

Reverse Atrial Electrical Remodeling Induced by Continuous Positive Airway Pressure
in Patients with Severe Obstructive Sleep Apnea

by

Helen Wai Kiu Pang

A thesis submitted to the Physiology Graduate Program in the Department of
Biomedical and Molecular Sciences in conformity with the
requirements for the degree of Master of Science

Queen's University,

Kingston, Ontario, Canada

July, 2011

Copyright © Helen Wai Kiu Pang, 2011

ABSTRACT

Background: Obstructive sleep apnea (OSA) has been associated with atrial enlargement in response to high arterial and pulmonary pressures and increased sympathetic tone. Continuous positive airway pressure (CPAP) is the gold standard treatment for OSA; its impact on atrial electrical remodeling has not been investigated however. Signal-averaged p-wave (SAPW) is a non-invasive quantitative method to determine p-wave duration, an accepted marker for atrial electrical remodeling. The objective was to determine whether CPAP induces reverse atrial electrical remodeling in patients with severe OSA.

Methods: Prospective study in consecutive patients attending the Sleep Clinic at Kingston General Hospital. All patients underwent full polysomnography. OSA-negative and severe OSA were defined as apnea-hypopnea index (AHI) < 5 events/hour and $\text{AHI} \geq 30$ events/hour, respectively. In severe OSA patients, SAPW was determined pre- and post-intervention with CPAP for 4 - 6 weeks. In OSA-negative controls, SAPW was recorded at baseline and 4 - 6 weeks thereafter without any intervention.

Results: A total of 19 severe OSA patients and 10 controls were included in the analysis. Mean AHI and minimum O_2 saturation were 41.4 ± 10.1 events/hour and $80.5 \pm 6.5\%$ in severe OSA patients and 2.8 ± 1.2 events/hour and $91.4 \pm 2.1\%$ in controls. Baseline BMI was different between severe OSA patients and controls (34.3 ± 5.4 vs 26.6 ± 4.6 kg/m^2 ; $p < 0.001$). At baseline, severe OSA patients had a greater SAPW duration than controls (131.9 ± 10.4 vs 122.8 ± 10.5 ms; $p = 0.02$). After CPAP intervention, there was a significant reduction of SAPW duration in severe OSA (131.9 ± 10.4 to 126.2 ± 8.8 ms; $p < 0.001$). In controls, SAPW duration did not change within 4 - 6 weeks.

Conclusion: CPAP induced reverse atrial electrical remodeling in patients with severe OSA as represented by a significant reduction in SAPW duration.

ACKNOWLEDGEMENTS

I am sincerely thankful to my supervisor, Dr. Adrian Baranchuk, for all the support and guidance he provided me throughout my graduate studies. I am grateful for all the learning opportunities that he has given me and I am certain that the completion of this thesis would not have been possible without his guidance.

I would also like to express gratitude to the physicians at the Sleep Clinic who have assisted me in patient recruitment: Dr. Michael Fitzpatrick, Dr. Peter Munt, and Dr. Ron Wigle. As well, I thank all of those who have helped me in any respect during the completion of this project.

Lastly, I thank my parents for supporting and motivating me as always.

I acknowledge the Clinical Teacher's Association at Queen's for their financial support for this project.

TABLE OF CONTENTS

Abstract	i
Acknowledgements	iii
Table of Contents	iv
List of Tables	vi
List of Figures	vii
List of Abbreviations	viii
CHAPTER 1: GENERAL INTRODUCTION	1
Obstructive Sleep Apnea	1
Atrial Remodeling.....	3
Structural Remodeling.....	3
Electrical Remodeling	4
Cardiac Arrhythmias in OSA.....	6
Atrial Fibrillation.....	7
Substrates of AF in OSA	8
Atrial Enlargement	9
Other Mechanisms.....	11
P-wave Duration	12
Signal-Averaged P-Wave	12
Reverse Atrial Remodeling.....	13
Treatment Options for OSA.....	14
Continuous Positive Airway Pressure	14
Alternative Treatments	16
Summary	17
CHAPTER 2: METHODS AND MATERIALS	18
Overview	18
Inclusion Criteria	19
Exclusion Criteria	19

Polysomnography	20
Split-night Polysomnography	21
High-resolution P-wave Signal-Averaging	21
Outcome Assessment	22
Statistical Analysis	22
CHAPTER 3: RESULTS	24
Study Population	24
SAPW Duration Pre- and Post-intervention	27
Correlation between SAPW and Polysomnography Measurements	27
Correlation between SAPW and Clinical Characteristics	27
Magnitude of Changes in SAPW	33
Polysomnography Measurements Pre- and Post- CPAP	33
Correlation between Changes in SAPW and Changes in AHI	37
CHAPTER 4: DISCUSSION	39
Major Findings	39
SAPW Duration is increased in OSA	40
SAPW is Correlated with AHI	41
CPAP Treatment Reduces SAPW Duration	41
Limitations	43
Future Directions	44
Conclusion	46
Literature Cited	47
Appendix A	58
Appendix B	62

LIST OF TABLES

Table 1	Reasons for exclusion	25
Table 2	Clinical characteristics and polysomnography measurements	26
Table 3	SAPW duration pre- and post- intervention	28
Table 4	Polysomnography measurements and SAPW pre- and post-CPAP	36

LIST OF FIGURES

Figure 1	Reentry of conduction impulse.....	5
Figure 2	Atrial enlargement and reentry.....	10
Figure 3	SAPW analysis.....	23
Figure 4	SAPW duration vs. AHI.....	29
Figure 5	SAPW duration vs. O ₂ saturation.....	30
Figure 6	SAPW duration vs. age.....	31
Figure 7	SAPW duration vs. BMI.....	32
Figure 8	Changes in SAPW duration vs. AHI.....	34
Figure 9	Changes in SAPW duration vs. baseline SAPW duration.....	35
Figure 10	Changes in SAPW duration vs. changes in AHI.....	38

LIST OF ABBREVIATIONS

ABBREVIATION	TERM
AF	Atrial fibrillation
AHI	Apnea-hypopnea index
BMI	Body mass index
CPAP	Continuous positive airway pressure
ERP	Effective refractory period
LA	Left atrial
OSA	Obstructive sleep apnea
Pd	P-wave dispersion
Pmax	Maximum p-wave duration
SAPW	Signal-averaged p-wave

CHAPTER 1: GENERAL INTRODUCTION

Obstructive Sleep Apnea

Obstructive sleep apnea (OSA), the most extreme variant of sleep-disordered breathing, is a chronic airway disease caused by the complete or partial occlusion of the upper airway, resulting in the reduction or cessation of breathing during sleep.

Intermittent apneas and hypopneas are followed by blood oxygen desaturation, persistent respiratory attempts against the occluded airway, and finally termination by arousal from sleep (Arias & Sanchez, 2007). This interrupted ventilation during sleep may result in detrimental changes in autonomic, vascular, and hemodynamic regulation (Gami *et al.* 2005).

The diagnosis and severity of OSA are best determined by polysomnography. The severity is represented by the number of apneas and hypopneas per hour of sleep, the apnea-hypopnea index (AHI), or by the magnitude of oxygen desaturation throughout the night. A diagnosis of OSA is made when a patient demonstrates an $AHI \geq 5$ events/hour and displays symptoms of daytime somnolence. Common AHI cut-points of 5, 15, and 30 are used to indicate mild, moderate, and severe OSA, respectively (Young *et al.* 2004).

The prevalence of OSA is high in North America; OSA affects approximately 4% of the middle-aged male population and 2% of the female (Young *et al.* 1993). Up to 5% of adults in western countries have undiagnosed OSA (Young *et al.* 2002).

The risk factors for OSA are male gender, obesity, genetic predisposition, as well as craniofacial and upper airway abnormalities (Young *et al.* 2004).

Continuous positive airway pressure (CPAP) is the treatment of choice for OSA. It involves a nasal mask connected to a machine that continuously delivers compressed positive air to prevent the airway from collapsing during sleep (Ballester *et al.* 1999). Other treatment options are generally less effective, including uvulopalatopharyngoplasty (Sher *et al.* 1996) and oral-appliance device (Gotsopoulos *et al.* 2002).

The nocturnal intermittent apneas lead to a series of physiological disturbances: hypoxemia, hypercapnia, heightened sympathetic activity, shifts in intrathoracic pressure, vascular oxidative stress, and systemic inflammation (Gami *et al.* 2005). These triggered responses evoke acute and chronic changes in both neurobehavioral and cardiovascular functions (Hersi, 2010), which are responsible for the clinical complications including daytime somnolence, hypertension, stroke, and clinical depression (Oflaz *et al.* 2006). Cardiovascular disturbances remain the most serious and the least manageable complications increasing morbidity and mortality.

OSA is associated with multiple cardiac structural and functional abnormalities such as atrial enlargement, ventricular hypertrophy, and left ventricular dysfunction (Otto *et al.* 2007). Repetitive inspiratory efforts against the occluded airway generate significant shifts in intrathoracic pressure that can approach -65 mm Hg, increasing cardiac wall stress and atrial size (Somers *et al.* 2008). Heightened sympathetic tone and endothelial dysfunction associated with OSA elevate systemic blood pressure, increase afterload, and consequently promote ventricular hypertrophy (Budhiraja *et al.* 2007). Furthermore, OSA has been reported to induce atrial remodeling at the structural and electrical level, which may implicate in the development of cardiac arrhythmias.

Atrial Remodeling

Atrial remodeling is a phenomenon to describe persistent alterations in atrial tissue properties or function. The concept of atrial remodeling was first introduced in 1995 by Wijffels *et al*, who demonstrated that atrial fibrillation (AF) in goats induces atrial functional alterations that favour the maintenance of AF – “atrial fibrillation begets atrial fibrillation”. The emergence of this concept significantly enhanced our understanding of the pathophysiology implicated in atrial arrhythmias. In simplest terms, altered atrial structure or function may increase the likelihood of ectopic and reentrant activity, thus providing a substrate for the development of arrhythmias (Allessie *et al*. 2002). Amongst the clinical scenarios, the role of atrial remodeling as a cause or result of AF specifically has received increasing attention in recent literature.

Structural Remodeling

Reduced atrial contractility, development of fibrosis, and most importantly, atrial enlargement are the major characteristics of atrial structural remodeling. The compromised atrial contractile function is a result of the loss of sarcomeres or reduced Ca^{2+} release from the sarcoplasmic reticulum (Allessie *et al*. 2002). A reduction of ~75% in contractile force of right atrial appendages in chronic AF patients compared to controls had been reported (Schotten *et al*. 2001). Furthermore, interstitial fibrosis and its promotion of AF have also been documented. Studies using transgenic mice with cardiac-restricted overexpression of angiotensin-converting enzyme (Xiao *et al*. 2004) or transforming growth factor- β 1 (Verheule *et al*. 2004) reported a concurrent increase in atrial fibrosis and AF propensity. The loss of contractility and the formation of interstitial

fibrosis synergistically contribute to the atrial enlargement present in patients with AF or atrial tachyarrhythmias. In a canine model, echocardiography revealed enlargement of both atria after rapid atrial pacing for 6 weeks (Morillo *et al.* 1995). Atrial enlargement, especially left atrial (LA) enlargement, may also result from obesity, hypertension (Stritzke *et al.* 2009), and mitral stenosis (Keren *et al.* 1987), in which the left atrium must exert greater pressures to efficiently pump the blood. An increased atrial size is able to accommodate more reentry circuits (Figure 1) and is an important clinical predictor for the development and maintenance of AF (Henry *et al.* 1976). Some studies also demonstrated that increased LA size is associated with increased AF recurrence following catheter ablation (Parikh *et al.* 2010) or cardioversion (Volgman *et al.* 1996) for AF. Although seemingly detrimental, structural remodeling may actually be an adaptive response to the underlying disease.

