# *MULTIMODALITY IMAGING IN CARDIOVASCULAR DISEASE*

**KAREN S. L. TEO**

**M.B.,B.S., F.R.A.C.P.**

**Discipline of Pharmacology**

**University of Adelaide**

**Adelaide, SA, 5005**

**AUSTRALIA**

**Submitted in the total fulfillment of the requirements**

**for the degree of Doctor of Philosophy**

**University of Adelaide**

**AUSTRALIA**

**November 2007**

## DECLARATION

I performed the research presented in this thesis within the Department of Pharmacology, University of Adelaide, Adelaide, Australia. This work contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. I give consent to this copy of my thesis, when deposited in the University Library, being made available for loan and photocopying, subject to the provisions of the Copyright Act 1968.

Dr. Karen S.L. Teo
University of Adelaide
Adelaide
South Australia 5000
AUSTRALIA

# TABLE OF CONTENTS

## ACKNOWLEDGEMENTS

I would like to thank both my supervisors, Professors Stephen Worthley and Derek Frewin. I am indebted to Professor Worthley for his mentorship and guidance throughout this thesis. Professor Worthley's intellect, vision and infectious enthusiasm have inspired me greatly and have taught me much in all aspects of research. I also acknowledge his expertise in cardiac imaging, in particular cardiovascular magnetic resonance that has provided a firm foundation for me. I would also like to thank Professor Frewin for his guidance, wisdom and support from the time that we first embarked on the project as well as throughout this thesis.

I acknowledge my fellow co-workers of the Cardiovascular Research Centre at the Royal Adelaide Hospital for their help with work related to the projects and to Adelaide Cardiac Imaging for the use of both CMR and CT for our research projects.

I also acknowledge scholarships and financial support from the Royal Adelaide Hospital (Dawes scholarship), the Cardiac Society of Australia and New Zealand (CSANZ research scholarship), Pfizer Cardiovascular Research Scholarship and the CVL Research grant (Pfizer Australia).

Thanks also to my family and friends for their support during this thesis. I especially want to thank my parents, Jenny and Pek Kim Teo for their love, guidance and encouragement throughout my life. Finally, I give thanks to God.

# THESIS RELATED PUBLICATIONS

## *ORIGINAL RESEARCH*

**Teo KSL,** Carbone A, Piantadosi C, Chew DP, Hammett CJ, Brown MA, Worthley SG. Cardiac MRI assessment of left and right ventricular parameters in healthy Australian normal volunteers. Heart Lung and Circulation 2008 (in press).

## *RELATED WORK*

Duncan RF, **Teo KSL,** Worthley SG. Heart Lung and Circulation 2007. Cardiac magnetic resonance documentation of a double atrial septal defect before and after percutaneous closure with an Amplatzer septal occluder. Int J Cardiol. 2007 (in press).

O'Hanlon R, **Teo KSL,** Buchiarelli-Ducci C, Pennell DJ. Perfusion CMR and SPECT in hypertrophic cardiomyopathy. Int J Cardiol. 2007 (in press).

**Teo KSL**, Roberts-Thomson KC, Worthley SG. Utility of intravascular ultrasound in the diagnosis of ambiguous calcific left main stenoses. J Invasive Cardiol. 2004 Jul; 16(7): 385.

Roberts-Thomson KC, **Teo KSL,** Stuklis R, Worthley SG. Left atrial myxoma: magnet or echo? Intern Med J. 2004 Apr; 34(4): 210-1.

## *PRESENTATIONS*

Cardiovascular MR Advances and Read with the Experts: 10th Annual Course, National Heart and Lung Institute, London. November 2006. Read with the experts session (Cases in Heart Failure: Co-presenter).

## THESIS RELATED ABSTRACTS

**Teo KSL**, Korlaet M, Lott C, Brown MA, Worthley SG. Comparison of four and sixteen detector MDCT for noninvasive coronary angiographic imaging. *51st Scientific Sessions of the Cardiac Society of Australia and New Zealand*, Adelaide, August 2003.

**Teo KSL**, Ellis C, Lennon-George J, Fowler SM, Keenan RJ, Worthley SG. Cardiac MRI determines reproducibly left ventricular parameters in normal volunteers. *51st Scientific Sessions of the Cardiac Society of Australia and New Zealand*, Adelaide, August 2003.

