Sleep and Cardiac Tachyarrhythmia:

Results from the Cross-Sectional Sleep Heart Health Study

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ABSTRACT

Background:

Despite the well-known relationship between sleep disorders and general cardiovascular risk, relatively few studies have examined sleep quality and quality at pre-clinical levels in patients with cardiac arrhythmias (CA). Patients with CA have at a greatly elevated risk of stroke, sudden cardiac death, disability, and reduced quality of life. In this study, we therefore sought to elucidate the sleep-related predictors of arrhythmia by examining the relationship between objective (polysomnography assessed) and self-reported measures of sleep quality and quantity with CA.

Methods:

Baseline, comorbidity, electrocardiogram, and polysomnography data for all who participated in the Sleep Heart Health Study (age 44-90 y) was screened for this analysis. Participants with missing critical data were excluded from the final analysis. ECG data was utilized to find participants with cardiac arrhythmias. Exposure variables included blood oxygen saturation, sleep stages, and tertiles of sleep quality and quantity. Unadjusted and adjusted logistic regression was used to quantify the association between sleep and non-sleep related factors and arrhythmia.

Results:

Of the original SHHS sample, a total of 3,453 participants with complete variables of interest were included in the final analysis (mean age: 68.1± 10.6 Years, 54% male, 499 with arrhythmia (Rhythm Abnormalities and Conduction Abnormalities), and 2,954 with no pathology). At the bivariate level, underweight (OR: 2.86, 95% CI: 1.1 – 7.2, P<0.0001), sleep time < 6 hours (OR: 2.58, 1.5-4.3, P<0.0001), % time in REM sleep (<17.6; OR: 1.53, 1.2-1.0, P<0.0001), sleep efficiency (<81; OR: 1.9, 1.5-2.3) and regular afternoon naps (OR:1.8, 1.3-2.4, P<0.0001) were

significantly associated with CA. However, in age- and sex-adjusted analyses, only % time in REM sleep and minimum oxygen saturation during REM (OR: 0.97, 0.96-0.98, P=0.006, and; OR: 0.97, 0.96-0.98, P=0.001, respectively) remained associated with CA.

Conclusion:

Preliminary analyses suggest differences in the sleep stages and oxygen delivery as potential targets for future work in the prevention and early management of CA. Further study is necessary to understand the nature of these relationships using longitudinal data with adjustment for traditional CA markers.

Keyword: Cardiac Arrhythmia, Atrial Fibrillation, Polysomnography data, Sleep Measures, Sleep Quality, Rhythm Abnormality, Conduction Abnormality, Sleep Efficiency, WASO, Sleep Quantity

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“The more I learn, the more I realize how much I don't know.”

- Albert Einstein

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AUTHOR CONTRIBUTION

Publications:

- Sleep and Cardiac Tachyarrhythmia: Results from the Cross-Sectional Sleep Heart Health Study – Canadian Cardiovascular Congress – Fall 2019 – Montreal, QC, Canada

Author Contribution:

- Study Concept and Design: Pouria Alipour and Chris I. Ardern
- Acquisition of Data: Pouria Alipour, Jennifer Kuk and Chris I. Ardern
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- Drafting of Manuscript: Pouria Alipour
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- Statistical Analysis: Pouria Alipour

ABBREVIATIONS

CA	Cardiac Arrhythmia
RA	Rhythm Abnormalities
CAb	Conduction Abnormalities
NSR	Normal Sinus Rhythm (Participant with no history of arrhythmias)
ECG	Electrocardiogram
WPW	Wolff-Parkinson-White Syndrome
PSG	Polysomnography
EEG	Electroencephalogram
REM	Rapid Eye Movement
NREM	Non-Rapid Eye Movement
WASO	Wake After Sleep Onset
SWS	Sleep to Awake Shift
ICD	Implantable Cardiac Defibrillator

