

SUBSTRATE FOR ATRIAL FIBRILLATION IN CARDIOMYOPATHIES

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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.....	XVI
DECLARATION	XIX
ACKNOWLEDGEMENTS.....	XXI
PUBLICATIONS AND COMMUNICATIONS TO LEARNED SOCIETIES.....	XXII
PRIZES AND AWARDS DURING CANDIDATURE.....	XXVII
CHAPTER ONE.....	1
LITERATURE REVIEW.....	1
1.1 INTRODUCTION.....	1
1.1.1 <i>Consequences of Atrial Fibrillation.....</i>	<i>1</i>
1.1.2 <i>Current Management of Atrial Fibrillation</i>	<i>2</i>
1.2 MECHANISMS OF ATRIAL FIBRILLATION.....	3
1.2.1 <i>The Multiple Wavelet Hypothesis</i>	<i>4</i>
1.2.2 <i>Focal Electrical Discharges</i>	<i>5</i>
1.2.3 <i>Localized Re-entry with Fibrillatory Conduction</i>	<i>7</i>
1.2.4 <i>Rotors with Fibrillatory Conduction</i>	<i>9</i>
1.2.5 <i>Summary</i>	<i>10</i>
1.3 TACHYCARDIA RELATED ATRIAL REMODELING.....	11
1.3.1 <i>Atrial Electrical Remodeling</i>	<i>11</i>
1.3.1.1 <i>Atrial Refractoriness</i>	<i>11</i>

1.3.1.2	Fibrillatory Intervals	12
1.3.1.3	Atrial Conduction	13
1.3.1.4	Sinus Node Function	14
1.3.2	<i>Atrial Ionic Remodeling</i>	15
1.3.2.1	Calcium.....	15
1.3.2.2	Potassium.....	17
1.3.2.3	Sodium and Others	18
1.3.3	<i>Atrial Structural Remodeling</i>	19
1.3.3.1	Atrial Myocytes – Degeneration, De-differentiation or Apoptosis?.....	20
1.3.3.2	Gap Junctions.....	21
1.3.3.3	Atrial Interstitial Fibrosis.....	23
1.3.4	<i>Atrial Mechanical Remodeling</i>	24
1.3.5	<i>Time Course of Remodeling</i>	26
1.3.6	<i>Summary</i>	27
1.4	INFLAMMATION IN ATRIAL FIBRILLATION.....	27
1.5	AUTONOMIC NERVOUS SYSTEM AND ATRIAL FIBRILLATION.....	29
1.5.1	<i>Vagal Effects on Atrial Electrophysiology</i>	29
1.5.2	<i>Sympathetic Effects on Atrial Electrophysiology</i>	30
1.5.3	<i>Neural Modulation in Atrial Fibrillation</i>	30
1.5.4	<i>Summary</i>	31
1.6	STRETCH AND ATRIAL FIBRILLATION	31
1.6.1	<i>Cause and Consequence of AF</i>	32
1.6.2	<i>Atrial Remodeling due to Acute Stretch</i>	33

1.6.2.1	Animal Studies	33
1.6.2.2	Clinical Studies	34
1.6.3	<i>Chronic Stretch</i>	35
1.6.3.1	Animal Studies	35
1.6.3.2	Clinical Studies	36
1.6.4	<i>Underlying Mechanisms</i>	37
1.6.5	<i>Summary</i>	38
1.7	COMPLEX FRACTIONATED ATRIAL ELECTROGRAMS.....	38
1.7.1	<i>Definition of CFAEs</i>	38
1.7.2	<i>Mechanisms of CFAEs</i>	39
1.7.3	<i>The Odyssey of Mapping and Targeting CFAEs</i>	40
1.7.4	<i>Summary</i>	41
1.8	ATRIAL REMODELING IN COMMON CLINICAL SUBSTRATES	41
1.8.1	<i>Aging</i>	42
1.8.2	<i>Hypertension</i>	42
1.8.3	<i>Congestive Heart Failure</i>	44
1.8.4	<i>Mitral Valve Disease</i>	46
1.8.5	<i>Atrial Septal Defect</i>	47
1.8.6	<i>Sinus Node Disease</i>	48
1.8.7	<i>Myocardial Ischemia</i>	49
1.8.8	<i>Obstructive Sleep Apnea</i>	50
1.8.9	<i>Diabetes Mellitus</i>	51
1.8.10	<i>Summary</i>	52