**Teo KSL,** Ellis C, Lennon-George J, Keenan RJ, Worthley SG. Cardiac MRI determines reproducibly left ventricular parameters in normal volunteers. *Royal Australian and New Zealand College of Radiologists 54th Annual Scientific Meeting*, Brisbane, September 2003.

**Teo KSL,** Parkin G, Keenan RJ, Brown MA, Worthley SG. Tricuspid valve position using Cardiac MRI: Establishment of a surface anatomical algorithm for central venous pressure zero point. *Royal Australian and New Zealand College of Radiologists 54th Annual Scientific Meeting*, Brisbane, September 2003.

Lott C**, Teo KSL,** Korlaet M, Brown MA, Worthley. Comparison of Four and Sixteen Multi-detector CT for non-invasive coronary angiographic imaging. *Royal Australian and New Zealand College of Radiologists 54th Annual Scientific Meeting*, Brisbane, September 2003.

**Teo KSL**, Ellis CA, Lennon-George J, Worthley SG Assessment of Atrial Septal Defects: A comparative study in adult patients with cardiac magnetic resonance and transoesophageal echocardiography. *52st Scientific Sessions of the Cardiac Society of Australia and New Zealand*, Brisbane, August 2004. Heart Lung Circulation 2004; 13(Supp) 2:S57.

**Teo KSL**, Campbell P, Zaman AG, Worthley SG. Coronary Artery Bypass Graft Assessment with multi-detector CT in asymptomatic patients. *52st Scientific Sessions of the Cardiac Society of Australia and New Zealand*, Brisbane, August 2004. Heart Lung Circulation 2004;13(Supp)2:S58

**Teo KSL**, Ellis CA, Lennon-George J, Worthley SG. Assessment of Atrial Septal Defects: A comparative study in adult patients with cardiac magnetic resonance and transoesophageal echocardiography. *European Society of Cardiology Congress*, Munich, Germany, August 2004.

Brown G, Pontre B, **Teo KSL**, Taylor J, St.Pierre T, Chua-anusorn W, Worthley SG T2* Relaxometry in Secondary Haemochromatosis: Impact of Techinical Variations. *13th Scientific Meeting & Exhibition of the International Society for Magnetic Resonance in Medicine*, Miami, Florida, May 2005

**Teo KSL**, Grieve SM, Hammett, CJK, Piantadosi C, Chew DP, Korlaet M, Worthley SG. Common Carotid artery wall assessment with MRI: variations

between patients with severe versus absent internal carotid disease. *53rd Scientific Sessions of the Cardiac Society of Australia and New Zealand*, Perth, August 2005

**Teo KSL**, Piantadosi C, Hammett CJK, Ellis CA, Lennon-George J, Worthley SG. Utility of cardiovascular magnetic resonance in assessing cardiac volumes pre- and post- percutaneous ASD closure: A serial study. *53rd Scientific Sessions of the Cardiac Society of Australia and New Zealand*, Perth, August 2005. Heart Lung Circulation 2005;14S-S39.

Hammett CJK, **Teo KSL**, Piantadosi C, Grieve SM, Chew DP, Lennon-George J, Ellis CA, Worthley SG. Assessment of common and internal carotid artery vessel wall area: a feasibility study using high resolution MRI. *53rd Scientific Sessions of the Cardiac Society of Australia and New Zealand*, Perth, August 2005. Heart Lung Circulation 2005; 14(Supp) 1:S40.

Grieve SM, **Teo KSL,** Piantadosi C, Hammett CJK, Worthley SG. Algorithm for co-registration and analysis of mulit-contrast MRI sequence: utility in carotid atherosclerosis. *53rd Scientific Sessions of the Cardiac Society of Australia and New Zealand*, Perth, August 2005. Heart Lung Circulation 2005; 14(Supp) 1-S41.

Pontre B, Brown G, **Teo KSL**, Chua-anusorn W, St.Pierre T, Worthley SG. Iron Deposition patterns in the liver and heart of patients with beta-Thalassaemia: an MRI analysis. *53rd Scientific Sessions of the Cardiac Society of Australia and New Zealand*, Perth, August 2005. Heart Lung Circulation 2005;14S:S39.

