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The interrelationship between central sleep apnea and atrial fibrillation

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BOSTON UNIVERSITY
SCHOOL OF MEDICINE

Thesis

**THE INTERRELATIONSHIP BETWEEN CENTRAL SLEEP APNEA AND
ATRIAL FIBRILLATION**

by

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DEDICATION

I would like to dedicate this work to my family.

**THE INTERRELATIONSHIP BETWEEN CENTRAL SLEEP APNEA AND
ATRIAL FIBRILLATION**

DEBORAH LEE

ABSTRACT

Introduction

Research has consistently shown that sleep apnea is strongly associated with atrial fibrillation, with several lines of evidence demonstrating that this relationship is bidirectional and that each condition predisposes to and/or exacerbates the other. Many studies have suggested potential pathophysiologic mechanisms underlying this relationship, and that sleep apnea and atrial fibrillation share many of the same cardiovascular risk factors further implies that multiple pathways are likely involved in the mechanistic link between the two. Although the sleep apnea-atrial fibrillation relationship is quite established, numerous aspects of this association still require further study, such as the role of gender and the potential impact of positive airway pressure therapy. A deeper understanding of how these individual factors may be involved in the interrelationship between sleep apnea and atrial fibrillation has important clinical implications, such as for risk stratification and screening of patients. Thus, this study aims to further understand the different aspects and modulating factors of the sleep apnea-atrial fibrillation link, focusing on central sleep apnea as less is known about the central sleep apnea-atrial fibrillation relationship.

Methods

A total of 153 patients, originally seen at the cardiac electrophysiology clinic at Beth Israel Deaconess Medical Center and subsequently offered home sleep apnea testing, were included in this study. Several databases – home sleep apnea testing results, polysomnography reports, electrocardiogram reports and patient management systems – were used to obtain a variety of data on sleep pathology, high loop gain status, left ventricular ejection fraction and positive airway pressure therapy efficacy and compliance. Patients were considered to have central sleep apnea if home testing results demonstrated a central apnea-hypopnea index of 5 or greater and/or if the patient was documented as having high loop gain on polysomnography. Data were analyzed using the Statistical Package for Social Sciences software in order to examine how factors such as gender and therapy use may affect the sleep apnea-atrial fibrillation relationship, in a patient population with sleep pathology of at least moderate severity.

Results

Statistical analysis revealed significant sleep disturbances in the central sleep apnea patients compared to the non-central sleep apnea patients. Gender was found to be significantly associated with central sleep apnea, but not obstructive sleep apnea. When postmenopausal (age \geq 51) women were analyzed, very few patients met the study criteria for central sleep apnea, yet the majority were documented as having atrial fibrillation. As expected, positive airway pressure therapy was found to be beneficial for all users, but the common pattern of declining compliance to therapy was seen as adherence decreased

over the course of three months. Of the select central sleep apnea patients who had sufficient data available, comparison of positive airway pressure therapy and cardiac data revealed possible benefits to cardiac health with compliant use of positive airway pressure therapy.

Conclusion

Through examining different aspects of the sleep apnea-atrial fibrillation relationship, this study found promising evidence showing that gender and positive airway pressure therapy play important roles. Further studies, with larger sample sizes, need to be conducted in order to fully understand the specific impact of factors such as gender, gender and age and positive airway pressure therapy on the risks and outcomes in patients with sleep apnea and/or atrial fibrillation, and how these factors may change depending on the type of sleep apnea. Finally, these results further highlight the growing need for an effective collaborative care model between cardiologists and sleep medicine clinicians, as the management of patients with sleep apnea and atrial fibrillation requires an interdisciplinary approach in order to deliver the most optimal patient care.

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LIST OF ABBREVIATIONS

ACE.....	Angiotensin-converting enzyme
AF	Atrial fibrillation
AHI	Apnea-hypopnea index
ARB	Angiotensin receptor blocker
AT	Apneic threshold
AV.....	Atrioventricular
BMI.....	Body mass index
CA index	Central apnea index
CAD	Coronary artery disease
CAHI.....	Central apnea-hypopnea index
CHF.....	Congestive heart failure
CI.....	Confidence interval
CKD	Chronic kidney disease
CO ₂	Carbon dioxide
CPAP	Continuous positive airway pressure
CSA.....	Central sleep apnea
CSB.....	Cheyne-Stokes breathing
CVD	Cardiovascular disease
ECG.....	Electrocardiogram
EDS.....	Excessive daytime sleepiness
ESS.....	Epworth Sleepiness Scale

FDA	Food and Drug Administration
H2.....	Histamine type 2 receptor
HF	Heart failure
HLG	High loop gain
HR.....	Heart rate
ICSD	International Classification of Sleep Disorders
LVEF.....	Left ventricular ejection fraction
NIH	National Institutes of Health
NSAID	Non-steroidal anti-inflammatory drug
OA index.....	Obstructive apnea index
ODI	Oxygen desaturation index
OMR	Online medical record
OSA	Obstructive sleep apnea
OTC.....	Over-the-counter
P _a CO ₂	Partial pressure of carbon dioxide, arterial
P _a O ₂	Partial pressure of oxygen, arterial
PAP	Positive airway pressure
PAT	Peripheral arterial tonometry
PB.....	Periodic breathing
PDE5	Phosphodiesterase type 5
PPI.....	Proton-pump inhibitor
PSG	Polysomnography

PV	Pulmonary vein
RDI.....	Respiratory disturbance index
REM.....	Rapid eye movement
RERAS.....	Respiratory effort-related arousals
SA	Sinoatrial
SD	Standard deviation
SDB.....	Sleep-disordered breathing
SE.....	Sleep efficiency
SpO ₂	Oxygen saturation
SPSS.....	Statistical Package for Social Sciences
SR.....	Sinus rhythm
SVT.....	Supraventricular tachycardia
TST	Total sleep time

INTRODUCTION

Sleep-Disordered Breathing

Sleep-disordered breathing (SDB) is a general term describing a number of conditions whereby abnormal breathing occurs during sleep. The primary types of SDB are obstructive sleep apnea (OSA) and central sleep apnea (CSA), both of which cause repetitive partial or complete cessation of breathing during sleep (Mohammadiet al., 2017). However, while OSA is characterized by breathing cessations that are accompanied by respiratory effort to breathe, CSA presents with a lack of such respiratory drive (Malhotra and Owens, 2010). This section includes a discussion of the basic physiology of normal breathing, the classification, pathophysiology and diagnosis of OSA and CSA, epidemiology and clinical aspects.

Basic Physiology of Breathing

As the process of respiration is fundamental for normal physiological functioning, its regulation is consequently subject to tight control. This control of ventilation is conceptualized in terms of a feedback loop, in which information from central and peripheral sources are relayed to the respiratory center located in the medulla oblongata (Corne and Bshouty, 2005). This brainstem respiratory center, which consists of a network of neurons known as the pre-Bötzinger complex, then integrates feedback information to modify the breathing rhythm output and maintain homeostasis. Generally,

feedback to the respiratory center includes chemical, mechanical, and behavioral inputs (Chourpiliadis and Bhardwaj, 2020).

The chemical and metabolic influences on ventilation are mediated through central and peripheral chemoreceptors that are sensitive to changes in P_aO_2 and P_aCO_2 . The central chemoreceptors are found in many brainstem regions, whereas the peripheral chemoreceptors – the carotid bodies being the most important – are located in the bifurcation of each common carotid artery (Iturriaga et al., 2016). These chemoreceptors respond to hypoxic and hypercapnic stimuli to modulate ventilation accordingly. On the other hand, mechanical influences on ventilation are represented by sensory afferents from the chest wall and respiratory muscles (Chourpiliadis and Bhardwaj, 2020). Perhaps as an illustration of the intricacies of ventilation regulation, respiratory muscles such as the genioglossus – a pharyngeal dilator muscle that maintains patency of the upper airway – are activated by both mechanical and chemical stimuli (Pillar et al., 2001); for instance, the genioglossus has upregulated activity in the presence of hypoxia (Gauda et al., 1991). Lastly, behavioral inputs also represent an arm of feedback to the respiratory center. This category includes the changes in ventilation that occur as an individual transitions from wakefulness to sleep (Chourpiliadis and Bhardwaj, 2020). As will be further discussed, the loss of the wakefulness drive to breathe and subsequent reliance on chemical regulation of ventilation in sleep constitutes part of the pathophysiology of CSA (Malhotra and Owens, 2010).