CHAPTER TWO.....	53
CHARACTERIZATION OF CARDIAC REMODELING IN A LARGE ANIMAL 'ONE-KIDNEY, ONE-CLIP' HYPERTENSIVE MODEL	53
2.1 INTRODUCTION.....	53
2.2 METHODS	54
2.2.1 <i>Model Preparation and Study</i>	54
2.2.2 <i>One Kidney-One Clip Hypertension</i>	55
2.2.3 <i>Renal Surgeries.....</i>	56
2.2.4 <i>Cardiac Functional Assessment.....</i>	57
2.2.5 <i>Pathological Assessment.....</i>	57
2.2.6 <i>Statistical Analysis.....</i>	58
2.3 RESULTS	58
2.3.1 <i>Blood Pressure Profile</i>	59
2.3.2 <i>Cardiac Anatomical Changes</i>	59
2.3.3 <i>Cardiac Functional Changes</i>	60
2.3.4 <i>Serum Creatinine Level.....</i>	60
2.3.5 <i>Histopathological Changes.....</i>	60
2.4 DISCUSSION	61
2.4.1 <i>Functional Assessment Using CMR Imaging</i>	61
2.4.2 <i>Time Course of Cardiac Remodeling in Hypertension</i>	62
2.4.3 <i>Large versus Small Animal Models of Hypertension</i>	63
2.4.4 <i>Advantages of One Kidney, One Clip Hypertension</i>	64

2.4.5	<i>Potential Use of Model</i>	65
2.4.6	<i>Study Limitations</i>	65
2.5	CONCLUSIONS	66
	TABLE 1: CARDIAC MAGNETIC RESONANCE CHARACTERISTICS	67
	TABLE 2: CARDIAC ANATOMICAL CHARACTERISTICS	68
	FIGURE 1: 1K1C BLOOD PRESSURE PROFILE	69
	FIGURE 2: ATRIAL AND VENTRICULAR HYPERTROPHY IN	70
	THE HYPERTENSIVE HEARTS	70
	FIGURE 3: ATRIAL HISTO-PATHOLOGICAL CHANGES	71
	CHAPTER THREE	72
	SHORT TERM HYPERTENSION IS ASSOCIATED WITH THE DEVELOPMENT	
	OF ATRIAL FIBRILLATION SUBSTRATE:	72
	A STUDY IN AN OVINE HYPERTENSIVE MODEL	72
3.1	INTRODUCTION	72
3.2	METHODS	73
3.2.1	<i>Animal Preparation and Care</i>	73
3.2.2	<i>“One-Kidney, One-Clip” Hypertension</i>	73
3.2.3	<i>Cardiac Functional Assessment</i>	75
3.2.4	<i>Electrophysiological Study</i>	75
3.2.4.1	Atrial Effective Refractory Period	76
3.2.4.2	Atrial Conduction	76

3.2.4.3	P-wave Duration	77
3.2.4.4	AF Inducibility and Duration	77
3.2.5	<i>Pathology</i>	78
3.2.6	<i>Quantification of Collagen Matrix and Inflammatory Infiltrates</i>	78
3.2.7	<i>Statistical Analysis</i>	79
3.3	RESULTS	79
3.3.1	<i>Anatomical and Functional Remodeling due to Hypertension</i>	80
3.3.2	<i>Electrophysiological Remodeling due to Hypertension</i>	80
3.3.2.1	Atrial Refractoriness	80
3.3.2.2	Atrial Conduction	80
3.3.2.3	P-wave Duration	82
3.3.2.4	AF Inducibility and Duration	82
3.3.3	<i>Structural Remodeling due to Hypertension</i>	82
3.4	DISCUSSION.....	83
3.4.1	<i>Clinical Association between Hypertension and AF</i>	83
3.4.2	<i>Atrial Substrate for AF</i>	84
3.4.3	<i>Atrial Electrophysiological Abnormalities in Hypertension</i>	85
3.4.4	<i>Hypertensive Atrial Remodeling: Evidence for a Systemic Process</i>	85
3.4.5	<i>Clinical Implications</i>	86
3.4.6	<i>Study Limitations</i>	87
3.5	CONCLUSIONS	87
	TABLE 1: ANATOMICAL AND FUNCTIONAL CHARACTERISTICS	88
	FIGURE 1: EPICARDIAL PLAQUE DESIGN.....	89