Farquharson AL, Magarey J, **Teo KSL**, Roberts-Thomson K, Hutchinson MR. Comparison of manual anterolateral cardioversion with remote anteroposterior cardioversion of atrial fibrillation using current biphasic defibrillation. *53rd Scientific Sessions of the Cardiac Society of Australia and New Zealand*, Perth, August 2005.

Hammett CJK, **Teo KSL**, Piantadosi C, Grieve SM, Chew DP, Lennon-George J, Ellis CA, Worthley SG. Assessment of common and internal carotid artery vessel wall area: a feasibility study using high resolution MRI. *European Society of Cardiology Congress*, Stockholm, Sweden September 2005.

**Teo KSL**, Piantadosi C, Brown MA, Worthley MI, Disney PJ, Hammett CJK, Waddy PJ, Sanders P, Worthley SG. Percutaneous closure of atrial septal defects leads to a reduction in right ventricular volumes and corresponding normalisation of left ventricular volumes: ventricular interdependence and cardiac MRI. *54th Scientific Sessions of the Cardiac Society of Australia and New Zealand*, Canberra, August 2006. Heart, Lung and Circulation 2006;15S-83.

**Teo KSL**, Grieve SM, Worthley MI, Korlaet MB, Brown MA, Fitridge R, Thomas A, Carbone A, Worthley SG. Multi-detector CT imaging fails to accurately quantify vessel wall calcification: analysis of multiple algorithms and comparison with micro CT. *54th Scientific Sessions of the Cardiac Society*

*of Australia and New Zealand*, Canberra, August 2006. Heart, Lung and Circulation 2006;15S-85.

**Teo KSL**, Nicholls SJ, Kee P, Rye KA, Barter PJ, Worthley SG. Combination high-density lipoprotein infusion and atorvastatin significantly reduces experimental atherosclerosis compared to either therapy alone: serial analysis with high-resolution MRI. *54th Scientific Sessions of the Cardiac Society of Australia and New Zealand*, Canberra, August 2006. Heart, Lung and Circulation 2006;15S-86.

Greenwell TH**, Teo KSL**, Chew DP, Hammett CJK, Piantadosi C, Carbone A, Worthley MI, Worthley SG. Early Atherosclerotic Disease in the Carotid and Coronary Territories in At-Risk Individuals. *54th Scientific Sessions of the Cardiac Society of Australia and New Zealand*, Canberra, August 2006. Heart, Lung and Circulation 2006; 15S-111. Heart Lung Circulation 2006; 15 (Supp) 1:S47.

**Teo KSL**, Nicholls SJ, Kee P, Rye KA, Barter PJ, Worthley SG. Combination high-density lipoprotein infusion and atorvastatin significantly reduces experimental atherosclerosis compared to either therapy alone: serial analysis with high-resolution MRI. *European Society of Cardiology Congress*, Barcelona, Spain September 2006. European Heart Journal 2006,27(1): 827, P 5517.

Piantadosi C, Worthley MI, **Teo KSL**, Nalivaiko E, McAinch A, Wittert GA, Worthley SG. Effects of obesity and diet induced weight loss on Cardiovascular risk factors, vascular and ventricular structure and function in obsess men. International Atherosclerosis Society Scientific Sessions, Rome, Italy June 2006.

Leung MCH, Brown GC, Young AA, Cowan BR, Pontré B, **Teo KSL**, St. Pierre T, S.G. Worthley SG. 3D MRI Myocardial Strain in Patients with Transfusion-Induced Haemochromatosis. *55th Scientific Sessions of the Cardiac Society of Australia and New Zealand*, Christchurch, August 2007. Heart, Lung and Circulation 2007; 16 (Supp 2), S45.

Liew G, Hammett C, Dundon B, **Teo KSL**, M. Worthley MI, Nicholls SJ, Zaman A, Worthley SG Multi-Detector Computed Tomography (MDCT) and Magnetic Resonance Imaging (MRI) Non-Invasively Quantifies Saphenous Vein Graft Atherosclerotic Plaque: A Comparison with Intravascular Ultrasound (IVUS). *55th Scientific Sessions of the Cardiac Society of Australia and New Zealand*, Christchurch, August 2007. Heart, Lung and Circulation 2007; 16 (Supp 2), S45.

