ACUTE AND CHRONIC ATRIAL REMODELING IN OBSTRUCTIVE SLEEP APNOEA: IMPLICATIONS FOR ATRIAL FIBRILLATION

By

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Dedicated to

My Mother

My Father

&

My wife Rhiannon

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ABSTRACT

Atrial fibrillation (AF), the most common sustained arrhythmia, has been well studied; however, its underlying mechanisms and relationships to other disease processes have not been fully explored. Observational data from epidemiological studies have suggested a relationship between obstructive sleep apnoea (OSA) and AF. Recent clinical studies have implicated an adverse outcome to therapy in patients with AF and OSA. Despite several candidate mechanisms advanced, the acute and chronic changes to the atrial myocardium have not been fully characterised.

This thesis evaluates symptomatic patients with AF presenting for radiofrequency ablation of their arrhythmia. The acute and chronic electrophysiological and electroanatomical atrial substrate is characterised. Finally the effect on clinical outcomes of therapy directed at AF is evaluated with specific reference to the presence of OSA.

Chapter 2 demonstrates the differences in the atrial substrate in paroxysmal and persistent AF. This study found persistent AF was associated with a reduction in electrogram voltage and greater signal fragmentation, with these two attributes being negatively associated.

Chapter 3 examines patients presenting with symptomatic AF, previously not known to have sleep disordered breathing. OSA was associated with a greater symptomatic burden of AF as well as chronicity of the arrhythmia. In the presence of more severe OSA, there was a greater chance of failure of radiofrequency ablation in maintaining sinus rhythm.

Chapter 4 characterises the underlying atrial substrate resulting in AF in patients with moderate to severe untreated OSA. OSA patients had larger atria, greater areas of low voltage and areas of electrical silence, suggesting loss of atrial myocardium. There were also markedly reduced conduction velocities, longer corrected sinus node recovery times and more conduction abnormalities characterised by complex electrograms. These findings provide important insights into the adverse remodeling that may allow AF to develop and persist in these patients, and promote the failure of ablation strategies.

Chapter 5 examines nocturnal atrial electrophysiological alterations resulting from acute episodes of respiratory disturbance associated with hypopnoea and obstructive apnoea events the night after undergoing radiofrequency ablation for AF. Dynamic changes in effective refractory period (ERP), conduction times and conduction delay along linear catheters were documented. The changes appeared to be more marked for obstructive apnoeas than hypopnoeas. This study suggests a dynamic, pro-arrhythmic electrical substrate that could potentially lead to nocturnal triggering of AF and its maintenance.

Finally, Chapter 6 describes an *ex-vivo* rabbit model, created to examine the acute effects of hypoxia (moderate and severe) and hypercapnia. Left atrial ERP, conduction time and conduction heterogeneity were studied using a customised microelectrode array. During hypoxia, there was a dose dependent increase in ERP with only partial resolution on restoration of baseline oxygen levels. With hypercapnia, there was a slower rise in ERP that did not appear to recover. Slowing of conduction was most noted in severe hypoxia, with

only partial resolution in recovery. In hypercapnia, there was progressive slowing of conduction into recovery. Conduction heterogeneity was also increased in the presence of hypoxia and hypercapnia. These findings further suggest complex alterations to the atrial electrophysiology in the presence of hypoxia and hypercapnia, with dynamic changes to in refractory periods, conduction times and heterogeneity.

Together, a greater understanding of the acute and chronic effects of OSA on AF, and an appreciation of the failure of ablation strategies in the presence of this breathing disorder is attained. This paves the way for further studies on the mechanisms involved, and on the potential role for continuous positive airway pressure therapy (CPAP) in the management of patients with OSA and AF.

DECLARATION

This work was performed by the candidate at the Centre for Heart Rhythm Disorders at the University of Adelaide and Royal Adelaide Hospital, South Australia (during the years 2007 through 2011).

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. The author acknowledges that copyright of published works derived from this thesis (specifically, chapter 4) resides with the copyright holder of those works.

Hany Dimitri, Michelle Ng, Anthony G. Brooks, Pawel Kuklik, Martin K. Stiles, Dennis H. Lau, Nicholas Antic, Andrew Thornton, David A. Saint, Doug McEvoy, Ral Antic, Jonathan M. Kalman, Prashanthan Sanders. Atrial remodeling in obstructive sleep apnea: Implications for atrial fibrillation . *Heart Rhythm*. 2011;9:321-327

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SCHOLARSHIPS DURING CANDIDATURE

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PUBLICATIONS AND COMMUNICATIONS TO LEARNED SOCIETIES

CHAPTER 2:

ORAL PRESENTATION: CARDIAC SOCIETY OF AUSTRALIA AND NEW ZEALAND SCIENTIFIC SESSIONS 2008

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ABBREVIATIONS

AF	atrial fibrillation
AHI	apnoea hypopnoea index
CFAE	complex fractionated atrial electrograms
CPAP	continuous positive airway pressure
CSA	central sleep apnoea
CSNRT	corrected sinus node recovery time
ERP	effective refractory period
HR	hazard ratio
IQR	interquartile range
LA	left atrium
LV	left ventricle
OR	odds ratio
OSA	obstructive sleep apnoea
RA	right atrium
RDI	respiratory disturbance index
RR	relative risk
RV	right ventricle
SDB	sleep disordered breathing