Electrical Remodeling

In AF, atrial electrical remodeling is best represented by the shortening of atrial effective refractory period (ERP) and the loss of rate adaptation, and also includes spatial heterogeneity of atrial refractoriness and conduction velocity (Misier *et al.* 1992). The concept of atrial electrical remodeling was first introduced by Morillo *et al.* and Wijffels *et al.* in 1995, who concomitantly showed the shortening of atrial ERP in dogs with rapid atrial pacing and goats with sustained AF, respectively. The canine model also demonstrated increases in p-wave duration, dispersion in refractoriness, and vulnerability to AF. In contrast to structural remodeling, electrical remodeling occurs rapidly within days of AF and ERP reaches a new steady state within a few days (Wijffels *et al.* 1995). Refractory period abbreviation is attributable to the down-regulation of L-type Ca^{2+}

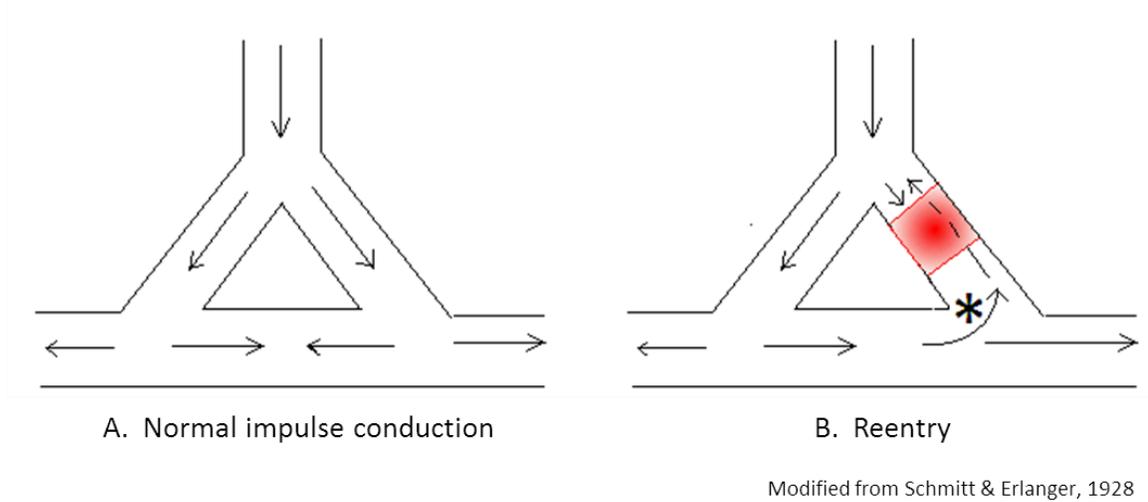


Figure 1. A. The propagation of an impulse in normal cardiac tissue. B. The antegrade propagation encounters a unidirectional block. The block may be a result of spatial heterogeneity of atrial ERP. The asterisk (*) indicates reentry of the impulse at previously inactivated area in a retrograde manner.

current (I_{CaL}) as a result of Ca^{2+} accumulation within atrial myocytes due to rapid atrial activation (Van Wagoner *et al.* 1999). The abbreviation in refractory periods shortens the wavelengths of atrial impulse, favouring the occurrence of multiple wavelet reentry and subsequently increasing the susceptibility to AF or stability of AF (Nattel *et al.* 2000).

While atrial *structural* remodeling in OSA has been well documented (Otto *et al.* 2007), atrial *electrical* remodeling is far less understood. Enlargement of the left atrium associated with OSA may well contribute to its electrical remodeling. Although it is established that arrhythmias are common amongst OSA patients (Mehra *et al.* 2006), the underlying mechanisms and etiological aspect remain controversial. Understanding the role of electrical remodeling in OSA will provide valuable insights into the pathophysiology of arrhythmias associated with the disease.

Cardiac Arrhythmias in OSA

Cardiac arrhythmias are one of the major cardiovascular complications in OSA (Todd *et al.* 2010). An elegant study by Hoffstein & Mateika (1994) demonstrated that cardiac arrhythmias are more prevalent in OSA patients than controls (58% vs 42%; $p < 0.0001$), and that the frequency of arrhythmias increases with the severity of OSA (70%; $AHI \geq 40$). Another study of morbidly obese patients supported an increased risk of arrhythmias in severe OSA patients ($AHI \geq 65$) (Valencia-Flores *et al.* 2000).

Furthermore, an earlier study also documented a high prevalence of cardiac arrhythmias in 400 OSA patients (48%, $AHI \geq 5$) (Guilleminault *et al.* 1983). In contrast, a study by Flemons *et al.* (1993) showed that the prevalence of arrhythmias in 76 OSA patients ($AHI \geq 10$) was low and did not differ significantly from controls. The discrepancy of these

findings may be explained by selection bias in that the inclusion criteria and severity of OSA in patients differed between studies.

Atrial Fibrillation

Amongst the cardiac arrhythmias associated with OSA, AF has received substantial attention. AF is the most common cardiac arrhythmia and accounts for one-third of all arrhythmia hospitalization (Fuster *et al.* 2006). It is associated with heart failure and a twofold increase in overall mortality (Feinberg *et al.* 1995). Cardiac diseases such as hypertension and coronary artery disease, as well as obesity, can increase the risk of AF (Fuster *et al.* 2006). Studies have identified chronic atrial stretch and structural changes as the common features of these conditions to the increased propensity for AF (John *et al.* 2010). A recent study also showed that in AF patients, OSA may increase the risk of stroke (Yazdan-Ashoori & Baranchuk, 2011).

Numerous studies supporting the association between OSA and AF have recently emerged one after another. A study by Guilleminault *et al.* (1983) reported a 3% prevalence of AF in 400 patients with moderate to severe OSA – three times that of the general population of 0.4% to 1% (Caples & Somers, 2009). A more recent Sleep Heart Health Study demonstrated an AF prevalence of 4.8% in patients with AHI ≥ 30 , which was five times that of controls (0.9%; AHI < 5) (Mehra *et al.* 2006). However, these results may have been inflated since there was no differentiation between OSA and CSA. Nevertheless, AF prevalence in OSA patients is generally increased. The reverse observation was also true; the proportion of OSA patients is significantly higher in patients with AF than in high-risk cardiovascular patients without AF (49% vs. 32%; $p =$

0.0004) (Gami *et al.* 2004). These observations were seen across other countries. A study from Japan of 1763 subjects reported an odds ratio for AF of 2.47 for mild sleep apnea ($5 \leq \text{AHI} < 15$) and 5.66 for moderate-severe sleep apnea ($\text{AHI} \geq 15$) after adjusting for confounders, suggesting the association of sleep apnea and AF is correlated with the severity of OSA (Tanigawa *et al.* 2006). In another cohort of 3542 patients with no previous history of AF, the diagnosis and severity of OSA predicted the incidence of AF over a period of 5 years (Gami *et al.* 2007). In addition, OSA patients ($\text{AHI} \geq 5$) also demonstrated a higher incidence of post-operative AF than controls after coronary artery bypass grafting surgery (39% vs. 18%; $p = 0.02$) (Mooe *et al.* 1996). Nonetheless, a handful of epidemiologic studies have reported contradicting results. A case-control study by Porthan *et al.* (2004) reported no difference in OSA prevalence between AF patients and controls matched for age, gender, and cardiovascular morbidity (32% vs. 29%). However, these results may have been influenced by selection bias since the control group was represented by snorers, which probably explains the high prevalence of OSA observed even in controls (Caples & Somers, 2008). Despite the few contradictory reports, it is generally accepted that the association between OSA and AF is firmly established, and that the frequency of AF is correlated with the severity of OSA (Todd *et al.* 2010).

Substrates of AF in OSA

Despite extensive efforts, it remains controversial whether OSA is a primary etiologic factor for AF. Proving this speculation has been unattainable due to the cardiovascular comorbidities often present in OSA patients, obscuring the link between OSA and AF (Somers *et al.* 2008). Nocturnal apneas and hypopneas in OSA occur for years and can lead to detrimental pathophysiologic effects possibly increasing the risk of

AF. The pathophysiologic effects associated with OSA include repetitive hypoxemia, increased sympathetic drive, fluctuations in intrathoracic pressure, and systemic inflammation, which may collectively promote atrial electrical remodeling and trigger the development of AF (Can *et al.* 2008).

Atrial Enlargement

Atrial enlargement is a well-recognized substrate associated with conduction abnormalities implicated in the increased propensity for AF (John *et al.*, 2010). Populations with clinical conditions associated with chronic stretch such as heart failure or hypertension demonstrated significant atrial enlargement and abnormal conduction (Sanders *et al.* 2003). As mentioned previously, physiological changes provoked by OSA, such as shifts in intrathoracic dynamic and augmented sympathetic tone may increase atrial stretch and afterload, ultimately contributing to atrial enlargement. Specifically, the increased systemic blood pressure can induce diastolic dysfunction, elevate left ventricular pressures, and promote LA enlargement (Baranchuk *et al.* 2008). Fung *et al.* (2002) reported a high frequency of abnormal diastole relaxation pattern in severe OSA patients (37%), determined by echocardiography, and that the diastolic dysfunction was related to the severity of OSA. An increased atrial size is able to accommodate more circuits, the electrical conduction of an impulse, and may increase the chance and occurrence of multiple-circuits reentry that can initiate AF (Figure 2) (Zou *et al.* 2005). At the molecular level, chronic atrial stretch may trigger the atrial stretch-activated ion channels involved in mechano-electrical feedback, promoting conditions that favour arrhythmogenesis (Franz & Bode, 2003). These ion channels pass Ca^{2+} , Na^{+} , and K^{+} non-selectively or K^{+} and Cl^{-} selectively, altering the membrane potential and disturbing

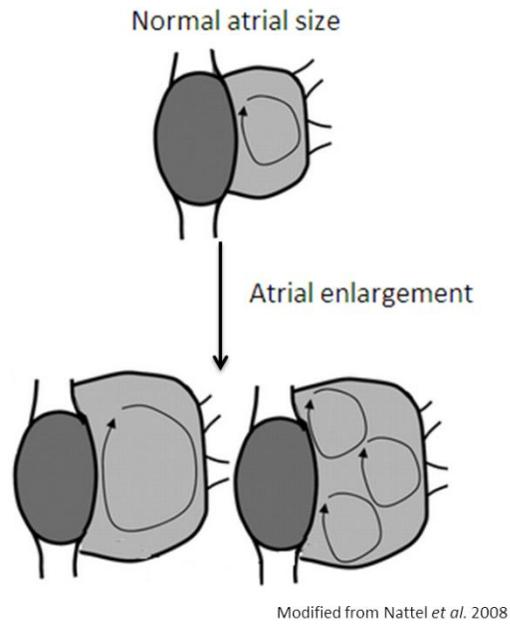


Figure 2. Atrial enlargement allows the existence of reentry circuits of longer wavelengths (left) and multiple reentry circuits (right).

regular atrial conduction. Consequently, atrial tissue becomes more vulnerable to AF. A study by Franz & Bode (2003) demonstrated reduced susceptibility to AF in atrial tissue after the application of stretch-activated channel blockers, gadolinium and GsMTx-4, suggesting a crucial role for the stretch-activated channels in the vulnerability for AF. It is important to note that atrial enlargement, although seemingly a mere structural remodeling, has the potential to induce serious electrical remodeling.

Other Mechanisms

In addition to elevating systemic blood pressure, the persistent enhanced sympathetic activity may also induce atrial electrical remodeling. It may abbreviate action potential duration and atrial refractoriness triggering automaticity by activating catecholamine-sensitive ion channels, subsequently increasing the atrial susceptibility to initiate AF (Huang *et al.* 1998).

Two studies reported that elevated level of C-reactive protein (CRP), an inflammatory marker, in OSA patients is proportional to the severity of OSA (Shamsuzzaman *et al.* 2002; Punjabi & Beamer, 2007). The association between increased CRP and AF has also been demonstrated (Chung *et al.* 2001).

Whether OSA directly causes or partially contributes to the development of AF as well as the exact mechanisms involved are yet to be revealed. The detrimental physiologic effects as a result of repetitive hypoxemia in OSA are intricate and cannot be easily studied or understood independently in human subjects. Furthermore, cardiovascular comorbidities and obesity often present in OSA patients further obscure the link of OSA and AF. Nonetheless, one may safely speculate that the physiologic

changes reviewed above can induce structural and electrical remodeling serving as a substrate, trigger, or initiator to the development of AF.