Classification, Pathophysiology and Diagnosis – Obstructive Sleep Apnea

In OSA, recurrent collapse of the upper airway during sleep occurs and results in reduced airflow, termed hypopnea, or a complete cessation of airflow altogether, termed apnea. Respiratory effort is maintained during the hypopneic or apneic event, which can be seen on polysomnography (PSG) as the presence of thoracic and abdominal movements.

Pathophysiologically, OSA can be due to any of a number of causes, including reduced pharyngeal dilator muscle forces, a susceptible upper airway anatomy, and excessive soft palate tissue. Airway obstruction is more likely to occur when an individual sleeps in the supine position, as upper airway collapsibility due to gravity increases (Arnold et al., 2017).

A diagnosis of OSA can be made through either PSG or home sleep apnea testing, using criteria from the *International Classification of Sleep Disorders* (ICSD) which specifies the presence of OSA if there are symptoms and comorbidities along with five or more predominantly obstructive respiratory events per hour or if there are 15 or more predominantly obstructive respiratory events per hour in an asymptomatic individual (Laratta et al., 2017). Additionally, the severity of OSA can be determined based on the apnea-hypopnea index (AHI), defined as the number of apneas and hypopneas per hour of total sleep time. Mild OSA is characterized by an AHI of 5 or greater, moderate OSA by an AHI of 15 or greater, and severe OSA by an AHI of 30 or greater (Laratta et al., 2017).

Classification, Pathophysiology and Diagnosis – Central Sleep Apnea

In CSA, impaired functioning of the medullary respiratory center responsible for breathing rhythm generation results in central apneas and hypopneas (Javaheri and Dempsey, 2013). In contrast to OSA, no thoracic and abdominal movements are seen on PSG.

It should be noted that while there is an abundance of pathology-associated cases of CSA, CSA can and does occur under normal physiological conditions as well; for instance, otherwise healthy individuals may experience sleep transition apneas caused by ventilatory instability during the transition from wakefulness to sleep (Malhotra and Owens, 2010). For pathologic cases of CSA, classifications are made depending on whether the CSA is nonhypercapnic, in which wakefulness P_aCO_2 levels are normal or slightly low, or hypercapnic, in which wakefulness P_aCO_2 levels are elevated (Eckert et al., 2007). The nonhypercapnic group of CSA syndromes includes idiopathic CSA and CSA related to medical conditions such as atrial fibrillation (AF), whereas the hypercapnic group of CSA syndromes encompasses disorders caused by either an impaired central respiratory drive or a downstream impairment in respiratory motor control (Eckert et al., 2007). Other pathologic cases of CSA include treatment-emergent or treatment-persistent CSA – CSA which arises with use of continuous positive airway pressure (CPAP) to treat existing OSA (Malhotra and Owens, 2010).

As a result of the aforementioned physiological differences between nonhypercapnic versus hypercapnic CSA, CSA pathophysiology varies greatly depending on the specific CSA syndrome. A general discussion of factors that increase risk of CSA

events describes the concepts of apneic threshold (AT) and loop gain (Javaheri and Dempsey, 2013, Dempsey et al., 2012). AT refers to a given individual's critical value of $P_a\text{CO}_2$ for which if the individual's $P_a\text{CO}_2$ level falls below this value, then a CSA event will occur. Thus, a given individual's CO_2 reserve is highly important as a larger reserve – a larger difference between the individual's eupneic $P_a\text{CO}_2$ level and AT – will protect against CSA events (Muza, 2015). Loop gain refers to the stability of ventilatory control, such that high loop gain denotes a system with high instability and low loop gain denotes a system with low instability. In a system with high loop gain, then, a given ventilatory disturbance results in an over-exaggerated ventilatory response that predisposes the individual to breathing instability; an example is the waxing and waning Cheyne-Stokes breathing (CSB) pattern – a type of periodic breathing associated with central events – experienced by individuals with high chemosensitivity to CO_2 levels (Malhotra and Owens, 2010).

A diagnosis of CSA, specifically using PSG (Riha, 2015), can be made when 50% or more of total respiratory events are central in nature. Similar to the use of AHI to quantify OSA severity, the central apnea-hypopnea index (CAHI) is used to quantify CSA severity; a CAHI of 5 or greater is considered abnormal (Muza, 2015).

Epidemiology, Prevalence and Risk Factors

SDB is commonly seen in the general population, with certain epidemiological studies reporting a community prevalence of up to 20% (Jennum and Riha, 2009). For OSA in particular, although prevalence estimates vary depending on severity – with

estimates of 3-28% for OSA with an $AHI \geq 5$ and estimates of 1-14% for OSA with an $AHI \geq 15$ – it has been reported that 1 in 20 adults experiences OSA with daytime impairment (Young et al., 2002). Furthermore, as OSA is a multifactorial disorder with many predisposing risk factors including obesity status, gender, age, and hormonal factors (Martins et al., 2007), prevalence estimates further vary when these factors are taken into account (Young et al., 2002, Garvey et al., 2015). CSA, as compared to OSA, has been reported to have a low prevalence at 0.9%, and can also be stratified based on factors such as gender and age (Donovan and Kapur, 2016). Current data indicate that CSA is commonly seen in older males, with one cohort reporting a prevalence of 7.5% for males aged 65 and older (Mehra et al., 2007). Other important risk factors for CSA include opioid use and AF in individuals with existing congestive heart failure (CHF) (Filiatrault et al., 2016, Sin et al., 1999).

Clinical Aspects – Symptoms and Comorbidities

In terms of the clinical presentation of SDB, OSA and CSA present in similar ways (Malhotra and Owens, 2010). Symptoms of both SDB phenotypes include sleep fragmentation, morning headaches, excessive daytime sleepiness (EDS), and more (Eckert et al., 2007, Muza, 2015). As the breathing irregularities lead to oxygen desaturations and arousals occur, increases in sympathetic nervous system activity ensue (Yoshihisa and Takeishi, 2019). This sympathetic activation is thought to contribute to the pathogenesis of cardiovascular disease (CVD) (Budhiraja et al., 2010). Therefore, major comorbidities associated with SDB include coronary artery disease (CAD), stroke,

and AF (Burman, 2017), all of which decrease quality of life and therefore highlight the importance of screening for and treating SDB. Figure 1 shows the different pathways through which SDB can lead to CVD.

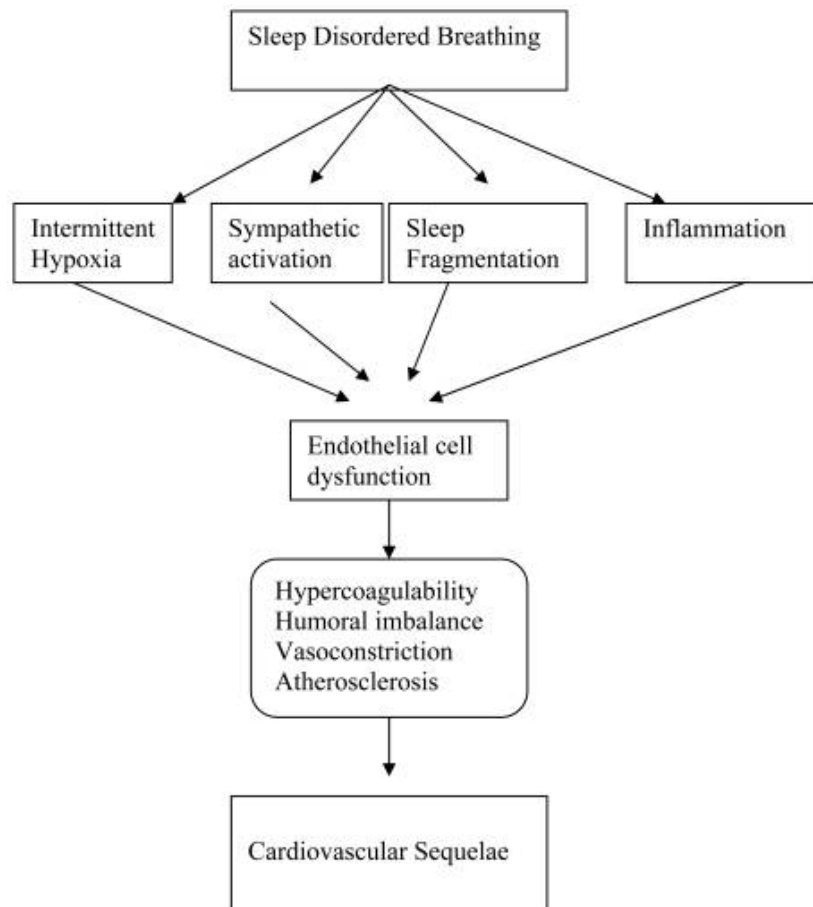


Figure 1: Mechanisms by which SDB may lead to CVD. Figure from Budhiraja et al., 2010.