Figure and Tables

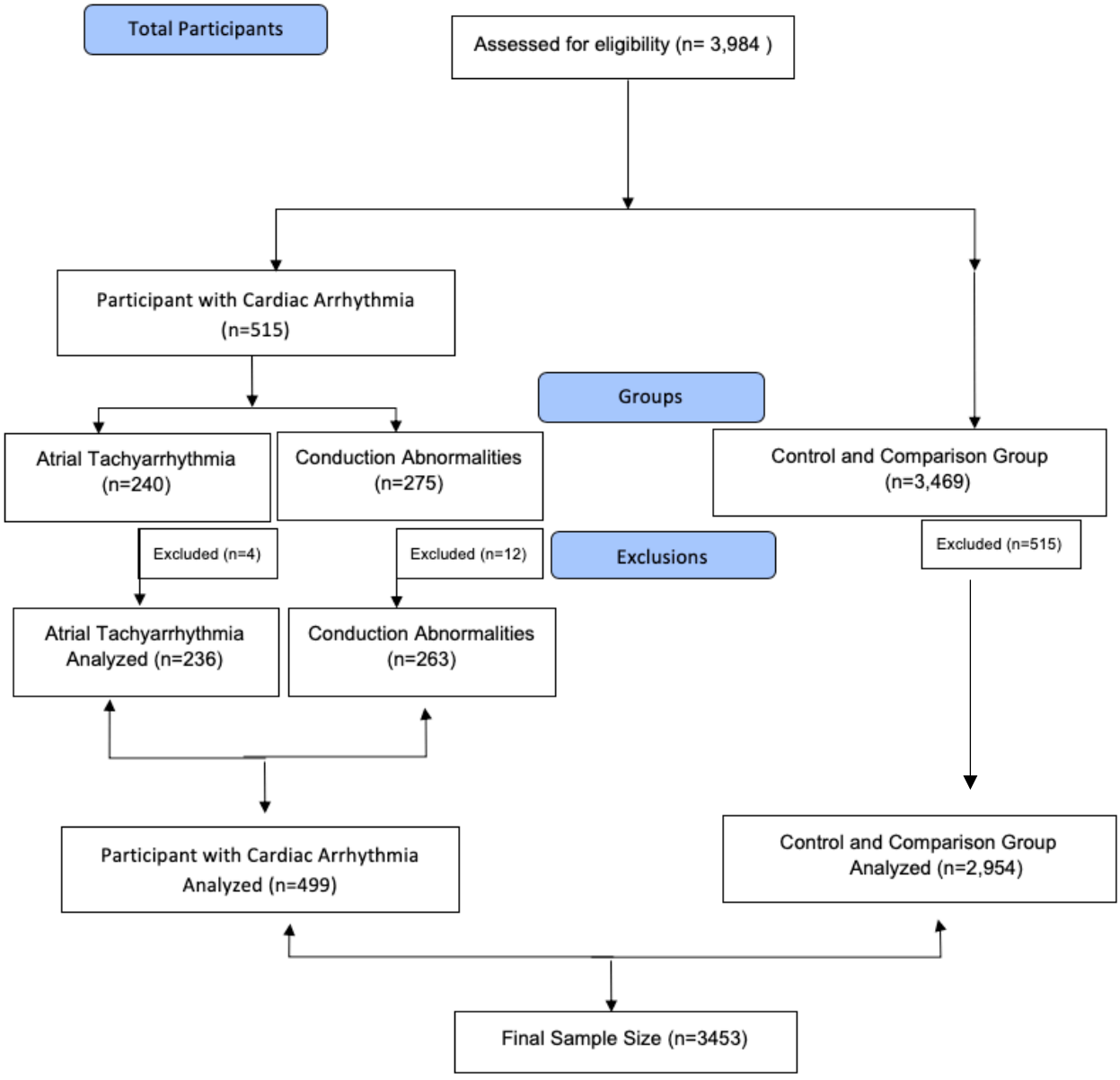

Figure 1: Consort Flow Diagram of Participant Selection for the study.