P-wave Duration

Electrocardiographic characterization of AF consists of an absence of p-waves, which are replaced with unorganized electrical activity. As mentioned above, atrial electrical remodeling associated with OSA may be a precursor of AF. An indirect marker for such electrical remodeling is the prolongation of atrial conduction time, represented by an increased maximum p-wave duration. Interestingly, prolonged p-wave is also indicative of an increased atrial size. Atrial conduction time can be quantitatively measured using non-invasive markers such as maximum p-wave duration (Pmax) and p wave dispersion (Pd) obtained with an electrocardiogram (ECG) (Can *et al.* 2008). P-wave dispersion is the difference between maximum and minimum p-wave duration. In various clinical settings, increases in Pmax and Pd have been used to predict AF development (Dilaveris & Gialafos, 2001). An elegant study by Can *et al.* (2008) reported a greater Pmax and Pd in OSA patients compared to controls (AHI < 5), and that Pd showed a positive correlation with the severity of OSA. The abnormal Pmax and Pd associated with OSA indicate a prolonged atrial conduction and an inhomogeneous propagation of sinus impulses, characteristics of the atrium prone to fibrillate.

Signal-Averaged P-wave

A more novel ECG marker for atrial electrical remodeling is the signal-averaged p-wave (SAPW) duration. In simplest terms, the average of all p-wave duration in consecutive heart beats is calculated using a computer program. Some studies have

demonstrated a prolonged SAPW can predict postoperative AF (Zaman *et al.* 1997). Interestingly, studies by Healey *et al.* (2004) and Chalfoun *et al.* (2007) concluded correspondingly that the change in SAPW, but not the direct measurement of SAPW, can predict the recurrence of AF. To the best of my knowledge, no studies have compared SAPW in OSA patients with controls.

Reverse Atrial Remodeling

Atrial remodeling is not a permanent event and has shown to be reversible by treatment in various clinical scenarios. For example, in patients with AF, the conversion to sinus rhythm is often accompanied by the reversal of atrial structural and electrical remodeling. Healey *et al.* (2004) showed a significant shortening of SAPW three days following successful atrial defibrillation in 44 patients who maintained sinus rhythm at 90 days (158 ± 28 to 152 ± 24 ms; $p = 0.009$). The shortening began immediately post-cardioversion and continued for at least three months. This is consistent with another study by Guo *et al.* (2003) that also reported shorter p-wave duration in patients who remained in sinus rhythm within six months post-cardioversion compared to those with AF recurrence (143 ± 17 vs 157 ± 24 ms; $p < 0.0001$). The shortening of SAPW duration and surface p-wave duration represent faster intra-atrial conduction and provide clear evidence for reverse atrial electrical remodeling. However, it remains inconclusive whether the reverse remodeling actually contributes to the maintenance of sinus rhythm. Similar findings were also demonstrated in a subsequent study (Chalfoun *et al.* 2007), which reported a significant reduction in SAPW post-cardioversion in 22 patients who maintained sinus rhythm at 1 month (159 ± 19 vs. 146 ± 17 ms; $p < 0.0001$).

The reversal of atrial electrical remodeling may be attributable to the structural changes after the treatment. John *et al.* (2010) reported that 21 patients with mitral stenosis showed improvements in conduction abnormalities after mitral commissurotomy. Atrial conduction velocity was improved, determined by electroanatomic mapping, and p-wave duration decreased, demonstrating evidence for reverse electrical remodeling. Correspondingly, fewer patients displayed sustained AF after the surgery (33% vs 19%), indicating a reduced vulnerability for AF. The authors speculated that the reverse remodeling resulted from the removal of chronic atrial stretch. More recently, Tops *et al.* (2011) reported a decrease in maximal LA volume following catheter ablation in patients with AF (30 ± 7 to 25 ± 7 ml/m², $p < 0.001$). Those who showed $> 15\%$ decrease in maximal LA volume were classified as responders and presented fewer AF recurrences than non-responders (12% vs. 69%, $p < 0.001$). These findings suggest that atrial structural and electrical remodeling are related and that the substrate predisposing to AF may be reversible by reversing atrial structural remodeling.

The findings of these studies investigating reverse atrial remodeling are intriguing. Although atrial enlargement and higher risk for cardiac arrhythmias have been reported in OSA, the reversibility of atrial remodeling in OSA has not yet been assessed. Previous studies suggest that atrial remodeling associated with OSA may be restored by treating the underlying disease.

Treatment Options for OSA

Continuous Positive Airway Pressure

There are a few treatment options for OSA. The current gold standard treatment is CPAP, which delivers a compressed positive air pressure to prevent the airway from

collapsing during sleep (Ballester *et al.* 1999). It is readily available and significantly less invasive than alternative therapies. CPAP improves sleep quality by eliminating apneas and improving nocturnal hypoxemia. A retrospective study (Meslier *et al.* 1998) in 3225 patients reported significant reduction in snoring, daytime sleepiness, and fatigue, symptoms associated with OSA. Despite the considerable benefits, general compliance to CPAP is low due to discomfort, nasal problems, and undesired noise (Pépin *et al.* 1995).

The benefits of CPAP treatment are not limited to the respiratory manifestations of OSA. A recent study reported a decrease in systolic and diastolic blood pressure in 178 patients treated with CPAP, providing evidence for improved cardiovascular functions from CPAP (Barbe *et al.* 2010). In particular, there is growing evidence that suggests CPAP can lower the incidence of AF in OSA patients. Kanagala *et al.* (2003) reported a lower rate of AF recurrence after cardioversion in OSA patients treated with CPAP compared to untreated patients (42 vs. 82%; $p = 0.01$). Moreover, control patients without diagnosed OSA showed a recurrence rate of 53%, significantly lower than that of untreated OSA patients, highlighting the role of OSA in compromised cardiovascular functions. The higher recurrence rate in controls than treated patients is probably because controls included patients with undiagnosed OSA. In another study, the use of CPAP abolished pathologically significant rhythm disturbances in 7 of the 8 severe OSA patients (Harbison *et al.* 2000). The only exception was found to have severe aortic valve disease justifying the persistent rhythm disturbance. In a prospective cohort study, Marin *et al.* (2005) showed a higher risk of cardiovascular events in severe OSA patients who were non-compliant with CPAP compared to treated patients. In another prospective study by Oliveira *et al.* (2009), only patients who received CPAP treatment showed

significant improvement in LA passive function represented by an increased LA passive emptying (28.8 ± 11.9 to $46.8 \pm 9.3\%$; $p = 0.01$) and a decreased LA active function (14 ± 6.5 to 6.3 ± 4.3 ml; $p = 0.05$), but not those who received sham CPAP. Furthermore, echocardiographic data of OSA patients showed an increase in LA volume of 15.5 ± 22.3 ml ($p < 0.006$) in CPAP-noncompliant patients while no significant change was observed in CPAP-compliant patients (Khan *et al.* 2008). In this study, CPAP showed a protective effect in the prevention of LA structural remodeling instead of reverse atrial remodeling. Although limited, initial results suggest that CPAP may reduce the risk of AF in OSA patients, probably by improving factors involved in the promotion of AF including hypertension, increased sympathetic drive, and systemic inflammation.

Alternative Treatments

Alternative OSA treatments and their effects on the reduction of AF incidence for OSA have also been explored. A study by Guilleminault *et al.* (1983) investigated the presence of cardiac arrhythmias or conduction abnormalities in 50 OSA patients before and after tracheostomy. Except for premature ventricular contractions, all arrhythmias were resolved post-tracheostomy including 8 patients who had AF. An initial report has proposed the use of atrial overdrive pacing in modulating cardiac rhythm in OSA patients (Garrigue *et al.* 2002). Although the concept is intriguing, a meta-analysis of 10 studies showed that atrial pacing was not therapeutically effective in treating the respiratory manifestations of OSA (Baranchuk *et al.* 2009). The role of pacing in sleep apnea is unclear. However, recent studies have reported that cardiac resynchronization therapy may help those with predominant central sleep apnea (Lamba *et al.* 2011). Its clinical benefits for OSA are yet to be assessed.

The knowledge that OSA therapies may potentially reduce the incidence or recurrence of AF not only emphasizes the importance of treating OSA, but also strengthens the causative relationship between OSA and AF. Studies suggest that CPAP treatment seems promising in reducing the burden of AF and other cardiac arrhythmias in OSA. Nonetheless, larger studies and more consistent results are necessary to affirm this notion.

Summary

OSA is a chronic disease associated with significant cardiac structural and electrical remodeling. The association between OSA and AF has been well established by previous studies. Atrial electrical remodeling, in addition to structural remodeling, plays a crucial role in promoting AF in OSA patients. Atrial electrical remodeling can be identified by a prolongation of the p-wave duration on an ECG, which has been reported in patients with OSA. Prolonged p-wave duration is a known predictor for AF. Therefore, it is in the best interest of OSA patients to identify those at risk for AF for immediate and effective treatment. A few studies have shown the ability of CPAP to attenuate the incidence or recurrence of AF. I speculate that the mechanism is through reversing atrial electrical remodeling.

The hypothesis of this study is that CPAP treatment in patients with severe OSA can resolve the p-wave abnormalities associated with the disease.

CHAPTER 2: MATERIALS AND METHODS

All procedures had been approved by the Health Sciences & Affiliated Teaching Hospitals Research Ethics Board of Queen's University, and are in accordance with the Helsinki declaration. All subjects have signed an informed consent upon participation.

Overview

During March 2009 to March 2011, patients who visited the sleep clinic at Kingston General Hospital, Kingston, Ontario, were screened by attending physicians for potential recruitment to the study. Physicians predicted the possibility of OSA based on the patient's reported symptoms, family history, and BMI. The patients who were suspected of severe OSA or OSA-negative were referred to me for recruitment. The details of the study were presented and explained thoroughly to the patient both orally and written. All questions and concerns, if any, were addressed to the patient's satisfaction. Should they decide to participate in the study, the patient was asked to provide written consent by signing the prepared consent form (Appendix 1). A photocopy of the consent form was given to each subject for personal records. After obtaining official consent, an initial SAPW recording was performed immediately. The subjects then attended their scheduled polysomnography as standard clinical procedure. Details of the SAPW recording technique and polysomnography are outlined below.

Each subject was either assigned to one of the two groups or excluded based on their polysomnography results. Those with severe OSA, indicated by an $AHI \geq 30$, were

assigned to the treatment group while those without OSA ($AHI < 5$) were assigned as controls. Finally, subjects with mild or moderate OSA ($5 < AHI < 30$) were excluded.

Inclusion Criteria

1. Treatment group: Severe OSA ($AHI \geq 30$)
2. Control group: OSA-negative ($AHI < 5$)

For the treatment group, prescription for the CPAP treatment was given by the physician and the subject was invited for a second SAPW recording after treating with CPAP for 4-6 weeks. The control group received no treatment and the subject was asked to return for a second SAPW recording 4-6 weeks after the initial recording. The reason for taking two recordings in controls without intervention was to demonstrate the reliability and consistency of SAPW measurement.

Clinical data relevant to the subject's age, weight, height, health, medical history, medications, as well as polysomnography results and SAPW measurements were collected and recorded on the data collection form (Appendix 2). In addition, measurements on post-CPAP AHI and nadir O_2 saturation were also recorded for subjects who had a split-night polysomnography.

If any of the following exclusion criteria applied during any time of the subject's participation in this study, he or she was excluded from the study.

Exclusion Criteria

1. Patients unable to provide consent
2. History of cardiac illness or abnormal baseline ECG:

- a. AF (paroxysmal, persistent, permanent)
 - b. Chronic/persistent atrial arrhythmias (atrial flutter, atrial tachycardia)
 - c. Permanent pacemakers/ICD
 - d. Abnormal p-wave morphology that is non-sinus in origin
 - e. Congenital heart disease
 - f. Mitral valve surgery
3. Patients taking beta-blockers or anti-arrhythmic medication
 4. Patients with central sleep apnea
 5. Unanalyzable SAPW data

Polysomnography

Standard overnight polysomnography (Driver *et al.* 2005) were conducted on all patients after initial clinical visit. This included 4 EEG channels (2 central – C3-A2, C4-A1, and 2 occipital – O2-A1, O1-A2), 2 EOG channels, submental EMG, finger pulse oximetry, lead II ECG, thoracic and abdominal movement (piezoelectric bands), right and left anterior tibialis EMG, diaphragmatic surface EMG, and snore vibration sensor. Airflow was measured with a nasal cannula pressure transducer and an oral thermistor. Blood pressure was also monitored throughout the study using a finger cuff. The recording duration was the patient's total sleep time. Standard criteria were used by sleep lab technicians for sleep stage scoring (Rechtschaffen & Kales, 1968) and scoring of respiratory events (American, 1999). The diagnosis of OSA was determined by physicians primarily based on the AHI and nadir oxygen desaturation.