Clinical Aspects – Treatment

Treatment of SDB depends on several factors, including disease and symptom severity, presence and extent of comorbidities, and patient preferences. Currently, the mainstay of SDB treatment is CPAP – a type of positive airway pressure (PAP) in which a machine delivers a constant and steady air flow to keep the airways open (Pinto and Sharma, 2020), although alternatives such as oral appliances are also available options. Importantly, addressing modifiable risk factors, such as weight, through an emphasis on lifestyle interventions should not be overlooked as part of SDB treatment (Stephen et al., 2004). Treatment of CSA in particular, however, is more challenging – options are limited and CPAP has failed to show an improvement in survival among patients with CSA and heart failure (HF) (Abraham et al., 2018, Bradley et al., 2005).

Atrial Fibrillation

AF occurs when disorganized electrical impulses in the atrial chambers of the heart lead to an irregular, oftentimes tachycardic, rhythm. As the most common type of cardiac arrhythmia, AF represents a significant public health burden (Nesheiwat et al., 2020). This section includes a discussion of basic heart rhythm physiology and AF pathophysiology, the types and diagnosis of AF, epidemiology, and clinical aspects.

Basic Cardiac Electrophysiology

A basic understanding of cardiac electrophysiology is essential for understanding the pathophysiology that underlies AF. Normal electrical conduction through the heart follows a specific pathway that starts at the sinoatrial (SA) node in the right atrium and ends in the many Purkinje fibers that supply the ventricles (Oberman and Bhardwaj, 2020). Of critical importance to maintaining a normal heart rhythm is the atrioventricular (AV) node, downstream of the SA node and located in the right atrium proximal to the interatrial septum, which ensures that ventricular contraction occurs following atrial contraction (Oberman and Bhardwaj, 2020). To achieve this, conduction is slow through the AV node and thus allows for proper ventricular filling with blood and maintenance of cardiac output.

The electrocardiogram (ECG) reflects the electrical activity of the heart by way of electrodes placed on the body surface that measure voltages generated by the different regions of the myocardium (Sattar and Chhabra, 2020). Used as a tool for diagnosis of CVD, including AF, ECG has major clinical significance. As illustrated in Figure 2, an ECG consists of waves, intervals, and segments, with the various terminology – P wave, PR interval, QRS complex, T wave, and QT interval – referring to depolarizations and repolarizations of specific parts of the heart. Briefly, the P wave represents atrial depolarization, the PR interval represents time from first atrial depolarization to first ventricular depolarization, the QRS complex – consisting of the Q, R and S waves – represents ventricular depolarization, the T wave represents ventricular repolarization,

and the QT interval represents time from first ventricular depolarization to last ventricular repolarization.

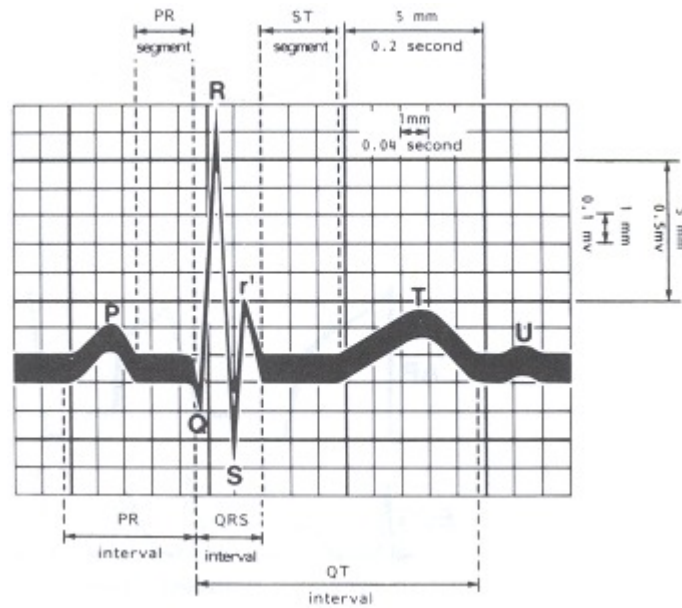


Figure 2: Normal ECG with waves, intervals and segments labeled. Figure from Noble et al., 1990.

Pathophysiology of Atrial Fibrillation

In AF, the normal sinus rhythm (SR) – the rhythm which originates from the SA node – is instead replaced by rapid and irregular atrial depolarizations, leading to uncontrolled electrical activity that cause the atria to quiver, or fibrillate (Dang et al., 2002). Mechanistically, AF pathogenesis has been described to occur through the processes of initiation, brought about by triggers, and perpetuation, brought about by a vulnerable atrial substrate (Staerk et al., 2017). AF initiation is described to be caused by triggers such as pulmonary vein (PV) ectopic activities. In fact, PV cardiomyocytes have

been found to have electrophysiological properties that increase their likelihood of causing arrhythmia (Ehrlich et al., 2003). AF perpetuation mechanisms have not yet been fully elucidated (Cheniti et al., 2018), but a vulnerable atrial substrate characterized by fibrosis and electrical remodeling is thought to promote AF perpetuation. Additional modulating factors, such as inflammation, have been found to be associated with AF pathogenesis (Phillips, 2013).

On ECG, classic features indicating AF include the absence of well-defined P waves – reflecting the lack of organized atrial depolarizations – and irregularly irregular R-R intervals – reflecting the lack of a pattern of ventricular contraction (Dang et al., 2002). These hallmark features are illustrated in Figure 3, which shows an ECG tracing of an individual with AF.



Figure 3: ECG tracing showing AF. Figure from Becker, 2006.

Classification and Diagnosis

AF is typically classified into three major types – paroxysmal, persistent and permanent. Paroxysmal AF is that which lasts less than 48 hours and usually resolves on its own; persistent AF is that which lasts for more than a week and continues until an

intervention is performed to terminate the arrhythmia; permanent AF is that which persists indefinitely despite attempts to restore SR (Dang et al., 2002).

AF diagnosis is usually confirmed using ECG when there is a clinical suspicion based upon factors such as elevated pulse rate and other symptoms including fatigue, palpitations, chest pain, syncope, and more. However, caveats include the fact that ECG may not detect a paroxysmal arrhythmia and the fact that patients with AF may be asymptomatic. Therefore, additional cardiac monitoring using devices that track activity over a 24-hour period or longer may be used in instances where presence of AF is inconclusive (Gutierrez and Blanchard, 2016).

Epidemiology, Prevalence and Risk Factors

AF is a condition on the rise – the 2001 Anticoagulation and Risk Factors in Atrial Fibrillation Study predicted a then-estimate of 2.3 million adults in the United States with AF and projected this number to increase to upwards of 5.6 million by 2050 (Go et al., 2001). This increase in AF prevalence reflects the aging population, as age is one of the risk factors associated with AF. In fact, AF is reported to be present in just 0.12%-0.16% of individuals younger than 49 years of age, but in 10%-17% of individuals at least 80 years of age. Besides age, sex is also implicated to affect AF occurrence – males are 1.2 times more likely than females to have AF (Zoni-Berisso et al., 2014). Other important risk factors for AF development include a wide range of conditions and lifestyle habits such as sleep apnea, HF, diabetes, hyperthyroidism, obesity, heavy alcohol consumption, and more (Brandes et al., 2018).

Clinical Aspects – Symptoms and Comorbidities

Typical AF symptoms include irregular palpitations, shortness of breath, exercise intolerance and a general lack of energy. Furthermore, the predominant symptom seen in clinic may vary depending on the type of AF (Dang et al., 2002). In terms of comorbidities, AF is known to be strongly associated with CVD; however, as previously mentioned, non-cardiovascular conditions such as diabetes and SDB have also been shown to impact AF development (Ferreira et al., 2015). This study will further examine the links between SDB – in particular, CSA – and AF.