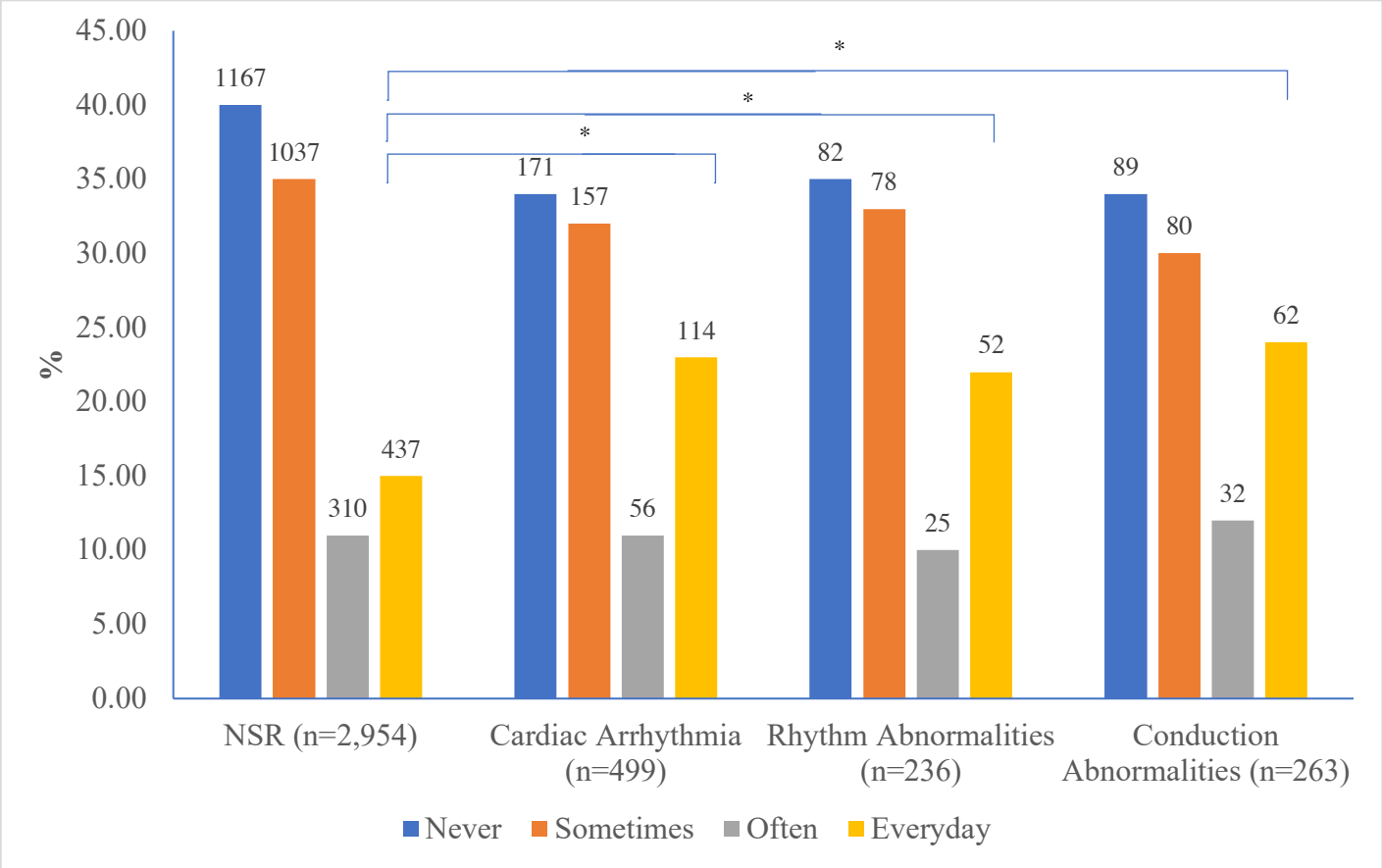

Figure 2: Afternoon Nap habit of participants. * = P<0.05

Table 1: Demographics and Characteristics

	Total (n=3,453)	NSR (n=2,954)	Cardiac Arrhythmia (n=499)	Rhythm Abnormalities (n=236)	Conduction Abnormalities (n=263)
% Male[*†‡]	54%	55.8%	56.3%	55.1%	57.4%
Mean Age[*†‡]	68.1±10.6	67±10.5	74.4±9.2	74.6±9.3	74.1±9.1
Race					
White	87.8%	87.5%	89.6%	90.3%	89%
Black	6.1%	5.8%	8.2%	7.2%	9.1%
Other	6.1%	6.7%	2.2%	2.5%	1.9%
Marital Status					
Married	81%	81%	80.8%	79.7%	82.7%
Divorced	7.7%	8.1%	5.4%	11.9%	11.5%
Widowed	8.4%	7.9%	11.6%	5.9%	5%
Never Married	2.8%	3%	1.6%	2.5%	0.8%
Hypertension[*†‡]	55.9%	53%	72.9%	73.3%	72.6%
History of Myocardial Infarction (MI)[*†‡]	5.3%	4.9%	12.2%	13.6%	11%
History of Stroke	3.1%	2.7%	5.6%	5.9%	5.3%
Congestive Heart Failure (CHF)[*]	1.6%	1.4%	2.2%	3.8%	0.8%
History of Coronary Artery Bypass Graft	3.2%	2.3%	8.4%	8.1%	8.8%

Procedure (CABG)*†‡					
History of Coronary Artery Disease (CAD)†	2.8%	2.3%	5.2%	5.9%	4.6%
History of Chronic Obstructive Pulmonary Disease (COPD)‡	1.8%	1.4%	2.6%	2.1%	3%
BMI					
≤17.9	0.6%	0.5%	1.4%	1.7%	1.5%
18-24.9	25.7%	25.8%	24.9%	28.1%	22.1%
25-29.9	42.2%	41.9%	43.7%	42.4%	44.9%
30-34.9	21.9%	21.7%	22.7%	21.6%	23.6%
35-39.9	7.2%	7.4%	5.9%	4.8%	6.8%
≥40	2.4%	2.6%	1.4%	1.4%	1.1%