Split-night Polysomnography

After the initial clinical examination, if considered appropriate by the physician, a split-night polysomnography may be ordered in lieu of a diagnostic polysomnography. In this case, the attending sleep lab technicians would introduce the CPAP treatment during the polysomnography after making adequate observations supporting the presence OSA and the need for CPAP. The patient would be awakened during the polysomnography to be connected to the CPAP machine. Polysomnography measurements post-CPAP including AHI and nadir O₂ saturation are recorded.

High-resolution P-wave Signal Averaging

SAPW recordings were conducted on all patients at initial visit and 4 - 6 weeks thereafter for controls and after 4 – 6 weeks of CPAP treatment for OSA patients. Careful skin preparation and positioning of silver-silver chloride electrodes in an orthogonal manner preceded the recordings. Shielded cables were attached to the digital Holter monitor ('SpiderView', Italy) and the subjects lay still for 10 minutes during data acquisition. Derived analogue signals were amplified 10,000 times and band pass filtered between 1 and 300 Hz. The lead exhibiting the clearest p-wave was then further band pass filtered between 20 and 50 Hz and used as a trigger to align subsequent p-waves for signal averaging. The analogue data was sampled at 1 KHz with 12-bit resolution. Approximately 600 beats were stored for offline analysis and 100 beats with a final filtered noise of < 0.2 mV were averaged using an SAPW analysis software (Redfearn *et al.* 2006). A sample demonstration of a SAPW analysis is shown in Figure 3.

Outcome Assessment

1. To compare SAPW duration in severe OSA patients as a marker for atrial electrical remodeling with matched controls.
2. To compare SAPW duration pre- and post-intervention with CPAP in severe OSA patients as a marker for reverse atrial electrical remodeling.
3. To correlate changes in SAPW duration after CPAP treatment with clinical characteristics, AHI, and oxygen desaturation.

Statistical Analysis

Data were entered into a Microsoft Excel spreadsheet and imported into SPSS (Version 16.0, SPSS Incorporated, Chicago, Illinois, 2007). All data were expressed as the mean \pm SD or frequency expressed as percentage. For continuous variables, statistical differences were determined using independent *t*-test between groups and paired Student's *t*-test within groups. Fisher's exact test was performed for discrete clinical variables. Associations of SAPW measurements with clinical and polysomnographic variables were assessed by the Pearson's correlation coefficient. A 2-tailed *p* value < 0.05 was considered statistically significant.

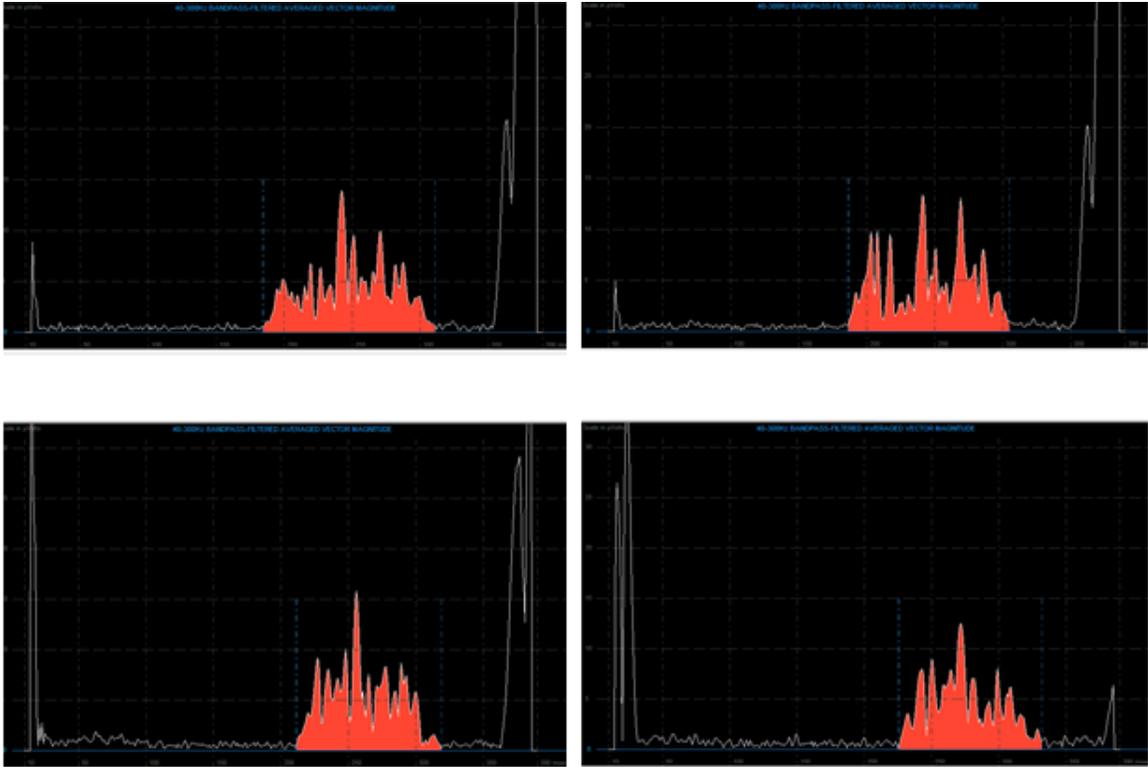


Figure 3. Sample SAPW analyses for an OSA subject (upper panels) and a control subject (lower panels), at first (left) and second (right) recording. Note: x-axis = msec; dotted blue lines indicate duration; y-axis = μ volts. The area in red represents the average p wave of 100 beats.

CHAPTER 3: RESULTS

From March 2009 to March 2011, a total of 73 patients were recruited to the study. At the conclusion of this study, only 29 have completed both first and second SAPW recordings while the remaining 44 patients were excluded for various reasons during the study (Table 1). Of the 29 subjects included in the final analysis, 19 were severe OSA patients and 10 were controls.

Study Population

Baseline clinical characteristics and polysomnography measurements of the study population are shown in Table 2. Mean AHI and minimum O₂ saturation were 41.4 ± 10.1 events/hour (range 30 to 60) and $80.5 \pm 6.5\%$ in severe OSA and 2.8 ± 1.2 (range 1.4 – 4.7) events/hour and $91.4 \pm 2.1\%$ in controls. Amongst the clinical characteristics, only BMI was significantly different, with the severe OSA patients demonstrating an overall greater BMI than controls (34.3 ± 5.4 vs 26.6 ± 4.6 kg/m²; $p < 0.001$). Generally, the severe OSA population was older (51.1 ± 12.3 vs 39.2 ± 20.9 ; $p = 0.12$) and showed a greater prevalence of hypertension (37% vs 10%; $p = 0.2$) but these differences did not reach statistical significance.

Table 1. Reasons for exclusion

Reason	n
Mild or moderate OSA ($5 \leq \text{AHI} < 30$)	18
Lost to follow-up	8
No polysomnography results	6
Withdrew	4
No CPAP treatment (for severe OSA)	3
Central sleep apnea	2
Unanalyzable SAPW recording	2
History of atrial fibrillation	1
Total	44

Table 2. Clinical characteristics and polysomnography measurements

	Severe OSA	Controls	<i>p</i>
n	19	10	
Age	51.1 ± 12.3	39.2 ± 20.9	<i>NS</i>
Male (%)	68	40	<i>NS</i>
BMI (kg/m²)	34.3 ± 5.4	26.6 ± 4.6	< 0.001
Hypertensive (%)	37	10	<i>NS</i>
Smoker (%)	16	10	<i>NS</i>
Diabetes (%)	5	0	<i>NS</i>
AHI	41.4 ± 10.1	2.8 ± 1.2	< 0.001
Nadir O₂ Saturation (%)	80.5 ± 6.5	91.4 ± 2.1	< 0.001

SAPW Duration Pre- and Post-intervention

The mean SAPW duration of severe OSA patients and controls are summarized in Table 3. At baseline, severe OSA patients had a greater SAPW duration than controls (131.9 ± 10.4 vs 122.8 ± 10.5 ms; $p = 0.04$). After treating with CPAP for 4 – 6 weeks, there was a significant reduction of SAPW duration in severe OSA patients (131.9 ± 10.4 to 126.2 ± 8.8 ms; $p < 0.001$), and the SAPW duration post-CPAP in severe OSA did not differ significantly from controls (126.2 ± 8.8 vs 122.6 ± 10.9 ms; $p = 0.4$). In controls, the mean SAPW duration did not change after 4 – 6 weeks (122.8 ± 10.5 to 122.6 ± 10.9 ms; $p = 0.8$).

Correlation between SAPW and Polysomnography Measurements

At baseline, SAPW duration was moderately, positively correlated with AHI ($r = 0.4$; $p = 0.03$) (Figure 4). The correlation between SAPW duration and nadir O₂ saturation was weakly negative, but it was short of statistical significance ($r = 0.34$; $p = 0.07$) (Figure 5).

Correlation between SAPW and Clinical Characteristics

At baseline, SAPW duration was also moderately, positively correlated with age ($r = 0.488$; $p = 0.007$) (Figure 6) and BMI ($r = 0.426$; $p = 0.02$) (Figure 7).

Table 3. SAPW duration

SAPW (ms)	Severe OSA	Controls	
Pre-	131.9 ± 10.4	122.8 ± 10.5	<i>p</i> = 0.04
Post-	126.2 ± 8.8	122.6 ± 10.9	<i>NS</i>
	<i>p</i> < 0.001	<i>NS</i>	

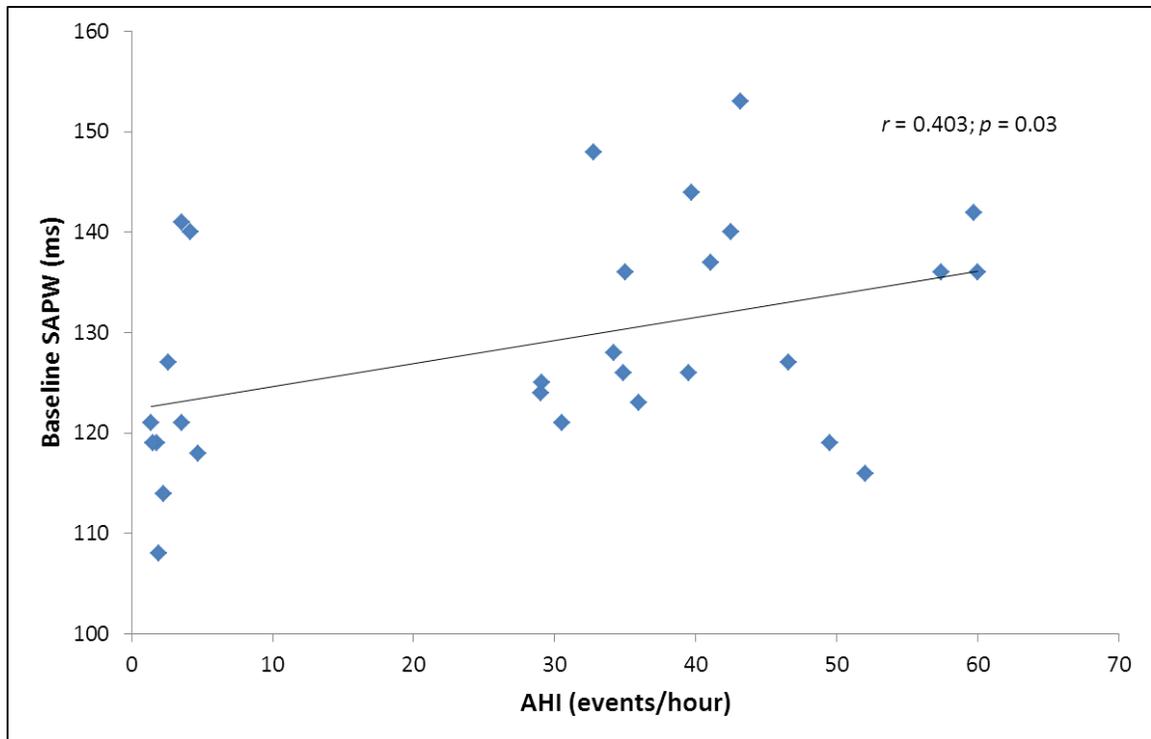


Figure 4. Positive correlation between AHI and SAPW duration.