Clinical Aspects – Treatment

As AF is known to confer an increased risk of adverse events – such as stroke, transient ischemic attack and even death – it is imperative that AF is properly managed (Amin et al., 2016). Generally, AF management is approached as acute treatment and long-term treatment. For AF which presents acutely, cardioversion to SR is usually an option and the probability of remission is greater than for chronic AF. For chronic AF, goals of treatment include symptom and rate control (Kakar et al., 2007).

The Relationship Between Sleep-Disordered Breathing and Atrial Fibrillation

SDB and AF are both major clinical entities, but the interrelationship between them is just as significant. As previously discussed, SDB and AF are commonly comorbid, and the presence of one condition is known to increase the risk of developing

or exacerbating the other condition. Thus, SDB and AF are putatively linked through a bidirectional relationship (Marulanda-Londoño and Chaturvedi, 2017, Leung et al., 2005). This section will discuss what is known about the relationships between OSA & AF and CSA & AF, with a focus on the latter.

Obstructive Sleep Apnea and Atrial Fibrillation

Many studies point to a strong association between OSA and AF. For instance, it has been shown that even after accounting for various CVD confounders – such as CAD, HF, and hypertrophic cardiomyopathy – the prevalence of AF is still higher if preexisting OSA is present (Lavergne et al., 2015). Conversely, research has also shown that OSA risk is greater in the presence of AF – one study found that AF patients were twice as likely to develop OSA compared to a general cardiology patient group with CVD but no concurrent or history of AF (Gami et al., 2004). Finally, studies have also found that untreated OSA negatively impacts AF treatment, as patients using CPAP have lower rates of AF recurrence (Marulanda-Londoño and Chaturvedi, 2017).

Central Sleep Apnea and Atrial Fibrillation

While the association between OSA and AF is quite firmly established, the links between CSA and AF are less robust. As is the case for OSA and AF, several lines of evidence have indicated that the relationship between CSA and AF is also likely bidirectional. In a large retrospective study of CHF patients who were evaluated at a

sleep center, researchers found that having AF significantly increased the risk of CSA but not OSA (Sin et al., 1999). It has also been demonstrated that this link between CSA and AF persists even in the absence of underlying CVD. One study found a higher AF risk in patients with idiopathic CSA who did not have a history of CHF (Leung et al., 2005).

Several studies have concluded that the association between CSA and AF is even more pronounced than that between OSA and AF (Tung et al., 2017). This warrants deeper investigations into the CSA-AF relationship, as there are still numerous gaps in knowledge; researchers have described how there is a paucity of data on the prevalence of CSA in patients with AF (Lavergne et al., 2015). For instance, although studies have reported that male gender and increasing age are independent risk factors for CSA (Sin et al., 1999), less clearly established are more specific details about the potential effects of age and gender – for instance, how CSA in individuals with AF is either over- or underrepresented across age groups and between males and females. Furthermore, more research is needed in the realm of treatments – in particular, in identifying how treatment of CSA affects AF and how efficacious this CSA treatment is (Tung et al., 2017). Because of the increased mortality and risk of adverse outcomes associated with having both conditions, knowledge regarding treatment effects are of major clinical importance. Finally, this also raises the question of how improvements can be made in screening for CSA, as patients can present with minimal or no symptoms (Abraham et al., 2018).

A Collaborative Care Model: Sleep Medicine and Cardiology

As SDB and AF are commonly encountered conditions in their respective specialties - sleep medicine and cardiology - but also commonly comorbid and known to affect each other, it becomes apparent that a collaborative care system between these two medical specialties is essential in order to deliver optimal patient care. A collaborative care model recognizes the inherent complexities in managing two or more chronic conditions that, together, have significant negative impacts on health outcomes, and attempts to better facilitate management of such conditions through coordinated partnership. Such collaboration in healthcare not only improves individual and community health outcomes, but has also been shown to be cost-effective (Ivbijaro et al., 2014).

Numerous examples of successful collaboration have been noted; for instance, that between primary care and mental health care (Ivbijaro et al., 2014). Currently, the collaboration between sleep medicine and cardiology – especially that relating to sleep apnea management – is a work in progress, but one that is clinically important as it enhances patient care (Kwon et al., 2018). In this study, the collaboration between sleep medicine and cardiology is seen through the referrals and management of patients with AF who are evaluated for SDB.

Specific Aims

- 1) Summarize sleep testing and sleep apnea therapy results, focusing on sleep pathology, treatment patterns and treatment outcomes.
- 2) Explore the relationship of central sleep apnea or high loop gain effects in atrial fibrillation patients.
- 3) Assess the impact of gender on the type of sleep apnea and treatment outcomes.
- 4) Describe a collaborative care model for sleep management in atrial fibrillation.

METHODS

Study Design and Subjects

This is a retrospective analysis of clinical patient data from home sleep apnea testing, PAP therapy and cardiac reports. Subjects are cardiology patients who were seen in the cardiac electrophysiology clinic at Beth Israel Deaconess Medical Center (Boston, Massachusetts, USA) for cardiac arrhythmia – predominately AF – management, and subsequently offered the WatchPAT home sleep apnea testing device.

WatchPAT sleep study reports were collected for a total of 153 patients; these reports contain data collected between 2018 and 2020. Parameters examined in the reports – including respiratory indices, oxygen saturation and sleep phases – are used to understand how much sleep pathology is present in the study population. Additionally, information from these reports are used to explore relationships between SDB, AF and gender.

PAP therapy compliance and efficacy data were available for only 28 patients. Many patients had different data available (three-month data only or three- and six-month data); however, these data were collected largely between 2018 and 2019, with some patients whose therapy is currently ongoing and thus these patients have data in 2020. These therapy data are used to understand treatment efficacy outcomes, patterns of adherence to therapy over time and any potential effects on cardiac status later on through comparison with data from ECG reports.

WatchPAT Device

The WatchPAT device (Itamar Medical, Ltd) was used to screen patients for SDB. WatchPAT is a home sleep apnea testing device, approved by the Food and Drug Administration (FDA), that is used to detect SDB – both OSA and CSA. The portable device is worn on the wrist and uses peripheral arterial tonometry (PAT), pulse oximetry, and actigraphy to generate information regarding respiratory disturbances; this allows the WatchPAT device to indirectly detect apnea and hypopnea events through measuring the changes in peripheral arterial volume using finger plethysmography (Yalamanchali et al., 2013). Then, this information is analyzed by an automated algorithm, and the results are available in a sleep study report.

There are many advantages to using the WatchPAT device – the technology is portable, non-invasive and accurate. The portability and user-friendliness of WatchPAT makes the device a valuable alternative to PSG, which is logistically more difficult for patients as testing is performed in a laboratory setting and waiting times to have testing done can oftentimes be long (Yalamanchali et al., 2013). However, WatchPAT has nevertheless been shown to provide accurate and reliable results, with an abundance of studies showing that sleep indices – for instance, AHI – measured using PAT are similar to those measured using PSG (Bar et al., 2003, Penzel et al., 2002, Ayas et al., 2003). Furthermore, the algorithm used to generate results may be seen as superior to the inherent variability in PSG scoring (Yalamanchali et al., 2013).

Reports and Databases

Each WatchPAT sleep study report contains a wide range of information and graphical displays – patient characteristics such as body mass index (BMI) and Epworth Sleepiness Scale (ESS) score, medical history, concurrent medications, respiratory indices, oxygen saturation statistics, pulse rate statistics, sleep stage percentages, and more. In addition to the WatchPAT sleep study report generated for each patient, compliance and efficacy data from use of different PAP therapy devices were also utilized – those from the AirView and Encore databases. AirView and Encore are patient management systems used to monitor therapy compliance. AirView and Encore reports contain information regarding patient compliance and therapy efficacy and can be customized to generate data of a desired timeframe. For this study, three- and six-month compliance data were utilized; parameters describe device usage, mask leak and respiratory indices. Of note, a substantial number of patients did not have compliance and efficacy data available in either of the AirView or Encore databases. Finally, the online medical record (OMR) was used to obtain high loop gain data from PSG reports and cardiac data from ECG reports. Again, these data were not available for all patients.

Statistical Analysis

Data from each patient's WatchPAT sleep study report, PAP therapy reports from AirView and Encore and OMR reports, the latter two if applicable, were entered into

Excel and subsequently analyzed using Statistical Package for Social Sciences (SPSS) (IBM Corporation, USA).