FIGURE 2: ATRIAL ERP AT DIFFERENT PACING CYCLE LENGTHS AND SITES.....	90
FIGURE 3: CONDUCTION VELOCITY AND CONDUCTION HETEROGENEITY	91
FIGURE 4A: REPRESENTATIVE ACTIVATION MAPS	92
FIGURE 4B: CORRESPONDING PHASE HISTOGRAMS.....	93
FIGURE 5: REPRESENTATIVE PICROSIRIUS RED SECTIONS.....	94
FIGURE 6: REPRESENTATIVE H & E SECTIONS	95
FIGURE 7: HISTOLOGICAL ANALYSES	96
CHAPTER FOUR.....	97
HYPERTENSION AND ATRIAL FIBRILLATION:	97
EVIDENCE OF PROGRESSIVE ATRIAL REMODELING WITH.....	97
ELECTRO-STRUCTURAL CORRELATE IN A CONSCIOUS	97
CHRONICALLY INSTRUMENTED OVINE MODEL	97
4.1 INTRODUCTION.....	97
4.2 METHODS	98
4.2.1 <i>Study Protocol</i>	98
4.2.2 <i>General Anesthesia</i>	99
4.2.3 <i>“One Kidney-One Clip” Hypertension</i>	99
4.2.4 <i>Cardiac Functional Assessment.....</i>	99
4.2.5 <i>Electrophysiological Study.....</i>	100
4.2.5.1 <i>Atrial ERP.....</i>	100

4.2.5.2	Atrial Conduction	101
4.2.5.3	P-wave Duration	102
4.2.5.4	AF Inducibility and Duration	102
4.2.5.5	Electrogram Fractionation during AF.....	102
4.2.6	<i>Structural Analysis</i>	103
4.2.7	<i>Statistical Analysis</i>	103
4.3	RESULTS	104
4.3.1	<i>Anatomical and Functional Remodeling</i>	104
4.3.2	<i>Sequential Closed Chest Electrophysiological Studies: Progressive Electrical Remodeling</i>	105
4.3.2.1	Atrial Refractoriness	105
4.3.2.2	Atrial Conduction	105
4.3.2.3	P-wave Duration	106
4.3.2.4	AF Inducibility	106
4.3.2.5	Atrial Fractionation during AF.....	106
4.3.3	<i>Structural Remodeling</i>	107
4.3.4	<i>Open Chest Electrophysiological Studies: Electro-Structural Correlation</i>	107
4.4	DISCUSSION.....	108
4.4.1	<i>Time Course of Atrial Remodeling in Hypertension</i>	110
4.4.2	<i>Compounding Detrimental Effects of Hypertension and AF</i>	111
4.4.3	<i>Upstream Targeting as Primary AF Prevention?</i>	111
4.4.4	<i>Clinical Significance</i>	112
4.4.5	<i>Study Limitations</i>	113

4.5	CONCLUSIONS	113
	TABLE 1: ANATOMICAL AND FUNCTIONAL CHARACTERISTICS	114
	TABLE 2: SEQUENTIAL CLOSED CHEST	115
	ELECTROPHYSIOLOGICAL PARAMETERS	115
	FIGURE 1: STUDY DESIGN	116
	FIGURE 2: “ONE KIDNEY-ONE CLIP” BLOOD PRESSURE PROFILE.....	117
	FIGURE 3: REPRESENTATIVE (A) ACTIVATION MAPS AND (B) CORRESPONDING PHASE HISTOGRAMS AT DIFFERENT STAGES OF HYPERTENSION	118
	FIGURE 4A & B: ATRIAL STRUCTURAL REMODELING IN HYPERTENSION.....	119
	FIGURE 4C & D: ATRIAL STRUCTURAL REMODELING IN HYPERTENSION.....	120
	FIGURE 5: ATRIAL ELECTRO-STRUCTURAL CORRELATE	121
	FIGURE 6: REMODELING OCCURS AT DIFFERENT TIME DOMAINS	122
	CHAPTER FIVE.....	123
	ATRIAL REMODELING IN AN OVINE MODEL OF	123
	ANTHRACYCLINE-INDUCED NON-ISCHEMIC CARDIOMYOPATHY: “REMODELING OF THE SAME SORT”	123
5.1	INTRODUCTION.....	123
5.2	METHODS	124
	<i>5.2.1 Doxorubicin Non-ischemic Cardiomyopathy Model.....</i>	<i>124</i>
	<i>5.2.2 General Anesthesia</i>	<i>125</i>