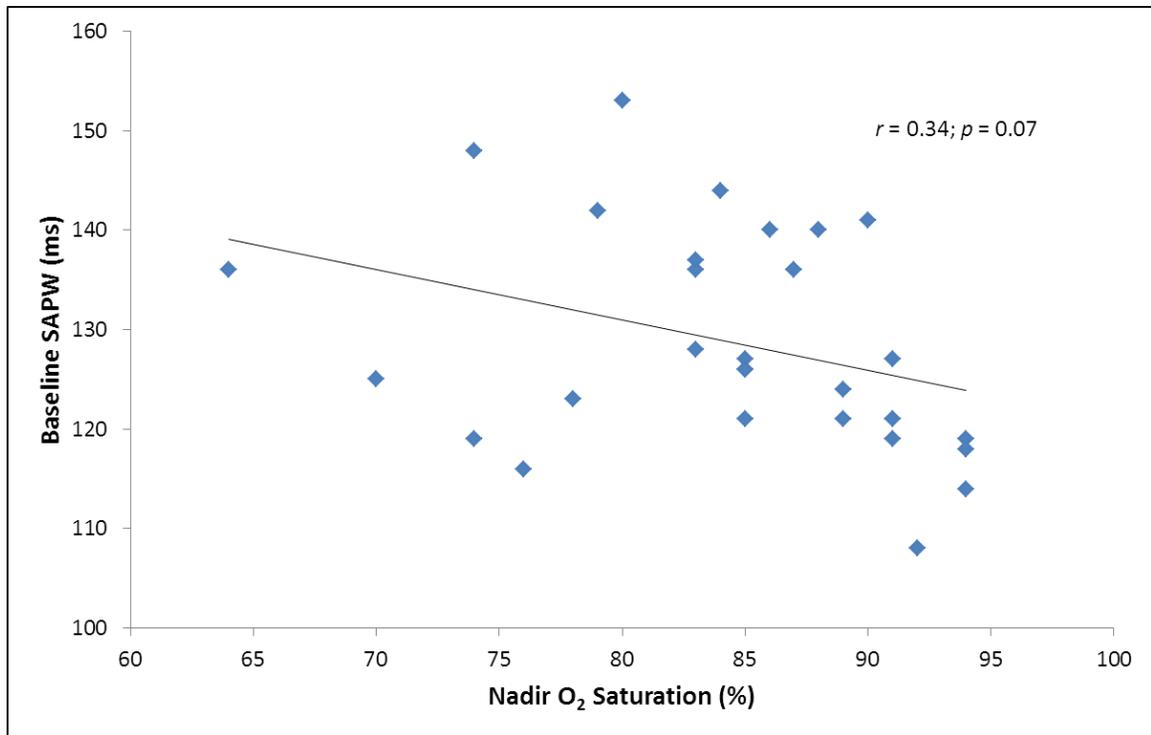


Figure 5. Negative correlation between nadir O₂ saturation and SAPW duration.

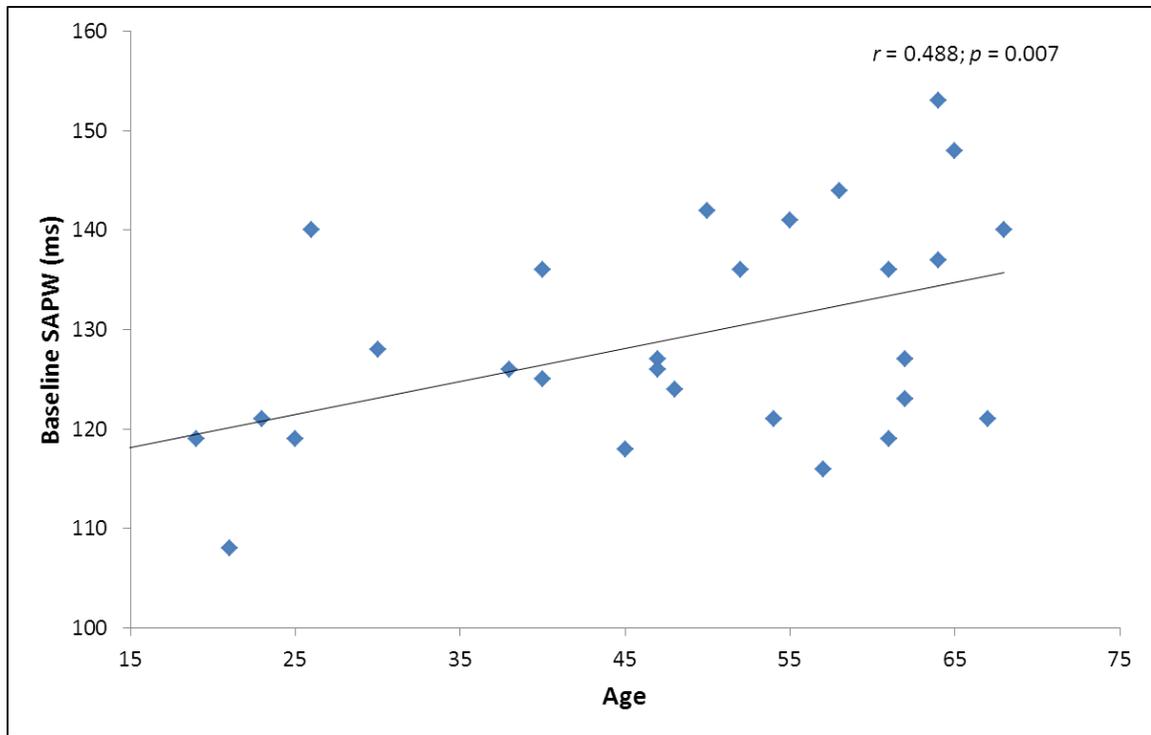


Figure 6. Positive correlation between age and SAPW duration.

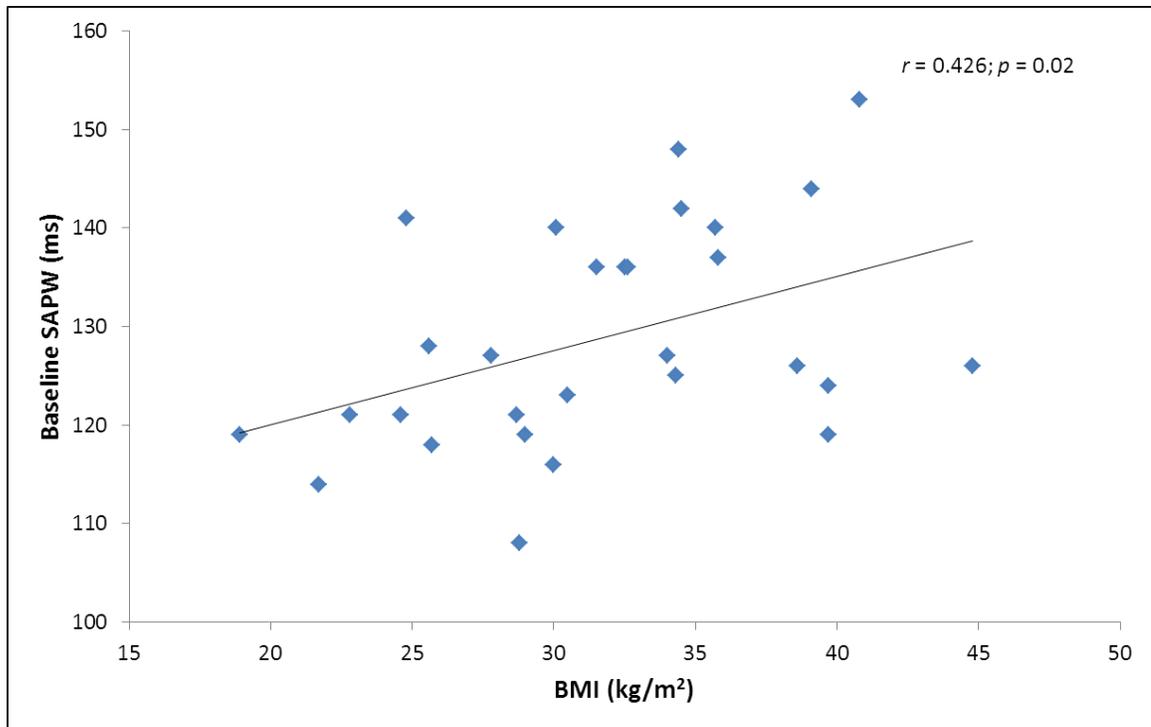


Figure 7. Positive correlation between BMI and SAPW duration.

Magnitude of Changes in SAPW

After treating with CPAP for 4 – 6 weeks, all severe OSA patients demonstrated a shortening of SAPW duration ranging from 1 to 11 ms. The reduction in SAPW duration was positively correlated with AHI ($r = 0.450$; $p = 0.05$) (Figure 8) and baseline SAPW duration ($r = 0.640$; $p = 0.003$) (Figure 9), but not with nadir O₂ saturation ($r = 0.24$; $p = 0.33$) (data not shown).

Polysomnography Measurements Pre- and Post-CPAP

Out of the 19 severe OSA patients, 8 had a split-night polysomnography in lieu of a standard diagnostic polysomnography. Data on post-CPAP AHI and nadir O₂ saturation are summarized in Table 4. After commencing CPAP during the polysomnography, there were a significant reduction in AHI (48.7 ± 11.0 to 25.6 ± 10.0 events/hour; $p = 0.002$) as well as an improvement in O₂ saturation (77.5 ± 8.1 to $86.6 \pm 2.4\%$; $p = 0.01$). Consistent with the overall severe OSA population, this subgroup also demonstrated a reduction in SAPW duration after 4 – 6 weeks of CPAP treatment (132.3 ± 10.8 to 125.6 ± 8.8 ms; $p < 0.001$).

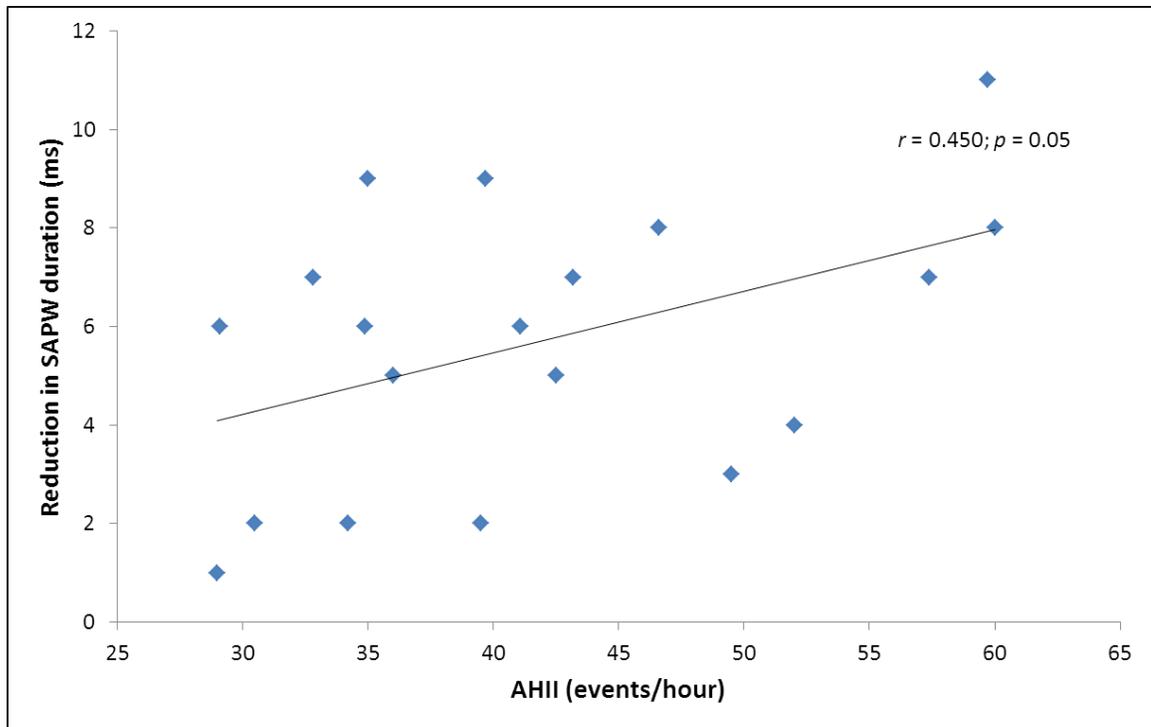


Figure 8. Positive correlation between AHI and changes in SAPW duration after 4 – 6 weeks of CPAP treatment in severe OSA patients.