Crosstabulation tables were frequently utilized in order to understand any potential association between two categorical variables. Significance values (two-tailed p-values) were obtained from the chi-square and Fisher's exact tests; the latter was preferably used whenever a 2x2 contingency table was to be analyzed, since the sample sizes were often small. Additionally, two-tailed p-values were also obtained from independent samples t-tests that were performed to compare means. For these tests, the significance value for Levene's test for equality of variances was checked; if significance was <0.05 , then the two-tailed p-value corresponding to "equal variances not assumed" was used. Finally, descriptive statistics on frequencies were obtained for categorical variables, in order to understand prevalence, and also for scale variables, in order to understand measures of central tendency and dispersion.

RESULTS

Patient Characteristics and Sleep Pathology

Of the 153 patients, 111 were male and 42 were female. The mean and median age of patients were 63.4 and 63 years, respectively. 94 patients had an ESS score and 150 patients had a BMI reported on their WatchPAT sleep study report; the mean and standard deviation for these parameters were 6.14 ± 4.52 for ESS and 29.87 ± 5.65 for BMI. When analyzed by gender, the mean and standard deviation for ESS in males and females were 5.90 ± 4.47 and 7.04 ± 4.70 , respectively. The mean and standard deviation for BMI in males and females were 30.30 ± 4.96 and 29.25 ± 6.49 , respectively.

Included in each WatchPAT sleep study report are sections detailing the patient's medical history and current medications. CVD, for instance, is pertinent to a discussion of SDB and AF as it is oftentimes a comorbidity shared by both. These clinical data on patient comorbidities and medications are summarized in Tables 1 and 2. As shown in Table 1, of the arrhythmias, AF was most commonly reported (72.5%). Other frequently reported conditions include hypertension (40.5%), hyperlipidemia (17.6%) and thyroid diseases such as hyperthyroidism (9.8%); these conditions are indeed all known to be associated with either CVD, which predisposes to AF, or AF itself (Ogunsua et al., 2015, N and Francis, 2005, Nelson, 2013). Table 2 captures the wide range of medications taken by the patients in this study; again, the most commonly used medications were those that treat arrhythmias and/or CVD, such as anticoagulants (63.4%), beta-blockers

(50.3%), lipid-lowering therapies (39.2%), antiarrhythmics (25.5%), ACE inhibitors (22.9%) and antiplatelets (20.9%).

Table 1. Frequency table of patient comorbidities.

CAD: coronary artery disease, AF: atrial fibrillation, SVT: supraventricular tachycardia, CKD: chronic kidney disease, HF: heart failure.

	Percentage
Hypertension	40.5
Diabetes	6.5
CAD	3.3
Stroke	0.7
AF	72.5
Atrial flutter	9.2
SVT	3.3
Ventricular tachycardia	0.7
Atrial tachycardia	2.6
Other arrhythmia	3.9
Depression	2.6
CKD	2.6
HF	2.6
Hyperlipidemia	17.6
Dyslipidemia	3.3
Obesity	4.6
Thyroid disease	9.8
Cancer	5.2
Acid reflux	13.1
Allergies	9.2
Asthma	5.2
Anxiety	5.2
Syncope	4.6
Cardiomyopathy	1.3
Carotid stenosis	1.3
Valvular disease	2
Other	24.8

Table 2. Frequency table of patient medications.

ACE inhibitor: angiotensin-converting enzyme inhibitor, PPI: proton-pump inhibitor, ARB: angiotensin receptor blocker, NSAID: nonsteroidal anti-inflammatory drug, H2 blocker: histamine type 2 receptor blocker, PDE5 inhibitor: phosphodiesterase type 5 inhibitor, OTC: over-the-counter.

	Percentage
Diuretic	17.6
ACE inhibitor	22.9
Beta-blocker	50.3
Lipid-lowering therapy	39.2
Diabetes therapy	10.5
Antidepressant	19.6
Antianxiety	10.5
Antibiotic	2
Stimulant	0.7
Anticoagulant	63.4
PPI	17.6
Antiarrhythmic	25.5
Thyroid medicine	11.8
Calcium-channel blocker	18.3
Antiplatelet	20.9
ARB	15.7
Bronchodilator	7.8
Corticosteroid	13.7
Melatonin/Sedative	7.2
Nitrate	2
Cancer therapy	2
Antihistamine	4.6
Anti-gout	4.6
NSAID	5.9
H2 blocker	2.6
Digoxin	2.6
Alpha-adrenergic blocker	3.9
PDE5 inhibitor	2.6
Antianginal	0.7
Other	21.6
OTC	29.4

Table 3 shows the means and standard deviations for the three respiratory indices recorded by WatchPAT – AHI, respiratory disturbance index (RDI) and CAHI. The RDI is similar to the AHI, but takes into account respiratory effort-related arousals (RERAS) in addition to apneas and hypopneas (Krakow et al., 2014). RERAS are defined as breathing events, neither classified as apneas nor hypopneas, that are characterized by a reduced flow of air due to an obstructed upper airway and that ultimately lead to arousal (Tsara et al., 2009). As seen in Table 3, the patients in this study population represent, on average, OSA of at least moderate severity (mean AHI of 15.45 and mean RDI of 19.20). It should be noted that a considerable number of patients had a CAHI of 0 (n=77); these individuals account for almost two-thirds of all patients with a CAHI<5 (n=127). For those patients with a CAHI \geq 5 (n=22), the mean and standard deviation for CAHI were 14.05 and 9.29, respectively. Thus, the overall patient population may not, on average, present with CSA based on CAHI criteria (mean CAHI of 2.60), but for those 22 patients with a CAHI \geq 5, the CSA is, on average, of at least moderate severity. These respiratory indices thus demonstrate that the patients in this study represent a group with at least moderate sleep pathology.

Table 3. WatchPAT respiratory index data.

Values are reported as mean±SD. AHI: apnea-hypopnea index, RDI: respiratory disturbance index, CAHI: central apnea-hypopnea index.

All patients (n=153)	
AHI	15.45±15.85
RDI	19.20±15.64
CAHI	2.60±6.02

Patients with high loop gain were also defined as having CSA; thus, patients were classified as having CSA if they had a CAHI \geq 5 and/or high loop gain present on PSG. Patients were classified as not having CSA only if they had a CAHI $<$ 5 and had no high loop gain present on PSG. A total of 14 patients in this study were recorded as having high loop gain.

Table 4 summarizes the remaining quantitative parameters measured by WatchPAT, with the results categorized by presence or absence of CSA based on the aforementioned criteria. Four patients with missing data, either for CAHI or high loop gain or both, were excluded from this analysis. The means and standard deviations for all parameters reported in Table 4 are quite similar between all patients and patients with a CAHI $<$ 5 and no high loop gain. However, statistically significant differences were found between patients with CAHI $<$ 5 and no high loop gain and patients with CAHI \geq 5 and/or high loop gain for two parameters: percentage of deep sleep and oxygen desaturation index (ODI). The most pronounced differences shown in Table 4 are thus between

patients without CSA and patients with CSA. For these CSA patients, then, the sleep pathology is such that sleep architecture and oxygen saturation are significantly affected. The results of deep sleep in particular will be further discussed in a subsequent section.

Table 4. Summary of quantitative WatchPAT data. Values are reported as mean±SD. Two-tailed p-values are calculated using the independent samples t-test (test variables are each of the nine quantitative parameters examined, grouping variable is the presence or absence of CSA: CAHI<5 and no HLG and CAHI≥5 and/or HLG). Statistically significant p-values (<0.05) are in bold. A confidence interval (CI) of 95% was used. HLG: high loop gain, TST: total sleep time, SE: sleep efficiency, REM sleep: rapid eye movement sleep, ODI: oxygen desaturation index, SpO₂: oxygen saturation, HR: heart rate.

