SUBSTRATE FOR ATRIAL FIBRILLATION IN CARDIOMYOPATHIES

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A thesis submitted to The University of Adelaide

in fulfillment of the requirements of the degree of

Doctor of Philosophy

July 2010

To my dad Kah Ding

my wife Phoebe

and my children Justus & Hayley

In loving memory of my mum Suok King

Table of Contents

Abstract

Atrial Fibrillation is the most common heart rhythm disorder. However, our understanding of the underlying patho-physiological mechanisms of AF remains limited. Both hypertension and heart failure are known to play an important role as risk factors for AF. With the increase in the incidence and prevalence of both these conditions and the predicted atrial fibrillation epidemic, their underlying mechanistic associations require careful attention. This thesis focused on the evaluation of atrial remodeling in large animal models of these common substrates.

Chapter 2 presents the detailed anatomical, histological and functional characterization of the cardiac changes in the ovine “one-kidney, one-clip” model of hypertension using state of the art cardiac magnetic resonance imaging. Chapter 3 presents the significant atrial electrical, structural and functional remodeling evident with short duration (mean of 7 weeks) of hypertension. Pivotal changes were seen in increased atrial interstitial fibrosis and the resultant conduction abnormalities. This highlighted the importance of early and aggressive therapy of hypertension which may prevent the development of an arrhythmogenic atrial substrate.

Chapter 4 examines the time course of atrial remodeling during the development of hypertension over a period of 15 weeks. Anatomical and

functional remodeling started early while structural changes in increased fibrosis occurred later in the remodeling process. The early changes were associated with increased atrial fibrillation inducibility while the late changes were associated with more prolonged induced atrial fibrillation episodes. This understanding of the time course of remodeling provided important insights, whereby a narrow window of opportunity exists for preventing more permanent structural changes that can sustain atrial fibrillation. This work also implicates the need to maintain good blood pressure levels in atrial fibrillation patients. In particular, recent evidence has shown that pre-hypertension is associated with increased incidence of atrial fibrillation.

To date, experimental studies on atrial remodeling in heart failure had utilized one single animal model of rapid ventricular tachypacing induced heart failure. This model may not be representative of all types of cardiomyopathy in the heart failure syndrome since different underlying causes of heart failure have been shown to portend different prognostic value. Chapter 5 further evaluates atrial remodeling in heart failure using a recently characterized ovine model of non-reversible doxorubicin-induced non-ischemic cardiomyopathy. The main feature of atrial remodeling lies in the structural changes of atrial interstitial fibrosis with increased conduction heterogeneity which resulted in longer induced atrial fibrillation episodes. These findings suggest a consistent substrate

for atrial fibrillation in different heart failure models indicating ‘remodeling of the same sort’.

Chapter 6 presents the atrial effects of omega-3 fatty acids treatment in ovine heart failure. Omega-3 fatty acids prevented atrial enlargement, reduced atrial fibrosis and the related conduction abnormalities resulting in shorter atrial fibrillation episodes. Clinically, omega-3 fatty acids have been shown to provide additional albeit modest improvement in outcomes of heart failure patients above current evidence-based therapies. Therefore, omega-3 fatty acids may potentially provide a relatively affordable and non-toxic option to prevent adverse atrial remodeling and reduce atrial fibrillation burden in this subgroup of patients with heart failure.

Declaration

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 to Dennis Lau 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.

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Lau DH, Mackenzie L, Rajendram A, Psaltis PJ, Kelly DR, Spyropoulos P, Zhang Y, Olakkengil S, Russell CH, Brooks AG, Faull RJ, Saint DA, Kelly DJ, Rao MM, Worthley SG, Sanders P. Characterization of Cardiac Remodeling in a Large Animal 'One-Kidney, One-Clip' Hypertensive Model. **Blood Pressure** 2010; 19:119-125

Lau DH, Mackenzie L, Kelly DJ, Psaltis PJ, Worthington M, Rajendram A, Kelly DR, Nelson AJ, Zhang Y, Kuklik P, Brooks AG, Worthley SG, Faull RJ, Rao M, Edwards J, Saint DA, Sanders P. Short Term Hypertension is Associated with the Development of Atrial Fibrillation Substrate: A Study in an Ovine Hypertensive Model. **Heart Rhythm** 2010; 7:396-404

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Lau DH, Psaltis PJ, Mackenzie L, Kelly DJ, Carbone A, Worthington M, Brooks AG, Nelson AJ, Zhang Y, Kuklik P, Wong CX, Edwards J, Saint DA, Worthley SG, Rao M, Sanders P. Atrial Remodeling in an Ovine Model of Anthracycline-induced Non-ischemic Cardiomyopathy: "Remodeling of the Same Sort". **J Cardiovasc Electrophysiol;** *In Press*

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Dennis H S Lau
July 2010

Acknowledgements

I would like to thank Professor Prashanthan Sanders, my primary supervisor, for his mentorship and support during my doctoral training. I am particularly encouraged by his enthusiasm and innovation in these research projects. He has demonstrated the fine art in balancing a successful career as a clinician, scientist, teacher, husband and father. I am also thankful to my co-supervisors, A/Professor David Saint and Dr Lorraine Mackenzie, for their guidance and encouragement over the years. I am grateful for the scholarship support from: National Health and Medical Research Council of Australia, Kidney Health Australia and The University of Adelaide (Earl Bakken Electrophysiology Scholarship).