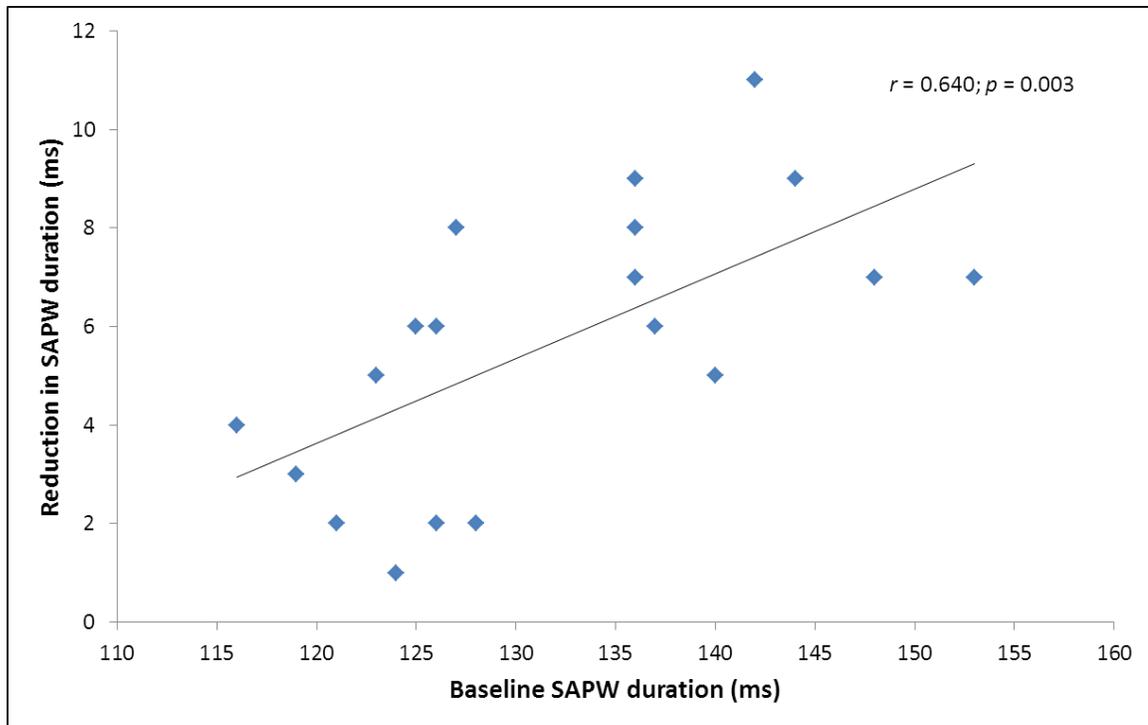


Figure 9. Positive correlation between baseline SAPW duration and changes in SAPW duration after 4 – 6 weeks of CPAP treatment in severe OSA patients.

Table 4. Polysomnography measurements and SAPW pre- and post-CPAP (n = 8)

	Pre-CPAP	Post-CPAP	<i>p</i>
AHI	48.7 ± 11.0	25.6 ± 10.0	0.002
Nadir O₂ Saturation (%)	77.5 ± 8.1	86.6 ± 2.4	0.01
SAPW duration (ms)	132.3 ± 10.8	125.6 ± 8.8	< 0.001

Correlation between Changes in SAPW and Changes in AHI

All 8 patients experienced a reduction of AHI (range 7.2 – 43.6 events/hour) following CPAP intervention during the polysomnography. There was a positive trend between the reduction in AHI with that of SAPW duration (Figure 10); however, this could not reach statistical significance due to the small sample size.

Interestingly, all but one patient experienced an improvement in O₂ saturation (range 4 – 24%); however, there was no trend between these improvements and the reduction of SAPW duration (data not shown).

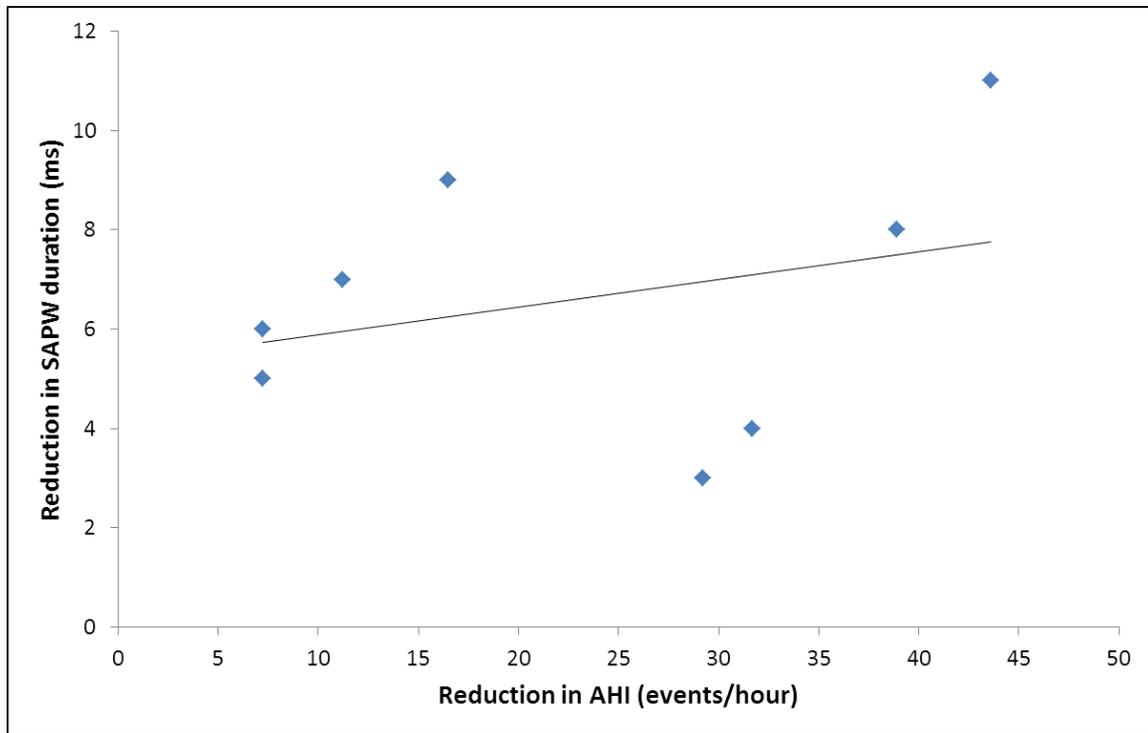


Figure 10. Positive trend between reduction in AHI after CPAP during polysomnography and reduction in SAPW duration after 4 – 6 weeks of CPAP treatment in severe OSA patients.

CHAPTER 4: DISCUSSION

Major Findings

Symptoms like snoring or sleepiness are not considered unbearable or life-threatening. As such, the seriousness of OSA is often understated by the general public, resulting in an overall underdiagnosis of the disease (Young *et al.* 2002). Nonetheless, the cardiovascular complications associated with OSA may significantly increase morbidity and mortality.

Numerous studies have reported a higher prevalence of arrhythmias, including AF, in patients with OSA (Guilleminault *et al.* 1983). While this relationship has been established, the exact mechanisms leading up to AF remains unclear. Atrial enlargement and prolonged p-wave duration have been documented in OSA patients, suggesting the role of atrial structural and electrical remodeling. Therefore, reversal of atrial remodeling in OSA may alleviate the cardiovascular burden on OSA patients.

CPAP is the gold standard treatment for OSA. Patients treated with CPAP have demonstrated improved cardiovascular functions. However, the effects of CPAP on atrial conduction have yet to be assessed.

The main findings of this study in patients with severe OSA are 1) SAPW duration is increased compared to controls; 2) SAPW is correlated with the severity of the disease; and 3) CPAP treatment reduces the SAPW duration.

SAPW Duration is Increased in OSA

In this study, severe OSA patients demonstrated a greater SAPW duration than controls before receiving CPAP treatment (131.9 ± 10.4 vs. 122.8 ± 10.5 ms; $p = 0.04$). The increase in SAPW, approximating 10 ms, represents severe intra-atrial conduction disturbance and slowed atrial conduction.

This is the first study to measure SAPW duration in OSA patients. The findings of this study are consistent with a previous study by Baranchuk *et al.* (2011), who reported an increase in Pmax of 7.6 ms and Pd (14.6 ± 7.5 vs 8.9 ± 3.1 ms; $p < 0.001$) in moderate-severe OSA patients. An earlier study also consistently reported an increased Pmax in severe OSA compared to controls (128.9 ± 10.7 vs. 101.2 ± 11.8 ms; $p < 0.001$), and in mild-moderate OSA compared to controls (117.5 ± 13.7 vs. 101.2 ± 11.8 ms; $p < 0.001$) (Can *et al.* 2008). The increase in p-wave duration in severe OSA in this study was almost 30 ms, three times the difference measured in my study population. Differences in the p-wave duration markers employed or the study populations may account for the discrepancy.

In this study population, there was a positive correlation between SAPW duration and BMI. At baseline, BMI was significantly greater in severe OSA, which may have contributed to the increased SAPW duration compared to controls.

Although results are currently limited, studies have consistently demonstrated a significant increase of p-wave duration in OSA using Pmax and SAPW. The prolongations of p-wave duration and Pd are clear indication of atrial electrical remodeling associated with OSA.

SAPW is Correlated with AHI

Previous study reported that the severity of OSA was positively correlated with Pmax ($r = 0.44$; $p = 0.002$) and Pd ($r = 0.56$; $p < 0.001$) (Can *et al.* 2008). This study is the first to report a similar observation using SAPW ($r = 0.403$; $p = 0.03$).

The prolongation of p-wave duration is a known predictor for AF. The observation that SAPW is related to AHI suggests that the risk of AF may differ amongst OSA patients depending on the severity of the disease. However, the use of the direct measurement of SAPW as a predictor for AF has not been established. In fact, Healey *et al.* (2004) and Chalfoun *et al.* (2007) concluded that the change in SAPW, but not the direct measurement of SAPW, can predict the recurrence of AF. Therefore, the positive correlation observed in this study may not signify that more severe OSA represents a greater risk of AF. Further research into the relationship of SAPW measurements and the risk of AF is warranted.

CPAP Treatment Reduces SAPW Duration

In this study, the use of CPAP for 4 – 6 weeks reduced SAPW duration in all severe OSA patients (131.9 ± 10.4 to 126.2 ± 8.8 ms; $p < 0.001$), indicating a reversal of atrial electrical remodeling associated with OSA. This provides clear evidence that the prolongation of SAPW may be resolved by treating the underlying disease.

No change in SAPW duration was observed in controls, which supports that the change observed in severe OSA was not due to variability of the SAPW measurement.

The findings of this study showed that SAPW duration was positively correlated with BMI and age. As mentioned above, severe OSA patients had an overall greater BMI and were generally older compared with controls; therefore, these could have contributed to the increased SAPW duration observed in severe OSA. However, the reduction in SAPW after CPAP despite the BMI and age remained the same supports that the prolongation of SAPW was primarily a result of the disease itself.

The shortening of SAPW duration in this study population was approximately 6 ms at 4 – 6 weeks. In other clinical scenarios, previous studies have reported a decrease of about 6 ms 3 days post-cardioversion (Healey *et al.* 2004), and 13 ms 30 days post-cardioversion (Chalfoun *et al.* 2007), that continued for at least three months. In OSA patients, it is unclear whether the shortening continues beyond 4 – 6 weeks of CPAP treatment.

As previously mentioned, two independent studies have concluded that the clinical significance lies in the change of SAPW, but not its direct measurement. At this point, the link between changes in SAPW duration and the risk of AF in this population is uncertain.

The reduction in SAPW duration was positively correlated with AHI and baseline SAPW. These observations suggest that more severe OSA demonstrates greater SAPW duration and experience greater reduction as a result of CPAP. This may signify that the effects of CPAP are not identical in all OSA patients. Changes in SAPW duration could possibly be related to improvements in AHI, although initial results did not reach statistical significance.