Liew G, Hammett C, Dundon B, **Teo KSL**, Worthley MI, Nicholls SJ, Zaman A, Worthley SG. Predictors of Atheroembolic Complications During Saphenous Vein Graft Percutaneous Coronary Intervention. *55th Scientific Sessions of the Cardiac Society of Australia and New Zealand*, Christchurch, August 2007. Heart, Lung and Circulation 2007; 16 (Supp 2), S105.

## THESIS RELATED AWARD

Oral Presentation Winner: Diagnostic Imaging Paper (Mayne Health Scientific Paper Prize). Annual Scientific Sessions of the Royal Australian and New Zealand College of Radiology 2003, Brisbane, Australia

Abstract: Cardiac MRI determines reproducibly left ventricular parameters in normal volunteers.

Authors: **Teo KSL**, Ellis C, Lennon-George J, Fowler SM, Keenan RJ, Worthley SG.

# LIST OF ABBREVIATIONS

| | |
|---|---|
| **ASD** | Atrial septal defect |
| **CAC** | Coronary Artery Calcium |
| **CNR** | Contrast-to-Noise |
| **CT** | Computerised Tomography |
| **CMR** | Cardiovascular Magnetic Resonance |
| **EBCT** | Electron Beam Computerised Tomography |
| **ECG** | Electrocardiograph |
| **ESP** | Echo Spacing |
| **ETL** | Echo Train Length |
| **FOV** | Field Of View |
| **FSE** | Fast Spin Echo |
| **Gd-DTPA** | Gadolinium-DiethyleneTriamine PentaAcetate |
| **HDL** | High Density Lipoprotein |
| **HU** | Hounsfield Units |
| **IVUS** | Intravascular Ultrasound |
| **LAD** | Left Anterior Descending |
| **LCx** | Left Circumflex |
| **LDL** | Low Density Lipoprotein |
| **LV** | Left ventricle |
| **MHz** | Megahertz |
| **MRI / MR** | Magnetic Resonance Imaging / Magnetic Resonance |
| **MWT** | Mean Wall Thickness |
| **NMR** | Nuclear Magnetic Resonance |
| **PDW** | Proton Density Weighted |
| **PET** | Positron Emission Tomography |
| **RCA** | Right Coronary Artery |
| **RF** | Radiofrequency |
| **RV** | Right ventricle |
| **SD** | Standard Deviation |
| **SEM** | Standard Error of the Mean |
| **SSFP** | Steady-state free precession |
| **T** | Tesla |
| **TE** | Echo Time |

| | |
|---|---|
| **TGF-β** | Transforming Growth Factor-β |
| **TI** | Inversion Time |
| **TOF** | Time Of Flight |
| **tPA** | tissue-type Plasminogen Activator |
| **TR** | Recovery Time |
| **T1W** | T1 Weighted |
| **T2W** | T2 Weighted |
| **VCAM-1** | Vascular Cellular Adhesion Molecule-1 |
| **VEC** | Velocity Encoded Contrast |
| **VWA** | Vessel Wall Area |

## SYNOPSIS

The non-invasive cardiovascular imaging modalities, cardiovascular magnetic resonance (CMR) and multi-detector computer tomography (MDCT) are playing an increasing role in both clinical and research settings.

CMR is a unique imaging modality due to unsurpassed contrast between soft tissue structures that is non-invasive, does not use ionising radiation and is able to provide high-resolution information about cardiac anatomy, function, flow, perfusion, viability and metabolism. It has provided the gold standard in imaging in congenital heart disease. Recent advances in this technology have led to images of high spatial and temporal resolution that has made the characterisation of atheroma possible. While currently spatial resolution still limits its ability to characterise atheroma in native human coronary arteries in living patients, CMR imaging of the coronary arteries has future potential with further technological and sequence advances.

MDCT has been used in clinical settings to measure of the amount of calcification in the coronary arteries with “coronary artery calcium scoring” of the coronary tree a surrogate marker of atherosclerosis. MDCT has also become the gold standard for angiographic imaging in most arterial beds such as the carotid and peripheral vascular systems. In the coronary arteries in particular, there have been major advances in the accuracy of coronary MDCT angiography, particularly with regards to its negative predictive value, although excessive calcification and blooming artefacts still limit the diagnostic accuracy of the technique for assessing stenotic severity.