	All patients (n=153)	CSA status		P-value
		CAHI<5 and no HLG (n=113)	CAHI≥5 and/or HLG (n=36)	
TST (min)	409.45±72.21	410.35±65.99	402.58±82.81	0.565
SE (%)	83.95±7.53	84.23±6.29	82.39±10.55	0.327
Light sleep (%)	66.71±10.45	66.11±10.24	68.39±11.41	0.270
Deep sleep (%)	13.65±5.94	14.33±5.81	11.53±6.19	0.016
REM sleep (%)	19.64±7.26	19.56±7.09	20.08±8.10	0.715
ODI	12.83±13.58	8.25±8.53	26.76±16.36	0.000
Mean SpO ₂	94.01±1.46	94.14±1.52	93.61±1.20	0.058
Time (min) SpO ₂ <88%	6.35±18.06	4.73±16.00	12.04±23.47	0.088
Mean HR	61.87±13.44	62.21±13.05	61.58±14.63	0.807

Central Sleep Apnea-Atrial Fibrillation Interface and Gender Effects

Based on the medical history provided in the WatchPAT sleep study reports, 111 patients were documented as having AF. To explore the relationship between preexisting AF and CSA risk, a crosstabulation table was generated using presence or absence of AF and presence or absence of a CAHI \geq 5 and/or high loop gain as categorical variables. The results, shown in Table 5, show that CSA was considered to be present in 6 out of 22 patients with no preexisting AF and 23 out of 109 patients with preexisting AF. While the table shows a greater absolute number of patients deemed as having CSA in the group of patients with AF, statistical analysis using Fisher’s exact test generated a two-tailed p-value of 0.576. Therefore, in the study population examined, no significant relationship was found between CSA and AF.

Table 5. Crosstabulation table for relationship between AF and CSA.

**Atrial Fibrillation * CAHI \geq 5 and/or HLG
Crosstabulation**

		CAHI \geq 5 and/or HLG		Total
		No	Yes	
Atrial Fibrillation	Absent	16	6	22
	Present	86	23	109
Total		102	29	131

In order to better understand the impact of gender on the type of SDB (OSA or CSA), a crosstabulation table showing the relationship between gender and OSA frequency was generated and compared to a crosstabulation table showing the

relationship between gender and CSA frequency. Presence or absence of OSA was determined based on AHI score; patients were considered to have OSA if their AHI was 5 or greater. These results, shown in Tables 6 and 7, demonstrate a statistically significant relationship between gender and CSA (chi-square two-tailed p-value of 0.027), but not between gender and OSA (chi-square two-tailed p-value of 0.203). Both OSA and CSA, however, appear to be more prevalent in males than in females.

Table 6. Crosstabulation table for relationship between gender and OSA frequency.

Gender * AHI Groups Crosstabulation

		AHI Groups		Total
		AHI<5	AHI≥5	
Gender	Male	32	76	108
	Female	17	25	42
Total		49	101	150

Table 7. Crosstabulation table for relationship between gender and CSA frequency.

**Gender * CAHI≥5 and/or HLG
Crosstabulation**

		CAHI≥5 and/or HLG		Total
		No	Yes	
Gender	Male	75	31	106
	Female	37	5	42
Total		112	36	148

The vast majority of female patients were 51 years of age or older (40 out of 42); these patients were identified in order to examine, as a sub-analysis, the effect of postmenopausal status on CSA risk. This age cutoff was based on literature that reports the median age of menopause to be 51 years of age (Peacock and Ketvertis, 2020).

Table 8 shows the results of postmenopausal status on CSA risk in females. These results show that postmenopausal females (females ≥ 51 years of age) do not seem to be at an increased risk for CSA compared to premenopausal females (females < 51 years of age). Importantly, however, there are significantly fewer females < 51 years of age; nevertheless, that only 5 out of 40 postmenopausal females had a CAHI ≥ 5 and/or high loop gain suggests that postmenopausal status may not play a major role in conferring an increased risk of CSA.

Table 9 shows that although the majority of postmenopausal females did not have a CAHI ≥ 5 and/or high loop gain (n=35), the majority, 27 out of 30 patients, were still documented to have AF. Five patients were excluded due to missing AF data. Since AF is generally thought to be associated with CSA, there may be other factors influencing CSA risk in this specific cohort of patients.

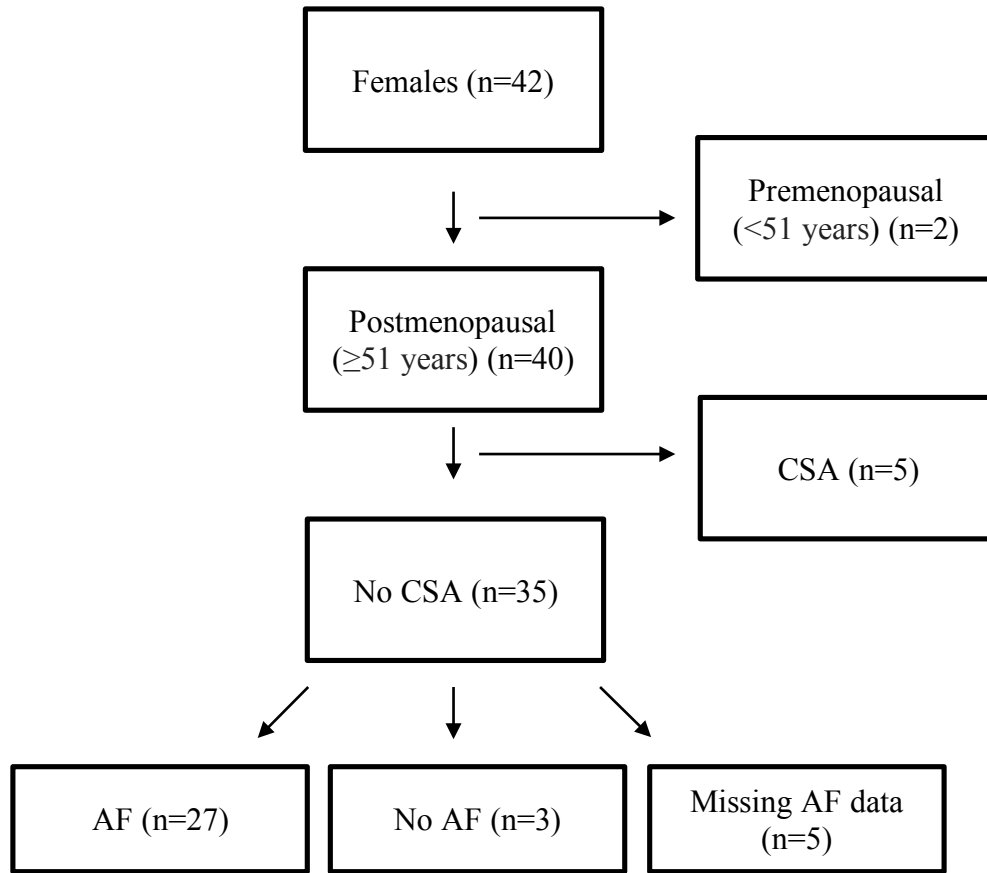


Figure 4: Flowchart classifying female patients by menopausal, CSA and AF statuses.

Table 8. Crosstabulation table for relationship between menopausal status and CSA frequency.

**Female Gender * CAHI≥5 and/or HLG * Menopause Status
Crosstabulation**

		Age	CAHI≥5 and/or HLG		Total
			No	Yes	
Gender	Female	<51	2	0	2
		≥51	35	5	40
		Total	37	5	42

Table 9. Frequency table displaying prevalence of AF in postmenopausal females without CSA (n=35).

Atrial Fibrillation in Postmenopausal Females without CSA

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Absent	3	8.6	10.0	10.0
	Present	27	77.1	90.0	100.0
	Total	30	85.7	100.0	
Missing	System	5	14.3		
Total		35	100.0		

Positive Airway Pressure Therapy Treatment Outcomes and Attrition

The compliance and efficacy outcomes of PAP therapy, retrieved from the Encore database, are shown in Table 10. The parameters describe device usage, device leak, respiratory indices and periodic breathing. The results show that, over a period of three months, usage generally declined and leakage increased; but, overall, improvements were made in the respiratory indices that characterize SDB severity.

Table 10. PAP therapy compliance and efficacy data, over three and six months, for patients with both three- and six-month data (n=20). Values are reported as mean±SD. AHI: apnea-hypopnea index, OA index: obstructive apnea index, CA index: central apnea index, PB: periodic breathing.

	3 months	6 months
Days with device usage	83.25±11.75	159.45±34.03
Days with usage \geq 4 hours (%)	79.19±21.97	77.12±24.54
Average usage, days used (min)	373.00±80.79	378.85±80.17
Average usage, all days (min)	340.95±102.36	335.85±116.39
Average time in large leak (min)	12.85±32.46	15.05±42.83
Average % of night in large leak	4.23±11.51	4.93±15.03
Average AHI	3.91±2.97	3.44±2.38
Average OA index	1.10±1.14	0.94±1.05
Average CA index	0.60±0.85	0.50±0.74
Average % of night in PB	2.29±3.25	2.16±3.05

On the other hand, Table 11 shows the average residual AHI, average OA index and average CA index – each examined over three and six months of therapy use – for males and females. As noted in Table 10, all three respiratory indices decreased from three to six months of therapy; Table 11 shows that both males and females saw decreases in all indices. However, the results demonstrate that gender did not have a significant impact on treatment efficacy outcomes in the patient population studied, as all p-values were greater than 0.05.