The change in SAPW duration post-CPAP not only represents reverse electrical remodeling, but may also indicate a restoration of structural changes. Previous studies have demonstrated concurrent reduction in LA volume and SAPW duration in other clinical settings (John *et al.* 2010). The reduction of SAPW duration in this study could also reflect a reduction in atrial size. However, no echocardiographic data was available to validate this speculation.

This is the first study to demonstrate reverse atrial electrical remodeling in OSA. The findings of this study further support the role of electrical remodeling underlying AF in OSA and open the possibility that its reversal may deter AF development, as in other clinical settings. Although CPAP is the treatment of choice for OSA, the general compliance has been suboptimal. The knowledge that CPAP may improve atrial conduction and prevent AF could possibly increase the compliance to CPAP in OSA patients.

Limitations

The study group involved a small number of patients. A larger sample size would have permitted multiple linear regression to identify independent predictors for SAPW duration. Nonetheless, the results of this study were statistically significant.

There were no echocardiographic data available to correlate changes in SAPW duration with changes in atrial size, if any, after CPAP treatment. The echocardiographic data would allow us to determine whether the reverse atrial electrical remodeling is associated with structural changes of the atria and may elucidate the pathophysiology of

electrical remodeling in OSA. Nonetheless, the findings of this study are sufficient to support that the atrial electrical remodeling could be reversed by CPAP.

Other events occurring concomitantly with CPAP treatment may contribute to the observed changes in SAPW duration. Changes in lifestyle or drastic weight loss can improve cardiovascular functions, thus amplifying the effects of CPAP. Since obesity is an established risk factor for OSA, weight loss may alleviate the severity of OSA and improve atrial conduction. I have illustrated that SAPW duration was positively correlated with the severity of disease. Therefore, CPAP treatment may not entirely account for the observed SAPW duration reduction. However, no significant improvement in atrial conduction as a result of changes in lifestyle or weight is expected to occur within 4 – 6 weeks.

Non-compliance to CPAP treatment may understate its therapeutic effects. As aforementioned, the general tolerance and compliance to CPAP is suboptimal due to discomfort and nasal problems. The potential effects of CPAP on improving atrial conduction could be understated if the treatment has not been used maximally by the study population. I have minimized this limitation by confirming with the patients that they have used CPAP every night for at least 4 consecutive weeks.

Future Directions

To the best of my knowledge, this is the first study to demonstrate 1) SAPW duration is correlated with AHI; and 2) CPAP treatment reduces SAPW duration.

In a basic science perspective, the future direction is to relate the reversal of atrial electrical remodeling with structural changes. This will enhance our understanding of the

pathophysiology underlying AF in OSA. Future studies should include echocardiographic data to measure any changes in atrial size following CPAP treatment and determine if they are associated with reduction in SAPW duration. In this study, I only repeated the SAPW recording once; however, it would be useful to take more repeated measurements at different times of the CPAP treatment to determine the temporality of reverse atrial remodeling. It was previously demonstrated that reverse electrical remodeling occurs more rapidly than structural remodeling. Investigation into the effects of CPAP on these phenomena will elucidate the remodeling processes and its reversal in OSA patients. Furthermore, OSA patients of different severity as well as those not receiving CPAP treatment may be included to further define the effects of CPAP on SAPW duration.

In a clinical perspective, the future direction in this field is to relate these findings to the development of AF in OSA. Future studies should include patients with AF or history of AF to assess whether CPAP may reduce the burden of AF in OSA patients, either by lowering the incidence or recurrence after cardioversion, which has been observed in other clinical scenarios. The clinical relevance of SAPW changes to AF incidence should also be assessed. In addition, the conditions under which AF is prevented or deterred could also possibly be identified. These findings will have tremendous clinical value.

The relationship between OSA and AF is intricate and involves some common risk factors. The ultimate objective is to understand the pathophysiology in order to lower the incidence of AF in OSA patients. Future studies must be carefully designed to avoid effects from confounders.

Conclusion

In this study, I conclude that severe OSA patients have longer SAPW duration compared to healthy controls, and that CPAP treatment in severe OSA induces reverse atrial electrical remodeling, represented by a shortening of SAPW duration.

LITERATURE CITED

Allessie M, Ausma J & Schotten U (2002). Electrical, contractile, structural remodeling during atrial fibrillation. *Cardio Res* **54**, 230-246.

American Academy of Sleep Medicine Task Force (1999). Sleep-related breathing disorders in adults: Recommendations for syndrome definition and measurement techniques in clinical research. *Sleep* **22**, 667-689.

Arias MA & Sanchez AM (2007). Obstructive sleep apnea and its relationship to cardiac arrhythmias. *J Cardiol Electrophys* **18**, 1006-1014.

Ballester E, Badia JR, Hernandez L, et al (1999). Evidence of the effectiveness of continuous positive airway pressure in the treatment of sleep apnea/hypopnea syndrome. *Am J Respir Crit Care Med* **159**, 495-501.

Baranchuk A, Healey JS, Simpson CS, Redfearn DP, Morillo CA, Connolly SJ & Fitzpatrick M (2009). Atrial Overdrive Pacing in Sleep Apnea: A Meta-Analysis. *Europace* **11**, 1037-1040.

Baranchuk A, Parfrey B, Lim L, Morriello F, Simpson CS, Hopman WM, Redfearn DP & Fitzpatrick M (2011). Interatrial Block in Patients with Obstructive Sleep Apnea. *Cardiol J* **18**, 171-175.

Baranchuk A, Simpson CS, Redfearn DP & Fitzpatrick M (2008). It's time to wake up! Sleep apnea and cardiac arrhythmias. *Europace* **6**, 666-667.

Barbe F, Duran-Cantolla J, Capote F *et al* (2010). Long term effects of continuous positive airway pressure in hypertensive patients with sleep apnea. *Am J Respir Crit Care Med* **181**, 718-726.

Budhiraja R, Parthasarthy S & Quan S (2007). Endothelial dysfunction in obstructive sleep apnea. *J Clin Sleep Med* **3**, 409-415.

Can I, Aytemir K, Demir AU, Deniz A, Ciftci O, Tokgozoglu L, Oto A & Sahin A (2008). P-wave duration and dispersion in patients with obstructive sleep apnea. *Int J Cardiol* **133**, e85-e89.

Caples SM & Somers VK (2009). Sleep-disordered breathing and atrial fibrillation. *Prog Cardio Dis* **51**, 411-415.

Chalfoun N, Harnick D, Pe E, Undavia M, Mehta D & Gomes JA (2007). Reverse electrical remodeling of the atria post cardioversion in patients who remain in sinus rhythm assessed by signal averaging of the p-wave. *PACE* **30**, 502-509.

Chung MK, Martin DO, Spencer D, et al (2001). C-reactive protein elevation in patients with atrial arrhythmias: inflammatory mechanisms and persistence of atrial fibrillation. *Circulation* **104**, 2886-2891.

Dilaveris PE & Gialafos JE (2001). P-wave dispersion: a novel predictor for paroxysmal atrial fibrillation. *Ann Noninvasive Electrocardiol* **6**, 159-165.

Driver HS, McLean H, Kumar DV, Farr N, Day AG & Fitzpatrick MF (2005). The influence of the menstrual cycle on upper airway resistance and breathing during sleep. *Sleep* **28**, 449-456.

Feinberg WM, Blackshear JL, Laupacis A, Kronmal R & Hart RG (1995). Prevalence, age distribution, and gender of patients with atrial fibrillation: analysis and implications. *Arch Intern Med* **155**, 469-473.

Flemons WW, Remmers JE & Gillis AM (1993). Sleep apnea and cardiac arrhythmias. Is there a relationship? *Am Rev Respir Dis* **148**, 618-621.

Franz MR & Bode F (2003). Mechano-electrical feedback underlying arrhythmias: the atrial fibrillation case. *Prog Biophys Mol Biol* **82**, 163-174.

Fung JWH, Li TST, Choy DKL, Yip GWK, Ko FWS, Sanderson JE & Hui DSC (2002). Severe obstructive sleep apnea is associated with left ventricular diastolic dysfunction. *CHEST* **121**, 422-429.

Fuster V, Ryden LE, Connors DS, *et al* (2006). ACC/AHA/ESC 2006 Guidelines for the management of patients with atrial fibrillation. *Circulation* **114**, e257-e354.

Gami AS, Hodge DO, Herges RM, Olson EJ, Nykodym J, Kara T & Somers VK (2007). Obstructive sleep apnea, obesity, and the risk of incident atrial fibrillation. *J Am Coll Cardiol* **49**, 565-571.

Gami AS, Howard DE, Olson EJ & Somers VK (2005). Day-night pattern of sudden death in obstructive sleep apnea. *New Eng J Med* **352**, 1206-1214.

Gami AS, Pressman G, Caples SM, Kanagala R, Gard JJ, Davison DE, Melouf JF, Ammash NM, Friendmas PS & Somers VK (2004). Association of atrial fibrillation and obstructive sleep apnea. *Circulation* **110**, 364-367.

Garrigue S, Bordier P, Jaas P *et al* (2002). Benefit of atrial pacing in sleep apnea syndrome. *N Engl J Med* **346**, 404-412.

Gotsopoulos H, Chen C, Qian J & Cistulli PA (2002). Oral appliance therapy improves symptoms in obstructive sleep apnea: a randomized, controlled trial. *Am J Respir Crit Care Med* **166**, 743-748.

Gulleminault C, Connolly SJ & Winkle RA (1983). Cardiac arrhythmia and conduction disturbances during sleep in 400 patients with sleep apnea syndrome. *Am J Cardiol* **52**, 490-494.

Guo XH, Gallagher MM, Poloniecki J & Yi G (2003). Prognostic significance of serial P wave signal-averaged electrocardiograms following external electrical cardioversion for persistent atrial fibrillation: a prospective study. *Pacing Clin Electrophysiol* **26**, 299-304.

Harbison J, O'Reilly P & McNicholas WT (2000). Cardiac rhythm disturbances in the obstructive sleep apnea syndrome: effects of nasal continuous positive airway pressure therapy. *CHEST* **118**, 591-595.

Healey JS, Theoret-Patrick P, Green MS, Lemery R, Birnie D & Tang ASL (2004). Reverse atrial electrical remodelling following atrial defibrillation as determined by signal-averaged ECG. *Can J Cardiol* **20**, 311-315.

Henry WL, Morganroth J, Pearlman AS, et al (1976). Relation between echocardiographically determined left atrial size and atrial fibrillation. *Circulation* **53**, 273-279.

Hersi AS (2010). Obstructive sleep apnea and cardiac arrhythmias. *Annals of Thoracic Med* **5**, 10-15.

Hoffstein V & Mateika S (1994). Cardiac arrhythmias, snoring, and sleep apnea. *CHEST* **106**, 466-471.

Huang JL, Wen ZC, Lee WL, Chang MS & Chen SA (1998). Changes of autonomic tone before the onset of paroxysmal atrial fibrillation. *Int J Cardiol* **66**, 275-283.

John B, Stiles MK, Kuklik P, Brooks AG, Chandy ST, Kalman JM & Sanders P (2010). Reverse remodeling of the atria after treatment of chronic stretch in humans. *J Am Col Cardiol* **55**, 1217-1226.

Kanagala R, Murali NS, Friedman PA, Ammash NM, Gersh BJ, Ballman KV, Shamsuzzaman ASM & Somers VK (2003). Obstructive sleep apnea and recurrence of atrial fibrillation. *Circulation* **107**, 2589-2594.

Keren G, Etzion T, Sherez J, et al (1987). Atrial fibrillation and atrial enlargement in patients with mitral stenosis. *Am Heart J* **114**, 1146-1155.

Khan A, Latif F, Hawkins B, Tawk M, Sivaram CA & Kinasewitz G (2008). Effects of obstructive sleep apnea treatment on left atrial volume and left atrial volume index. *Sleep Breath* **12**, 142-147.

Lamba J, Simpson CS, Redfearn DP, Michael KA, Fitzpatrick M & Baranchuk A (2011). Cardiac Resynchronization Therapy for the Treatment of Sleep Apnea: A Meta-analysis. *Europace* (Epub ahead of print).

Marin JM, Carrizo SJ, Vicente E & Agusti AG (2005). Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnea with or without treatment with continuous positive airway pressure: An observational study. *Lancet* **365**, 1046-1053.