In this thesis, our aims were to address some specific novel areas advancing the utility of these imaging modalities in two major areas of interest, namely congenital heart disease and atheroma imaging.

Our first step was to validate the accuracy and reproducibility of CMR, the main imaging modality we utilised. To achieve this, we assessed MR imaging of cardiac volumes and function in a normal adult Australian population with a specific focus on the reproducibility of the technique. In confirming that this technique in our hands is both accurate and reproducible, we would then be in a position to be able to confidently use this technique in our future chapters. However, more than this, we sought to establish some normal ranges for left and right atrial and ventricular parameters in our local population. This would be crucial background information for us to be able to make comparisons with future studies in patients with congenital heart disease.

Having established our technique and reference ranges, we would then explore the two specific issues in the ensuing two chapters using CMR in one area of congenital heart disease, atrial septal defect. Atrial septal defect is the most common congenital heart defect first diagnosed in adults. The traditional method of assessment of these patients and for suitability for ASD closure involves semi-invasive investigation with transoesophageal echocardiography (TOE) for measurement of the defect size and atrial septal margins. MRI assessment of patients prior to percutaneous device closure compared to TOE assessment would provide information on the accuracy of TOE assessment and provide information of the utility of cardiac MRI as an alternative to TOE for the work-up of these patients prior to ASD closure.

In our third original research chapter, we utilised CMR to understand the effects of percutaneous ASD closure on cardiac chamber volumes. We achieved this by assessing with cardiac MRI pre-closure and post-closure atrial and ventricular cardiac volumes. Longstanding right heart dilatation in the setting of an ASD may lead to complications including right heart failure, pulmonary hypertension and arrhythmia. Closure of the ASD should reduce right heart volumes by removing left-to-right shunting and lead to normalisation of ventricular volumes. The assessment of atrial volume changes with ASD closure may be important in furthering our understanding in its contribution to arrhythmia.

Having assessed the ability of CMR to assess both the ASD dimensions, and therefore suitability for percutaneous closure, as well as the effects of ASD closure on cardiac chamber size, we look in the final two original research chapters to move to another area of research development with these high-resolution imaging technologies, atherosclerosis imaging. Two particular areas we wished to focus on included the potential of high-resolution MR imaging to monitor effects of HDL infusion on atherosclerosis, and secondly to explore mechanisms behind limitations in MDCT imaging of atherosclerosis, specifically calcification and blooming artifacts.

For assessing the effects of HDL infusion on atherosclerosis, we utilised a cholesterol-fed rabbit model of atherosclerosis. The abdominal aorta of the rabbit is comparable in size to the human coronary artery. Previous work with the rabbit model of atherosclerosis and magnetic resonance imaging of the aortic wall has

shown that it can provide information about atherosclerotic composition as well as provide serial data of the arterial wall. While high intensity lipid-lowering with statins remains the first line management of at risk individuals, modest manipulations of serum HDL levels are associated with a significant impact on cardiovascular risk. Thus, we assessed the effect of HDL infusion and atorvastatin in a rabbit model of using MRI aortic atherosclerosis as the end-point.

In our fifth and final original research chapter, we assessed the accuracy of quantification of atherosclerotic calcification with MDCT in the carotid arteries of patients undergoing carotid endarterectomy, and sought to identify algorithms or techniques that may improve quantification of calcification. This would potentially lead to an improvement in the ability of MDCT techniques to quantify stenotic severity in coronary arteries that were calcified. To achieve these we utilised MDCT in vivo and in comparison with carotid endarterectomy specimen micro-CT. Importantly, as part of this study, we undertook a thorough assessment of reproducibility of these techniques.

Thus, in summary, we have been able to confirm the accuracy and reproducibility of CMR and MDCT in the areas of a specific congenital defect (ASD) and atherosclerosis imaging, and utilised these techniques to advance our understanding of these disease states. This thesis identifies strengths and weaknesses of these techniques that will allow us to more appropriately use them for future purposes in cardiovascular disease. Future work directly stemming from this thesis has already begun, and now looks to address issues of whether CMR and MDCT may provide complimentary information about atherosclerotic

lesions that may benefit outcomes in certain conditions. Specifically the work in this thesis has led to studies commencing in carotid atherosclerosis and saphenous vein graft atherosclerosis and using these imaging techniques to potentially predict adverse future outcomes.