I cherish my clinical electrophysiology training at The Royal Adelaide Hospital with Drs Glenn Young, Daniel Cehic and Kurt Roberts-Thomson. I also enjoyed working alongside co-fellows: Drs Martin Stiles, Bobby John, Hany Dimitri, Han Lim, Darryl Leong, Muayad Alasady & Hany Abed. Special thanks must go to the following for their assistance with: SPSS & Adobe - Dr Anthony Brooks; epicardial plaques (Dr Douglas Kelly); plaque analysis software (Dr Pawel Kuklik); renal clamps (Brad Pullen); MRI scans (Kerry Williams); & ultrasound imaging (Peter Spyropoulos). Support from the following was also crucial: Dr Scott Willoughby, Dr Nicholas Shipp, Lauren Wilson, Karen Drury, Melissa Middeldorp and Aimie Paukner. All these individuals contributed to a very productive & successful research environment.

Collaborative work with Dr Peter Psaltis on similar basic research projects provided fruitful exchange in ideas and solutions during this doctoral journey. Specialty input from Professor Stephen Worthley, A/Professors Mohan Rao, Randall Faull & Darren Kelly, Drs James Edwards, Michael Worthington, Yuan Zhang and Arumuga Rajendram was of tremendous help. I am also indebted to the contribution made by Angelo Carbone, Adam Nelson and Christopher Wong together with the support from Drs Denise Noonan & Tim Kuchel, Laboratory Animal Services (esp. Pacita Wissell, Kellie Franke, Alice Jones, Luke Laing & Sarah Fisher) and IMVS Animal Facility (esp. Jodie Dier & Adrian Hines).

In particular, I am blessed by the understanding and unwavering support from my beloved wife, Phoebe who has also given us two beautiful children in Justus and Hayley during this research journey. I thank my dad: Kah Ding Lau, parents-in-law: You Lik & Su King Chieng and all my siblings: Jacqueline, Linda, Irene, Lily, Duncan & Darren for their support in my pursuit of academia. Above all, I thank our great GOD for His faithfulness and love that sustained our memorable times in Adelaide.

Publications and Communications to Learned Societies

Chapter Two

1. Manuscript: Lau DH, Mackenzie L, Rajendram A, Psaltis PJ, Kelly DR, Spyropoulos P, Zhang Y, Olakkengil S, Russell CH, Brooks AG, Faull RJ, Saint DA, Kelly DJ, Rao MM, Worthley SG, Sanders P. Characterization of Cardiac Remodeling in a Large Animal 'One-Kidney, One-Clip' Hypertensive Model. **Blood Pressure** 2010; 19:119-125

2. Presentation: Presented at the High Blood Pressure Research Council of Australia 2007 Annual Scientific Meeting, Adelaide, Australia and published in abstract form (**Hypertension** 2008; 52:170)

Chapter Three

1. Manuscript: Lau DH, Mackenzie L, Kelly DJ, Psaltis PJ, Worthington M, Rajendram A, Kelly DR, Nelson AJ, Zhang Y, Kuklik P, Brooks AG, Worthley SG, Faull RJ, Rao M, Edwards J, Saint DA, Sanders P. Short Term Hypertension is Associated with the Development of Atrial Fibrillation Substrate: A Study in an Ovine Hypertensive Model. **Heart Rhythm** 2010; 7:396-404

2. Presentation: Presented at the Heart Rhythm Society 29th Annual Scientific Sessions, May 2008, San Francisco, United States of America and published in abstract form (**Heart Rhythm** 2008; 5:S164)

3. Presentation: Presented at the Cardiac Society of Australia and New Zealand 56th Scientific Meeting, August 2008, Adelaide, Australia and published in abstract form (**Heart Lung Circulation** 2008; 17:S9)

4. Presentation: Presented at the European Society of Cardiology Congress, August 2008, Munich, Germany and published in abstract form (**Euro Heart J** 2008; 29(1):287-8)

5. Presentation: Presented at the American Heart Association Scientific Sessions, November 2008, New Orleans, United States of America and published in abstract form (**Circulation** 2008; 118:S435)

6. Presentation: Presented at the 1st Asia-Pacific Heart Rhythm Society Scientific Session, November 2008, Singapore and published in abstract form (**APHRS Conference Proceedings** 2008:162)

7. Presentation: Presented at the American College of Cardiology 58th Annual Scientific Session, March 2009, Orlando, United States of America and published in abstract form (**J Am Coll Card** 2009; 53:A463)

Chapter Four

1. Manuscript: Lau DH, Mackenzie L, Kelly DJ, Psaltis PJ, Brooks AG, Worthington M, Rajendram A, Kelly DR, Zhang Y, Kuklik P, Nelson AJ, Wong CX, Worthley SG, Rao M, Faull RJ, Edwards J, Saint DA, Sanders P. Hypertension and Atrial Fibrillation: Evidence of Progressive Atrial Remodeling with Electro-structural Correlate in a Conscious Chronically Instrumented Ovine Model. **Heart Rhythm;** 2010;7 1282-90

