ATRIAL ELECTROPHYSIOLOGICAL & STRUCTURAL CHANGES IN OBESITY & DIABETES MELLITUS

Melissa Neo

BSc. (Hons)

Centre for Heart Rhythm Disorders

The School of Medicine

The University of Adelaide

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To my beloved parents, Peter & Stella,

My sister Valerie,

& my partner Wei Wen

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ABSTRACT

Atrial fibrillation (AF) is the most commonly presented arrhythmia in the clinical setting, and its prevalence contributes significantly towards morbidity and mortality rates in the general population. Obesity and diabetes mellitus (DM, type I and type II DM) are recognised, well established independent risk factors of AF which can occur and contribute towards the development of AF both individually and in a concomitant fashion. The pathophysiological processes by which a proarrhythmic atrial substrate is produced in obesity and DM have not been fully elucidated. Further characterisation of the atrial substrate in obesity and DM induced AF is required.

Chapter one addresses the mechanistic components which may contribute towards establishing AF, and discusses the early and current insights underlying the pathogenesis of AF; This chapter describes the current literature available on the electrophysiological and structural components which may lead to the development of a vulnerable atrial substrate; these include the role of the action potential (AP), the relationship between the AP and the effective refractory period (ERP), and the contribution of inflammation and fibrosis towards AF development.

Chapter two investigates the feasibility and result of combined application of simultaneous high density conduction mapping with intracellular membrane potential recording to better understand the genesis and maintenance of arrhythmias in the isolated atria. Described are the ability to observe changes in action potential (AP) morphology at a given recording region, regional differences in AP restitution, lack of correlation between AP duration (APD) and the atrial effective refractory period (ERP), and AP alternans in amplitude, and, duration.

Chapter three assesses electrophysiological and structural changes in a rat model of type I DM (T1DM) using streptozotocin (STZ), which preferentially exerts toxicity to the insulin-producing beta cells of the pancreas to elicit the T1DM phenotype. This chapter demonstrates the impact of untreated T1DM on the atrial myocardium. At the structural level, T1DM animals demonstrated atrial cardiomyocyte hypertrophy with increased fibrosis. At the electrophysiological level, there was an abbreviation of the ERP with increased heterogeneity in conduction, as well as prolongation of the AP.

Chapter four describes the impact of obesity, type II DM (T2DM) and age on the electrical and structural properties of the atria using the Zucker (fa/fa) rat model. This chapter reports cardiomyocyte hypertrophy, increased fibrosis, prolongation of the APD, increased heterogeneity and slowed conduction, with differences in ERP between the left and right atrium of the DM animals. These results highlight the potential difference between the pathogenesis of T2DM from T1DM on the atrial myocardium in the predisposition towards development of AF.

Chapter five summarises the observations made in the T1DM and T2DM studies of chapters three and four respectively; this chapter discusses the similarities and differences shared in the data obtained from the studies, with a brief description of the potential mechanisms involved in DM-induced pathogenesis of AF, Additionally, the potential importance of segregating the diabetic states as having individual and differential influences on the atrial myocardium is highlighted. Future directions and areas of further research conclude this chapter.

THESIS DECLARATION

I certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name, 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. In addition, I certify that no part of this work will, in the future, be used in a submission in my name, for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint-award of this degree.

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Melissa Neo

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PUBLICATIONS AND COMMUNICATION TO LEARNED SOCIETIES

Chapter two

1. **Manuscript:** Simultaneous conduction mapping and intracellular membrane potential recording in isolated atria. Melissa Neo, David G. Morris, Pawel Kuklik, Dennis H. Lau, Hany Dimitri, Wei-Wen Lim, Prashanthan Sanders, David A. Saint. *Canadian Journal of Physiology and Pharmacology*, 2016, 94(5): 563-569, 10.1139/cjpp-2015-0194 (Accepted manuscript)
2. **Presentation:** Presented at the Cardiac Society of Australia and New Zealand Conference, August 2011, Perth, Australia
3. **Presentation:** Presented at the Faculty of Health Sciences Postgraduate Expo, August 2011, Adelaide, Australia

Chapter three

1. **Manuscript:** A Rodent Model of Streptozotocin-Induced Type 1 Diabetes: A Substrate for Atrial Fibrillation. Melissa Neo, Wei Wen Lim, Dennis H. Lau, Prashanthan Sanders, David A. Saint. (prepared in publication format)
2. **Presentation:** Presented at the Heart Rhythm Society Conference, May 2012, Boston, United States of America
3. **Presentation:** Presented at the the Asia Pacific Heart Rhythm Society Conference, October 2012, Taipei, Taiwan
4. **Presentation:** Presented at the Australian Physiological Society Conference, November 2014, Brisbane, Australia