Table 11. Three- and six-month average values for respiratory indices in male (n=13) versus female (n=7) patients, for patients with both three- and six-month data (n=20). Values are reported as mean±SD. Two-tailed p-values are calculated using the independent samples t-test (test variables are each of the three respiratory indices examined over three and six months, grouping variable is gender: male and female). None of the p-values were statistically significant (<0.05). A CI of 95% was used.

	Male (n=13)	Female (n=7)	P-value
3 month average AHI	3.79±3.05	4.13±3.03	0.817
6 month average AHI	3.29±2.23	3.73±2.79	0.702
3 month average OA index	0.82±0.73	1.63±1.60	0.132
6 month average OA index	0.66±0.55	1.46±1.54	0.229
3 month average CA index	0.49±0.62	0.80±1.19	0.452
6 month average CA index	0.39±0.51	0.70±1.06	0.388

Although PAP therapy data was scarce – available for only 28 patients and only 20 patients had both three- and six-month compliance data available on Encore – the available data show a pattern of attrition. Analysis of compliance data showed that, from three to six months, adherence to therapy slightly decreased (Table 10). Over the course of three months, the “days with device usage” parameter decreased from a mean of 91.2% to a mean of 87.4% (three- and six-month mean days with device usage were 83.25 and 159.45 days, respectively). The “percentage of days where usage was ≥4 hours per night” parameter also decreased from a mean of 79.2% to a mean of 77.1%, again, over the course of three months.

Cardiac Data

To assess the potential impact of PAP therapy for SDB on cardiac status, left ventricular ejection fraction (LVEF) data from patient ECG reports were obtained from the OMR. LVEF data was available for 75 patients; for these patients, the mean, standard deviation, minimum and maximum LVEF were 56%, 13.33, 10% and 79%, respectively. The use of LVEF to reflect cardiac status is based on literature that reports AF patients to have adverse hemodynamic changes – specifically, one study found LVEF to immediately increase in AF patients after cardioversion to SR (Manning et al., 1994). Thus, in this study, improvements in LVEF are used to reflect improvements in AF.

Focus was on the twelve patients with both LVEF data and three- and six-month PAP therapy compliance data. All twelve patients met the criteria for OSA and/or CSA as defined in this study: $AHI \geq 5$ for OSA and $CAHI \geq 5$ and/or high loop gain for CSA. Of these twelve patients, six had an ECG report dated after their PAP therapy start date. Of these six patients, five had a normal LVEF ($>50\%$) as defined in the literature (Hamdani and Paulus, 2011). Each patient's LVEF percentage was then compared to the approximate time elapsed since cardiac data collection and therapy start date, as well as their compliance change from three to six months. These comparisons provided the context for interpreting cardiac changes that may have been influenced by therapy use. These results are summarized in Table 12.

Table 12. LVEF data for the six patients with OSA and/or CSA and with three- and six-month PAP therapy compliance data. LVEF: Left ventricular ejection fraction. Compliance change from three to six months was calculated for each patient using the difference between the three- and six-month “Days with Device Usage” percentage values.

Patient	LVEF (%)	Approximate time elapsed between cardiac data collection & therapy start date	Compliance change from 3 to 6 months
1	63	1 month	96.4% → 96.4% No change
2	60	1 year	88.8% → 86.6% -2.2%
3	55	1 year	98.6% → 99.2% +0.6%
4	10-15	2 months	70.1% → 63.6% -6.5%
5	70	4 months	93.2% → 92.6% -0.6%
6	55	1 year	96.4% → 91.0% -5.4%

Epworth Sleepiness Scale and Deep Sleep

For the 94 patients for whom an ESS score was reported on their WatchPAT sleep study report, the mean ESS was 6.14 and only 18 patients had an ESS>10. The mean ESS for the 28 out of 36 patients with a CAHI \geq 5 and/or high loop gain for whom a value was reported was 5.89. This was not significantly different than the mean ESS for the 48 out

of 77 patients with a CAHI of 0 for whom a value was reported, which was 6.63. These results suggest that CSA did not seem to significantly impact subjective sleepiness.

For the 150 patients with available sleep phase percentage data, the mean and standard deviation for percentage of deep sleep were 13.65% and 5.94, respectively. Of note, a substantial number of patients – 48 out of 150 patients – had <10% deep sleep. This represents approximately 31% of all patients, which is higher than anticipated.

DISCUSSION

Patients and Sleep Pathology

Analysis of the medical history, concurrent medication and quantitative data from each WatchPAT sleep study report shows that the patient population studied has, on average, considerable cardiovascular comorbidity and at least moderate severity sleep apnea. When the sleep, oxygen saturation and pulse rate parameters were specifically examined between patients with CSA and patients without CSA, it was found that those with CSA had significantly less deep sleep and a greater ODI. These results are consistent with what is known about CSA, and SDB in general – that the repeated lapses in breathing not only cause oxygen saturation to decrease, but ultimately lead to arousals and less slow-wave, restorative sleep as well (Dempsey et al., 2010). Understanding the clinical background and disease severity of patients is important in order to correctly interpret the data and draw conclusions from the results.

Central Sleep Apnea, Atrial Fibrillation and Gender

Although Table 5, which displayed the relationship between patients with preexisting AF and CSA frequency, did not show that the association between these two variables was statistically significant, the pattern seen in the crosstabulation table still showed that those with preexisting AF met the study criteria for CSA more often than those without preexisting AF. It is likely that the small sample size of the study, including the largely unequal ratio of patients with AF to patients without AF, influenced these

results and therefore did not allow for the conclusion of a significant association between CSA and AF to be made.

Upon examining the impact of gender on the type of SDB, the patterns in the crosstabulation tables suggested that males generally have a higher frequency of both types of SDB – OSA and CSA, which is consistent with the literature that reports SDB to be more common in men than in women (Mieno et al., 2018). However, while the relationship between gender and CSA was found to be statistically significant, that between gender and OSA wasn't. This finding, especially given that roughly equal numbers of males and females were included in both Tables 6 and 7, may perhaps have been due to the fact that the females in this study simply had more risk factors for OSA than for CSA – such as, for instance, having an average BMI that falls into the category of “overweight” according to guidelines from the National Institutes of Health (NIH) (Nuttall, 2015). Another explanation for the different results could be that the criteria used to establish OSA presence in this study – namely, an $AHI \geq 5$ – had led to all patients, representing a wide range of disease severity, being included in the data analysis. Alternatively, it could be that some aspect of the underlying mechanism of CSA pathogenesis is simply more affected by factors unique to gender.

The results of the analysis of postmenopausal status on CSA risk were interesting in that although only 5 out of 40 postmenopausal females had a $CAHI \geq 5$ and/or high loop gain, of the remaining 35 postmenopausal females, the majority had AF (n=27 or 77.1%). Additionally, because five patients were missing information regarding their AF status, this percentage may be an underestimation. These results appear contradictory – on one

hand, research shows that the presence of AF increases CSA risk in both genders (Sin et al., 1999). At the same time, it has been reported that postmenopausal women have a higher risk of CSA than premenopausal women due to hormonal differences between the two groups (Grayburn et al., 2014). Thus, both AF and postmenopausal status increase CSA risk, yet in the study population examined, most postmenopausal women had AF but no CSA. These findings may be due to a variety of factors, such as the criteria used to classify CSA in this study ($CAHI \geq 5$ and/or high loop gain), the accuracy and reliability of the WatchPAT testing device in detecting central events, or perhaps the presence of other comorbidities whose effects on CSA risk haven't been examined. An important limitation is that females in this study were assumed to have reached menopause by age 51; this, of course, is not verified.

Treatment: Outcomes and Compliance

The PAP therapy treatment outcomes over three and six months, as shown in Table 10, are generally promising. The results show that the percentages of patients who can be considered to have good adherence to therapy – those who use their device at least 4 hours per night for 70% of nights or more – are relatively high at both the three and six month checkpoints (Miech et al., 2019). Additionally, the parameters describing sleep pathology – respiratory indices and periodic breathing – were all on a pattern of decline at both three and six months. These results and trends demonstrate that, on average, the patients studied are compliant with therapy and the therapy itself is effective in reducing disease severity.