2. Presentation: Presented at the Heart Rhythm Society 30th Annual Scientific Sessions, May 2009, Boston, United States of America and published in abstract form (**Heart Rhythm** 2009; 6:S424)

3. Presentation: Presented at the Cardiac Society of Australia and New Zealand 57th Scientific Meeting, August 2009, Sydney, Australia and published in abstract form (**Heart, Lung and Circulation** 2009; 18:S129)

4. Presentation: Presented at the 2nd Asia-Pacific Heart Rhythm Society Scientific Session, October 2009, Beijing, China and published in abstract form (**APHRS Conference Proceedings** 2009; 67)

5. Presentation: Presented at the American Heart Association Scientific Sessions, November 2009, Orlando, United States of America and published in abstract form (**Circulation** 2009; 120:S665)

6. Presentation: Presented at the American College of Cardiology 59th Annual Scientific Session, March 2010, Atlanta, United States of America and published in abstract form (**J Am Coll Card** 2010; 53:A463)

Chapter Five

1. Manuscript: Lau DH, Psaltis PJ, Mackenzie L, Kelly DJ, Carbone A, Worthington M, Brooks AG, Nelson AJ, Zhang Y, Kuklik P, Wong CX, Edwards J, Saint DA, Worthley SG, Rao M, Sanders P. Atrial Remodeling in an Ovine Model of Anthracycline-induced Non-ischemic Cardiomyopathy: "Remodeling of the Same Sort". **J Cardiovasc Electrophysiol;** *In Press*

2. Presentation: Presented at the Cardiac Society of Australia and New Zealand 57th Scientific Meeting, August 2009, Sydney, Australia and published in abstract form (**Heart, Lung and Circulation** 2009; 18:S130)

3. Presentation: Presented at the 2nd Asia-Pacific Heart Rhythm Society Scientific Session, October 2009, Beijing, China and published in abstract form (**APHRS Conference Proceedings** 2009; 76)

Chapter Six

1. Manuscript: DH Lau, PJ Psaltis, A Carbone, DJ Kelly, L Mackenzie, M Worthington, RG Metcalf, P Kuklik, AJ Nelson, Y Zhang, CX Wong, AG Brooks, DA Saint, MJ James, J Edwards, GD Young, SG Worthley, P Sanders. Atrial Protective Effects of n-3 Polyunsaturated Fatty Acids: A Long Term Study in Ovine Chronic Heart Failure. **Heart Rhythm;** *In Press*

2. Presentation: Presented at the American College of Cardiology 59th Annual Scientific Session, March 2010, Atlanta, United States of America and published in abstract form (**J Am Coll Card** 2010; 53:A463)

3. Presentation: Presented at the Heart Rhythm Society 31st Annual Scientific Sessions, May 2010, Denver, United States of America and published in abstract form (**Heart Rhythm** 2010; 6:S424)

4. Presentation: Presented at the Cardiac Society of Australia and New Zealand 58th Scientific Meeting, August 2010, Adelaide, Australia and published in abstract form (**Heart, Lung and Circulation** 2010; 19: S91)

5. Presentation: Presented at the 2nd Asia-Pacific Heart Rhythm Society Scientific Session, October 2009, Beijing, China and published in abstract form (**J Arrhythmia** 2010; 26:11)

Prizes and Awards during Candidature

1. Research Prize for best scientific oral presentation, Australian Chinese Medical Association (SA) 7th Annual Scientific Meeting 2008

2. Cardiac Society of Australia and New Zealand 56th Annual Scientific Meeting 2008 – Student Poster Prize

3. Nimmo Prize for best scientific oral presentation (full-time research category), The Royal Adelaide Hospital 2008 – Winner

4. Young Investigator Award (First Prize), 1st Asia Pacific Heart Rhythm Society Scientific Session 2008, Singapore

5. Best Poster Award (First Place), American College of Cardiology 58th Annual Scientific Session 2009, Orlando, FL, USA

6. Nimmo Prize for best scientific oral presentation (full-time research category), The Royal Adelaide Hospital 2009 – Finalist

7. Best Research Poster, The University of Adelaide, Faculty of Health Sciences Postgraduate Research Expo 2009

8. Best Poster Award (Third Place), American College of Cardiology 59th Annual Scientific Session 2010, Atlanta, GA, USA

9. Young Investigator Award (First Prize), 3rd Asia Pacific Heart Rhythm Society Scientific Session 2010, Jeju Island, South Korea

10. National Heart Foundation of Australia Travel Grant: 2007 & 2008

11. Cardiac Society of Australia and New Zealand Travelling Fellowship: 2008

12. Pfizer Cardio Vascular Lipid Travel Grant: 2008 & 2009

13. The University of Adelaide, Faculty of Health Sciences Postgraduate Travelling Fellowship: 2009

14. International Society for Heart Research (Australasian) Travel Grant: 2009

15. National Heart Foundation of Australia (SA) EO Myers Trust Fund Travel Grant: 2009 & 2010