than that of normal volunteers, even when matched for age. The luminal diameter however was maintained in both groups indicating that the CAD group has undergone positive remodelling at the site measured. This objectively visualised evidence of

coronary atherosclerosis with HRTTE would likely be undetected during coronary angiography that images the lumen and not the vessel wall.

HRTTE was also able to show non-invasively the effects of recognised vasodilators on the coronary circulation. The HRTTE technique was sufficiently sensitive to detect coronary artery vasomotion and may be able to determine endothelial dysfunction, a sign of subclinical CAD. It was also found that LAD wall thickness as determined by HRTTE was able to predict future cardiovascular events in subjects free of clinical CAD and had a better predictive power than conventional cardiovascular risk factors.

HRTTE was also sufficiently sensitive to determine stabilisation of LAD wall thickness using moderate dose statin therapy in subjects with new myocardial infarction indicating that this method may assist in individual tailoring of both primary and secondary prevention therapies.

## **Declaration**

I certify that this thesis does not incorporate without acknowledgment any material previously submitted for a degree or diploma in any university; and that to the best of my knowledge and belief it does not contain any material previously published or written by another person except where due reference is made in the text.

Signed

Rebecca Perry

## **Acknowledgment**

All the work in this thesis was carried out in the Echocardiography Department, Cardiac Investigations, Flinders Medical Centre, South Australia. Financial support was gained through the department and from a Cardiovascular Lipids grant from Pfizer Australia for which I am grateful. Many thanks must go to my supervisors for their amazing efforts over the time of my doctorate. Both Doctors Carmine De Pasquale and Majo Joseph have been instrumental in my work, despite not being their direct fields of interest and have helped me maintain my enthusiasm and work standards even during the tough times (and through 2 pregnancies!). Without their supreme efforts this body of work would not have come into fruition and for that I am most appreciative. To Professor Derek Chew for answering seeming limitless statistical questions from a stats novice without complaint and for helping me to see the bigger picture of what I was doing. To Professor Phil Aylward for having the ability to overcome obstacles when to me they were insurmountable without judgement and for his valuable input. I would like to thank all my supervisors for their support and giving me the confidence to present my work to a wider audience.

Thanks also to Dr Andrew Hamilton for putting me on the path to coronary artery imaging and giving me the basic tools to get started. To Dr Arduino Mangoni for his amazing ideas and input into the vasoreactivity study and to Professor Joseph Selvanayagam for his invaluable input.

To all the sonographers and reception staff in Echo, I owe so much to each of you for putting up with me on a day to day basis at work, demanding the echo machine and help with subject recalls. And to Lynn Brown and Amy Penhall who assisted with scanning and moral support in the larger projects, your confidence in me at times I thought was unfounded but it pulled me through a lot.

Finally I would like to thank my family; to my parents who have always allowed me to be an independent thinker and have been proud of everything that I have done and to my husband Simon who despite me giving up numerous times was always confident that I would achieve my goal and has provided unwavering support in everything that I have done.

## **Publications**

### **Papers:**

Perry R, Joseph MX, Chew DP, Hamilton AJ, Selvanayagam JB, Aylward PE, De Pasquale CG. Left Anterior Descending Coronary Artery Wall Thickness Detected by High Resolution Transthoracic Echocardiography Predicts Future Ischemic Events. Under review *Journal of the American Society of Echocardiography* 2012.

Perry R, Joseph MX, Chew DP, Aylward PE, De Pasquale CG. Coronary artery wall thickness of the left anterior descending artery using high resolution transthoracic echocardiography – normal range of values. Accepted for publication *Echocardiography* 2012.

Perry R, Joseph MX, Chew DP, Aylward PE, De Pasquale CG. Predictors of Statin Induced Regression of Left Anterior Descending Coronary Artery Wall Thickness as Measured by High Resolution Transthoracic Echocardiography. Accepted for publication *Echocardiography* 2012.

Perry R, De Pasquale CG, Chew DP, Brown L, Aylward PE, Joseph MX. Changes in Left Anterior Descending Coronary Artery Wall Thickness

Detected by High Resolution Transthoracic Echocardiography. *American Journal of Cardiology* 2008;101(7):937-40.

Perry R, Joseph MX, De Pasquale CG, Chew DP, Yiu D, Aylward PE, Mangoni AA. High-resolution transthoracic echocardiography of the left anterior descending coronary artery: a novel non-invasive assessment of coronary vasoreactivity. *Journal of the American Society of Echocardiography* 2008; 21:134-8.

**Presentations at accredited peer reviewed meetings:**

Perry R, De Pasquale CG, Chew DP, Brown L, Hamilton AJ, Aylward PE, Joseph MX. Coronary artery wall thickness of the left anterior descending artery using high resolution transthoracic echocardiography – intra and inter operator variability.

*European Journal of Echocardiography.* 2005; 6(S1):516, abstract number 202.

- Presentation 9<sup>th</sup> *Annual Meeting of the European Association of Echocardiography*, Florence 12/2005.

*Heart, Lung and Circulation.* 2005; 14(S1):S29, abstract number 69.

- Presentation 52<sup>nd</sup> *Annual Scientific Meeting of the Cardiac Society of Australia and New Zealand*, Perth 08/2005.

Perry R, Yiu D, Joseph MX, De Pasquale CG, Chew DP, Aylward PE, Mangoni AA. High resolution transthoracic echocardiography assessment of the left anterior descending coronary artery: a novel and non-invasive approach to study coronary vasomotion in humans.

*Journal of the American Society of Echocardiography*. 2006; 19(5):670, abstract number P1-52.

- Presentation 17<sup>th</sup> *Annual Scientific Sessions of the American Society of Echocardiography*, Baltimore 06/2006.

*Heart, Lung and Circulation*. 2006; 15(S1):S28, abstract number 64.

- Presentation 53<sup>rd</sup> *Annual Scientific Meeting of the Cardiac Society of Australia and New Zealand*, Canberra 08/2006.

Perry R, De Pasquale CG, Chew DP, Brown L, Aylward PE, Joseph MX. Non-invasive detection of coronary artery atherosclerosis: a high resolution transthoracic echocardiography study.



*Journal of the American Society of Echocardiography.* 2006; 19(5):598,  
abstract number P1-53.

- Presentation 17<sup>th</sup> *Annual Scientific Sessions of the American Society of Echocardiography*, Baltimore 06/2006.

*Heart, Lung and Circulation.* 2006; 15(S1):S83, abstract number 199.

- Presentation 53<sup>rd</sup> *Annual Scientific Meeting of the Cardiac Society of Australia and New Zealand*, Canberra 08/2006.

Perry R, Joseph MX, Chew DP, Aylward PE, De Pasquale CG. Moderate statin therapy does not change left anterior descending coronary artery wall thickness as measured by high resolution transthoracic echocardiography.

*Heart, Lung and Circulation.* 2008; 17(S1):S27, abstract number 63.

- Presentation 55<sup>th</sup> *Annual Scientific Meeting of the Cardiac Society of Australia and New Zealand*, Adelaide 08/2008.

Perry R, Joseph MX, Chew DP, Hamilton AJ, Selvanayagam JB, Aylward PE, De Pasquale CG. Left Anterior Descending Coronary Artery Wall Thickness Detected by High Resolution Transthoracic Echocardiography Predicts Future Ischaemic Events.

*Heart, Lung and Circulation.* 2012.

- Presentation to be done at the 59<sup>th</sup> *Annual Scientific Meeting of the Cardiac Society of Australia and New Zealand*, Brisbane 08/2012.

## **Dedication**

For the three loves of my life – Simon, Mia and Sam xxx