However, both of the parameters describing the amount of mask leak increased, albeit slightly, over the course of three months. Studies have found that a greater amount of mask leakage reflects greater non-adherence to therapy (Valentin et al., 2011). Furthermore, although the group of patients studied had, on average, relatively high adherence to therapy, there was nevertheless a pattern of attrition. Attrition is a common issue in treating patients with SDB, with one study reporting that data collected over a twenty-year period show consistently low levels of adherence to CPAP (Rotenberg et al., 2016). The reasons behind this consistent decrease in compliance is perhaps quite understandable from the standpoint of the patient who is required to wear a mask while sleeping, and may find doing so cumbersome or intolerable. Although the decreases in therapy use seen in this study population were relatively minor, the issue of compliance to PAP therapy is still an important clinical challenge in the treatment of individuals with SDB. As PAP therapy can significantly improve disease prognosis, it is imperative for clinicians to continue to encourage therapy compliance and for research to evaluate alternative methods that may be effective in improving adherence, such as, for instance, behavioral interventions (Weaver, 2019).

When considering how treatment efficacy outcomes may have varied by gender, no significant differences were found between males and females for the three respiratory indices examined, but both genders nevertheless saw improvements from three to six months of therapy use. These results are consistent with a previous study which reported that both males and females with OSA experienced beneficial changes through usage of CPAP (Ye et al., 2009). The interpretation for this finding is that perhaps the mechanism

of improvement in disease severity, as accomplished through use of PAP therapy, does not depend as heavily on gender as it does on modifiable factors such as compliance.

Treatment: Effects on Cardiac Status

As previously stated, research into the effects of PAP therapy on AF is limited, but of significant clinical importance. The results of Table 12, which compared LVEF data from ECG reports with PAP therapy compliance data, preliminarily demonstrate that therapy may indeed have a positive impact on AF. Although the sample size is very small and the LVEF percentages are solely estimates, the pattern seen in the table suggests that patients who had both a high initial compliance at three months and minimal changes in compliance at the six month checkpoint were able to have a normal LVEF, reflecting improvements in cardiac status and possibly AF as well. Given the bidirectional nature of the SDB-AF relationship, it is unsurprising that treating SDB may lead to improvements in AF.

While Patients 4 and 5 had both been on therapy for a few months when their LVEF data were collected, Patient 4 had a 6.5% decrease in compliance while Patient 5 had only a 0.6% decrease in compliance. Additionally, whereas Patient 4 had an initial three-month compliance of 70.1%, Patient 5 had a much higher compliance at three months, 93.2%. Taking these differences into consideration, it is possible that the lower compliance and attrition seen with Patient 4 may have negatively impacted cardiac outcomes; not only did Patient 4 have the lowest initial three-month compliance and greatest compliance change from three to six months, but he/she also had the lowest

LVEF seen in Table 12 as well. These results highlight the importance and potential effects of PAP therapy compliance on cardiac outcomes. Separately, and unsurprisingly, none of the patients in Table 12 were recorded as having significant increases in compliance from three to six months; most patients experienced decreases in compliance during this timeframe. This is consistent with the previous discussion on decreases in PAP therapy compliance being frequent amongst SDB patients. However, given that there is a possibility that therapy compliance can modulate cardiac outcomes, the importance of compliance becomes even greater.

Implications for Screening

Analysis of ESS data generated results that are consistent with what previous studies have reported – that although SDB is common in AF patients, the majority of these AF patients do not have high ESS scores (Lavergne et al., 2015). That the mean ESS for patients with a CAHI \geq 5 and/or high loop gain was similar to that for patients with a CAHI of 0 is perplexing, given that SDB is known to cause excessive daytime sleepiness. The reasons for patients with SDB – both OSA and CSA – not reporting high levels of subjective sleepiness are unclear; however, this finding has important implications for screening cardiology patients for SDB. Knowing that AF patients with undiagnosed SDB may report low levels of subjective sleepiness, other methods of screening for SDB in this patient population are necessary.

An important limitation to the ESS findings, however, is that not all patients had an ESS value reported on their WatchPAT sleep study report. Additionally, there are also

limitations due to technology – the percentages of deep sleep as recorded with WatchPAT are only rough estimates, as there are often inaccuracies in sleep phase percentage measurements with home testing devices.

Collaborative Care Model for Sleep Management in Atrial Fibrillation

As evident from the previous discussion on implications for screening, a new collaborative care model for managing SDB in AF patients is needed. Since a substantial number of AF patients may present with minimal SDB symptoms – such as low levels of subjective sleepiness – it becomes important to shift the focus on screening patients solely based on symptoms, as a symptom-based approach may not be as effective in this group of individuals. Instead, it may become necessary to screen all AF patients for SDB, especially those patients who have a high risk of SDB due to severe AF. In this case, home sleep apnea testing using, for instance, the WatchPAT device is less burdensome for patients. However, it should be emphasized that home testing tends to underestimate disease severity; thus, devices such as WatchPAT should only be used to preliminarily screen AF patients for SDB. It may become necessary to follow up on sleep testing using in-lab PSG, especially for those patients whose WatchPAT sleep study results are either inconclusive or indicative of a severe disease phenotype.

Since SDB and AF are conditions known to affect each other in a bidirectional relationship, it is necessary for sleep medicine clinicians and cardiologists to collaborate with one another in the interest of optimizing patient care. One way that improvements in managing SDB in AF patients can likely be achieved is through risk stratifying patients.

Given that this study found a significant association between gender and CSA in particular, it may be worthwhile to identify those male patients with preexisting AF who obtain high CAHI scores from initial home sleep apnea testing. Additionally, since PAP therapy treatment may impact cardiac status, it is important for patients who are referred for sleep management and treatment to continue to monitor their cardiac health with a clinician.

Limitations

Besides the limitations already mentioned, there are a number of other limitations in this study. Regarding the data used, some patients had an empty medical history section on their WatchPAT sleep study report, which may have led to an underreported frequency of AF or other important conditions such as HF. Second, the therapy data available were very mixed – not all patients had the same types of data available. For instance, some patients had only three-month compliance data, while others had both three- and six-month data. In terms of cardiac data, not all patients had LVEF data, and the LVEF data that was available was only an estimation – a 55% LVEF was used as a threshold and some patients reported a value more than 55%. These factors made direct comparisons between patients difficult. Moreover, there were patients with a $CAHI \geq 5$ and/or high loop gain who did not have compliance data; these patients were therefore not analyzed because of the inability to see the potential impact of PAP therapy on their cardiac status. Perhaps most important, however, is the fact that the improvement in

cardiac status cannot necessarily be attributed to the use of PAP therapy – no causality can be established.

Finally, the study design itself is limited in several aspects, such as the fact that a retrospective analysis was conducted and a small patient population was studied. These factors make the results more prone to bias and error and also decrease the power of the study. Furthermore, the largely unequal numbers of males and females made it difficult to draw definite conclusions regarding differences between genders.

Conclusion

This study, though limited by a small sample size, has verified the findings of previous studies regarding the association between AF and CSA risk, and has further explored how gender may impact the type of sleep apnea seen in an individual. However, this study has also examined the specific relationship between postmenopausal status in females and risk of CSA, generating mixed results that warrant further investigation into how AF and postmenopausal status influence CSA risk in this group of individuals, and whether or not other factors are involved in this interplay. Future directions include exploring whether or not males with AF present with CSA earlier than females with AF. Answers to questions of this nature would ultimately have important implications in screening for, diagnosing and treating CSA in the most susceptible group of patients.

In terms of the effects of PAP therapy, the results from analysis and comparison of cardiac and compliance data provided limited, yet promising evidence that therapy may be associated with positive changes in cardiac status, and suggested that compliance

may prove to play a major role in determining the extent of cardiac improvement.

However, further research with larger patient samples and more extensive data is needed to definitively establish these findings. Future studies should determine the specific types of PAP therapy that are most efficacious, as well as the minimum length of time an individual is required to be on therapy in order to experience beneficial changes in cardiac status.

In essence, this study has further strengthened the concept of an interrelationship between CSA and AF – not only does AF predispose to CSA, but treatment of CSA is also likely to have a positive impact on AF.

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CURRICULUM VITAE