5. **Presentation:** Presented at the Faculty of Health Sciences Conference, September 2014, Adelaide, Australia
6. **Presentation:** Presented at the Heart Rhythm Society Conference, May 2015, Boston, United States of America
7. **Presentation:** Presented at the Cardiac Society of Australia and New Zealand (CSANZ) Conference, August 2015, Melbourne, Australia

Chapter four

1. **Manuscript:** Obesity, Diabetes and Age: Risk factors for a proarrhythmic substrate for Atrial Fibrillation in a Rat Model of Type II Diabetes Mellitus. Melissa Neo, Wei Wen Lim, Dennis H. Lau, Prashanthan Sanders, David A. Saint. (prepared in publication format)
2. **Presentation:** Presented at the Cardiac Society of Australia and New Zealand (CSANZ) Conference, August 2012, Brisbane, Queensland.
3. **Presentation:** Presented at the Asia Pacific Heart Rhythm Society (APHRS) Conference, October 2012, Taipei, Taiwan
4. **Presentation:** Presented at the the Cardiac Society of Australia and New Zealand (CSANZ) Conference, August 2013, Gold Coast, Australia
5. **Presentation:** Presented at the Cardiac Society of Australia and New Zealand (CSANZ) Conference, August 2015, Melbourne, Australia
6. **Presentation:** Presented at the Heart Rhythm Society Conference, May 2016, San Francisco, United States of America

PRIZES AND AWARDS DURING CANDIDATURE

1. International Society for Heart Research Travel Bursary for CSANZ 2013
2. Australian Physiological Society Student Travel Claim for AUPS 2014
3. International Society for Heart Research Travel Bursary for CSANZ 2015
4. Heart Foundation E O Myers Trust Fund Travel Grant 2015

ABBREVIATIONS

Abbreviation	Explanation
AF	Atrial fibrillation
ACE	Angiotensin converting enzyme
Ang II	Angiotensin II
AP	Action potential
APD_{20}, APD_{50}, APD_{80}, APD_{90}	Action potential duration at 20, 50, 80, 90% of repolarisation respectively
AT1R	Angiotensin receptor type 1
BMI	Body mass index
CAF	Chronic atrial fibrillation
CamKII	Ca^{2+}/calmodulin-dependent protein kinase II
CHF	Congestive heart failure
CHI	Conduction heterogeneity index
CPAP	Continuous positive airway pressure
CRP	C-reactive protein
CV	Conduction velocity
Cx 40, 43	Connexin 40, 43
DAD	Delayed after depolarisation
DM	Diabetes mellitus
ELISA	Enzyme-linked immunosorbent assay
EPS	Electrophysiology study
ERP	Effective refractory period
fa/fa	Zucker rat fatty gene
GLUT2	Glucose transporter 2
HbA1c	Haemoglobin A1c (Glycated haemoglobin)
hs-CRP	High-sensitivity C-reactive protein
I_{CaL}	L-type Ca^{2+} current
ICAM-1	Intercellular Adhesion Molecule 1
IFN-γ	Interferon-γ
I_{K1}	Inward rectifier K^+ current

I_{Kr}	Rapid delayed rectifier K^+ current
I_{Ks}	Slow delayed rectifier K^+ current
I_{Kur}	Ultra-rapid delayed rectifier K^+ current
IL-1,6,8,10	Interleukin-1,6,8,10
I_{to}	K^+ transient outward current
IVC	Inferior vena cava
Kir	Inwardly rectifying potassium channel(s)
Kv	Voltage gated potassium channel(s)
LA	Left atrium
LDL-C	Low density lipoprotein-C
LV	Left ventricle
MCP-1	Monocyte chemoattractant protein-1
MEA	Multi-electrode array
NCX	Na^+/Ca^{2+} exchanger
NDP	NanoZoomer digital pathology system
NFκB	Nuclear factor kappa-B (light-chain-enhancer of activated B cells)
OSA	Obstructive sleep apnea
P_5, P_{50}, P_{95}	Phase mapping percentiles 5, 50 and 95
PAF	Paroxysmal atrial fibrillation
Pro-BNP	Pro B-type natriuretic peptide
RA	Right atrium
ROS	Reactive oxygen species
RV	Right ventricle
RyR	Ryanodine receptor
SAC	Stretch-activated ion channels
SERCA or SERCA2a	Sarco/endoplasmic reticulum Ca^{2+}-ATPase
SHIMP	Simultaneous high density mapping and intracellular membrane potential recording
SR	Sarcoplasmic reticulum
STZ	Streptozotocin

SVC	Superior vena cava
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
TGF-β1	Transforming growth factor beta 1
TIMP-1	TIMP metallopeptidase inhibitor 1
TNF-α	Tumor necrosis factor-α
Zfr	Zucker fatty rat