Mehra R, Benjamin EJ, Shahar E, Gottlieb DJ, Nawabit R, Kirchner HL, Sahadevan J & Redline S (2006). Association of nocturnal arrhythmias with sleep-disordered breathing: the sleep heart health study. *Am J Respir Crit Care Med* **173**, 910-916.

Meslier N, Lebrun T, Grillier-Lanoir V, Rolland N, Henderick C, Saily JC & Racineux JL (1998). A French survey of 3,225 patients treated with CPAP for obstructive sleep apnoea: benefits, tolerance, compliance and quality of life. *Eur Respir J* **12**, 185-192.

Misier AR, Opthof T, van Hemel NM, et al (1992). Increased dispersion of “refractoriness” in patients with idiopathic paroxysmal atrial fibrillation. *J Am Coll Cardiol* **19**, 1531-1535.

Moore T, Gullsbj S, Rabben T & Eriksson P (1996). Sleep-disordered breathing: a novel predictor of atrial fibrillation after coronary bypass surgery. *Coron Artery Dis* **7**, 475-478.

Morillo CA, Klein GJ, Jones DL & Guiraudon CM (1995). Chronic rapid atrial pacing. Structural, functional, and electrophysiological characteristics of a new model of sustained atrial fibrillation. *Circulation* **91**, 1588-95.

Nattel S, Burstein B & Dobrev D (2008). Atrial remodeling and atrial fibrillation: mechanisms and implications. *Circ Arrhythm Electrophysiol* **1**, 62-73.

Nattel S & Li Danshi (2000). Ionic remodeling in the heart. Pathophysiological significance and new therapeutic opportunities for atria fibrillation. *Cir Res* **87**, 440-447.

Oflax H, Cuhadaroglu C, Pamukcu B, Meric M, Ece T, Kasikciogly E & Koylan N (2006). Endothelial function in patients with obstructive sleep apnea syndrome but without hypertension. *Respiration* **73**, 751-756.

Oliveira W, Campos O, Cintra F, et al (2009). Impact of continuous positive airway pressure on left atrial volume and function in patients with obstructive sleep apnoea assessed by real-time three-dimensional echocardiography. *Heart* **95**, 1872-1878.

Otto ME, Belohlavek M, Romero-Corral A, et al (2007). Comparison of cardiac structural and functional changes in obese otherwise healthy adults with versus without obstructive sleep apnea. *Am J Cardiol* **99**, 1298-1302.

Parikh SS, Jons C, McNitt S, Daubert JP, Schwarz KQ & Hall B (2010). Predictive capability of left atrial size measured by CT, TEE, and TTE for recurrence of atrial fibrillation following radiofrequency catheter ablation. *Pacing Clin Electrophysiol* **33**, 532-540.

Pépin JL, Leger P, Veale D, Langevin B, Robert D & Lévy P (1995). Side effects of nasal continuous positive airway pressure in sleep apnea syndrome: study of 193 patients in two French sleep centers. *CHEST* **107**, 375-381.

Porthan KM, Melin JH, Kupila JT, *et al* (2004). Prevalence of sleep apnea syndrome in lone atrial fibrillation: a case-control study. *CHEST* **125**, 879-885.

Punjabi NM & Beamer BA (2007). C-reactive protein is associated with sleep disordered breathing independent of adiposity. *Sleep* **30**, 29-34

Rechtschaffen A & Kales A (1968). A manual of standardized terminology, techniques and scoring system for sleep stages of human subjects. Washington, D.C., US Government Printing Office. US Public Health Service. (NIH; publication No. 204).

Redfean DP, Skanes AC, Lane J & Stafford PJ (2006). Signaled-averaged p wave reflects change in atrial electrophysiological substrate afforded by verapamil following cardioversion from atrial fibrillation. *PACE* **29**, 1089-1095.

Sanders P, Morton JB, Davidson NC, Spence SJ, Vohra JK, Sparks PB & Kalman JM (2003). Electrical remodeling of the atria in congestive heart failure: electrophysiological and electroanatomic mapping in humans. *Circulation* **108**, 1461-1468.

Schmitt FO & Erlanger J (1928). Directional differences in the conduction of the impulse through heart muscle and their possible relation to extrasystolic and fibrillatory contractions. *Am J Physiol* **87**, 326.

Schotten U, Ausma J, Stellbrink C, *et al* (2001). Cellular mechanisms of depressed atrial contractility in patients with chronic atrial fibrillation. *Circulation* **103**, 691- 698.

Shamsuzzaman AS, Winnicki M, Lanfranchi P, Wolk R, Kara T, Accurso V & Somers VK (2002). Elevated C-reactive protein in patients with obstructive sleep apnea.

Circulation **105**, 2462-2464.

Sher AE, Schechtman KB & Piccirillo JF (1996). The efficacy of surgical modifications of the upper airway in adults with obstructive sleep apnea syndrome. *Sleep*. **19**, 156-177.

Somers VK, White DP, Amin R *et al* (2008). Sleep apnea and cardiovascular disease.

Circulation **118**, 1080-1111.

Stritzke J, Markus MRP, Duderstadt S, *et al* (2009). The aging process of the heart: obesity is the main risk factor for left atrial enlargement during aging. *JACC* **54**, 1982-1989.

Tanigawa T, Yanagishi K, Sakurai S, *et al* (2006). Arterial oxygen desaturation during sleep and atrial fibrillation. *Heart* **92**, 1854-1855.

Todd K, McIntyre WF & Baranchuk A (2010). Obstructive Sleep Apnea and Atrial Fibrillation: A review of the literature. *Nat Sci Sleep* **2**, 1-7.

Tops LF, Delgado V, Bertini M, *et al* (2011). Left atrial strain predicts reverse remodeling after catheter ablation for atrial fibrillation. *J Am Coll Cardiol* **57**, 324-331.

Valencia-Flores M, Orea A, Castano VA *et al* (2000). Prevalence of sleep apnea and electrocardiographic disturbances in morbidly obese patients. *Obes Res* **8**, 262-269.

Van Wagoner DR, Pond AL, Lamorgese M, Rossie SS, McCarthy PM & Nerbonne JM (1999). Atrial L-type Ca²⁺ currents and human atrial fibrillation. *Circ Res* **85**, 428-36.

Verheule S, Sato T, Everett T, et al (2004). Increased vulnerability to atrial fibrillation in transgenic mice with selective atrial fibrosis caused by overexpression of TGF-beta1. *Circ Res* **94**, 1458-1465.

Volgman AS, Soble JS, Neumann A, et al (1996). Effect of left atrial size on recurrence of atrial fibrillation after electrical cardioversion: atrial dimension versus volume. *Am J Card Imaging* **10**, 261-265.

Wijffels MC, Kirchhof CJ, Dorland R & Allessie MA (1995). Atrial fibrillation begets atrial fibrillation. A study in awake chronically instrumented goats. *Circulation* **92**, 1954-1968.

Xiao HD, Fuchs S, Campbell DJ, et al (2004). Mice with cardiac-restricted angiotensin-converting enzyme (ACE) have atrial enlargement, cardiac arrhythmia and sudden death. *Am J Pathol* **165**, 1019-1032.

Yazdan-Ashoori P & Baranchuk A (2011). Obstructive sleep apnea may increase the risk of stroke in AF patients: refining the CHADS₂ score. *Int J Cardiol* **146**, 131-133.

Young T, Palta M, Dempsey J, Skatrud J, Weber S & Badr S (1993). The occurrence of sleep-disordered breathing among middle-aged adults. *New Eng J Med* **328**, 1230-1235.

Young T, Peppard PE & Gottlieb DJ (2002). Epidemiology of obstructive sleep apnea: a population health perspective. *Am J Respir Crit Care Med* **165**, 1217-1239.

Young T, Skatrud J & Peppard PE (2004). Risk factors for obstructive sleep apnea in adults. *JAMA* **291**, 2013-2016.

Zaman AF, Alamgir F, Richens T, Williams R, Rothman MT & Mills PG (1997). The role of signal-averaged P wave duration and serum magnesium as a combined predictor of atrial fibrillation after elective coronary artery bypass surgery. *Heart* **77**, 527-531.

Zou R, Kneller J, Leon LJ & Nattel S (2005). Substrate size as a determinant of fibrillatory activity maintenance in a mathematical model of canine atrium. *Am J Physiol (heart Circ Physiol)* **289**, H1002-1012.

APPENDIX A



FAPC Level 3
Kingston General Hospital
76 Stuart, Kingston, ON
K7L 2V7
Tel. (613) 549-6666 • 3377
Fax (613) 548-1387

Hoshiar Abdollah, MB ChB
Adrian Baranchuk, MD
Damian Redfearn, MB ChB
Christopher Simpson, MD

Reverse Electrical Atrial Remodeling Induced by CPAP in Patients With Obstructive Severe Sleep Apnea

LETTER OF INFORMATION

Principal Investigator: Dr. A Baranchuk

This letter will provide you with all the information about the proposed study. Please read it carefully and feel free to ask for an explanation of anything you do not understand. Signing the consent form means that the study has been explained to you and that you give your permission to take part. It is required that your approval in writing be obtained before you take part in any research study. It is important that you know what will take place and if risks are involved before you decide whether or not to take part in this study.

1. RESEARCH PURPOSE, DURATION, AND PROCEDURES:

You are being invited to volunteer to provide recordings of your heart rhythm. The purpose of this research is to see if the recordings from your heart will differ from the recordings taken from a patient with a different breathing disorder, and if the recordings change after normal treatment.

The recorder is a small device that uses seven skin electrodes (patches on your chest) to monitor your heart rhythms.

At enrollment, as part of the research, we will collect basic data about you (i.e. your name, sex, and age) as well as the medication that you are taking. The information from your overnight sleep study will also be recorded.

This study will be done at the Kingston General Hospital and a total of 30 participants will be enrolled.

There are no extra visits required because of being in this research study. However, you will be asked to stay for an additional 12 minutes before or after your normal sleep studies in order to get a recording.

2. POTENTIAL RISKS

You may experience skin irritation from the electrodes that are placed on your chest while you are wearing the monitor. This irritation is usually minor and will clear up in a day or two.

3. POTENTIAL BENEFITS

There is no direct benefit to you for participating in the study.

4. ALTERNATIVE TREATMENTS

Participation is entirely voluntary; your care will not be affected by having the recording performed.

5. COST TO YOU FOR PARTICIPATING IN THE STUDY

There are no additional costs to you for participating in the study.

6. PAYMENT FOR TAKING PART IN THE RESEARCH STUDY

No payment or compensation will be made to you for your participation in this study.

7. PARTICIPATION IS VOLUNTARY

Your participation in this study is completely voluntary. You may refuse to participate, refuse to answer any questions or withdraw from the study at any time with no effect on your future care.

8. CONFIDENTIALITY

All information obtained during this study, including your medical records, personal data and research data, will be kept confidential. The Ontario Government has enacted legislation to protect the privacy rights of patients. The act is designed to protect the confidentiality of your personal health information. Any information obtained about you during the course of this study will remain confidential, as specified by the legislation.

Representatives of Queens University Health Sciences Research Ethics Board may require access to your study-related records or may follow up with you to monitor the conduct of the research. Your identity will be kept confidential. If the results of this study are published, your name will not be used and no information that discloses your identity will be released or published

9. WHOM TO CONTACT FOR ANSWERS

If you have any questions related to your taking part in this study, please contact any of the study physicians

Dr Adrian Baranchuk: 613 549 6666 ext 3801

OR

Dr John McCans (Head of Department of Medicine) on 613 533 6327

OR

If you have any questions regarding your rights as a research subject you can contact: Dr Albert Clark, Chair, Queens University Health Sciences and Affiliated Teaching Hospitals Research Ethics Board on 613 533 6081

Your signature on the consent form indicates that you have read about the nature of the study, and medical or practical consequences, and the potential risks and benefits associated with this study.

A copy of this letter of information and consent will be placed on your medical record and a copy will be given to you to take home.

**Reverse Electrical Atrial Remodeling Induced by CPAP in Patients
with Severe Sleep Apnea**

CONSENT

I have read the letter of information, have had the nature of the study explained to me and I agree to participate. All questions have been answered to my satisfaction.

Signature of Patient

Date

Printed Name of Patient

Date

Signature of Person Responsible for
Obtaining Consent

Date