5.2.3	<i>Cardiac Functional Assessments</i>	126
5.2.4	<i>Electrophysiological Study</i>	126
5.2.4.1	Atrial ERP.....	127
5.2.4.2	Atrial Conduction	127
5.2.4.3	Direction-dependent Conduction Abnormalities	128
5.2.4.4	P-wave Duration	129
5.2.4.5	AF Inducibility and Duration	129
5.2.5	<i>Structural Analysis</i>	129
5.2.6	<i>Statistical Analysis</i>	130
5.3	RESULTS	131
5.3.1	<i>Atrial Functional Remodeling due to Doxorubicin Cardiomyopathy</i>	132
5.3.2	<i>Atrial Electrical Remodeling due to Doxorubicin Cardiomyopathy</i>	132
5.3.2.1	Atrial Refractoriness	132
5.3.2.2	Atrial Conduction	133
5.3.2.3	Direction-dependent Conduction Abnormalities	134
5.3.2.4	P wave Duration.....	134
5.3.2.5	AF Inducibility and Duration	134
5.3.3	<i>Atrial Structural Remodeling due to Doxorubicin HF</i>	135
5.4	DISCUSSION	135
5.4.1	<i>Rapid Ventricular Pacing Model of HF</i>	136
5.4.2	<i>Advantages of Doxorubicin Non-Ischemic Cardiomyopathy Model</i>	137
5.4.3	<i>Remodeling of the Same Sort?</i>	138
5.4.4	<i>Clinical Significance</i>	140
5.4.5	<i>Study Limitations</i>	140

5.5	CONCLUSION	141
	TABLE 1: ANIMAL CHARACTERISTICS.....	142
	FIGURE 1: ATRIAL ERP	143
	FIGURE 2: ATRIAL CONDUCTION.....	144
	FIGURE 3: ATRIAL ACTIVATION MAPS AND PHASE HISTOGRAMS	145
	FIGURE 4: REPRESENTATIVE PICROSIRIUS RED SECTIONS.....	146
	FIGURE 5: QUANTIFICATION OF COLLAGEN MATRIX	147
	CHAPTER SIX.....	148
	ATRIAL PROTECTIVE EFFECTS OF N-3 POLYUNSATURATED FATTY ACIDS: A LONG TERM STUDY IN OVINE CHRONIC HEART FAILURE.....	148
6.1	INTRODUCTION.....	148
6.2	METHODS	149
	<i>6.2.1 Study Protocol</i>	<i>149</i>
	<i>6.2.2 Doxorubicin Non-ischemic Cardiomyopathy Model.....</i>	<i>150</i>
	<i>6.2.3 n-3 PUFAs Supplementation Protocol</i>	<i>151</i>
	<i>6.2.4 Cardiac Functional Assessments</i>	<i>151</i>
	<i>6.2.5 Electrophysiological Study.....</i>	<i>152</i>
	<i>6.2.5.1 Atrial ERP.....</i>	<i>152</i>
	<i>6.2.5.2 Atrial Conduction</i>	<i>153</i>
	<i>6.2.5.3 P-wave Duration</i>	<i>154</i>
	<i>6.2.5.4 AF Inducibility and Duration</i>	<i>154</i>

6.2.6	<i>Structural Analysis</i>	154
6.2.7	<i>Statistical Analysis</i>	155
6.3	RESULTS	155
6.3.1	<i>n-3 PUFAs and Cardiac Functional Remodeling</i>	157
6.3.2	<i>n3-PUFAs and Atrial Electrical Remodeling</i>	157
6.3.2.1	Atrial Refractoriness	157
6.3.2.2	Atrial Conduction	158
6.3.2.3	P wave Duration.....	159
6.3.2.4	AF Inducibility and Duration	159
6.3.3	<i>n3-PUFAs and Atrial Structural Remodeling</i>	159
6.4	DISCUSSIONS	160
6.4.1	<i>Lessons from Existing Studies: Importance of Underlying Substrate</i>	161
6.4.2	<i>n3-PUFAs in Heart Failure</i>	162
6.4.3	<i>Atrial Electrophysiology and n-3 PUFAs</i>	163
6.4.4	<i>Clinical Significance</i>	165
6.4.5	<i>Study Limitations</i>	166
6.5	CONCLUSIONS	166
	TABLE 1: ANIMAL CHARACTERISTICS	167
	FIGURE 1: MODEL TIMELINE	168
	FIGURE 2: ATRIAL ERP	169
	FIGURE 3: ATRIAL CONDUCTION	170
	FIGURE 4: ACTIVATION MAPS AND PHASE HISTOGRAMS	171

FIGURE 5: REPRESENTATIVE PICROSIRIUS RED STAINS.....	172
CHAPTER SEVEN	173
FINAL DISCUSSIONS	173
CHAPTER EIGHT	177
FUTURE DIRECTIONS.....	177
APPENDIX 1	179
CUSTOM DESIGNED EPICARDIAL PLAQUE	179
CHAPTER NINE.....	180
REFERENCES	180

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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Publications and Communications to Learned Societies

Chapter Two

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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)
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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)

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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