Table 2: Comparing the difference in Sleep Quality variables and time spent in each Sleep stage between NSR and those with CA (P<0.05=*). These patients were further subdivided and categorized to RA (P<0.05=†), and Conduction Abnormalities (P<0.05=‡), and compared to participants in the NSR group.

	NSR (n=2,954)	**Cardiac Arrhythmia (n=499)**	**Rhythm Abnormalities (n=236)**	**Conduction Abnormalities (n=263)**
Sleep Time (Minutes)[*†‡]	603.4±99.20	581.3±107.7	575.4±106.9	586.6±108.3
WASO (Minutes)[*†‡]	58.1±40.1	69.9±47.8	72.7±50.8	67.4±44.8
Sleep Efficiency (%)[*†‡]	83.9±9.53	80.8±11.1	80.3±11.4	81.6±10.8
Sleep Latency (Seconds)	805.1±1162	864.2±1240	906.6±1355	825.0±1127
Sleep to Awake Shift[*†‡]	27.9±13.1	30.4±16.6	31.2±18.1	29.6±15.1
% Time in SA[*†‡]	2.7±6.1	4.8±8.8	4.3±8.3	5.5±9.4
% Time in Hypopnea[*‡]	16.5±8.82	18.3±9.10	17.6±8.34	19.1±9.87
% Time in NREM Stage 1	5.2±3.7	6.1±4.5	5.9±4.6	6.2±4.5
% Time in NREM Stage 2	56.2±11.4	58.1±12	57.7±11.7	58.4±12.4
% Time in NREM Stage 3/4[‡]	18.2±11.4	16.9±12.3	17.9±12.1	15.8±12.5
% Time in REM[*†‡]	20.4±6.03	18.8±6.11	18.3±6.00	19.4±6.12

Table 3: Comparing the difference in Oxygenation During different sleep stages between NSR and those with CA (P<0.05=*). These patients were further subdivided and categorized to RA (P<0.05=†), and Conduction Abnormalities (P<0.05=‡) and compared to participants in NSR group.

	NSR (n=2,954)	**Cardiac Arrhythmia (n=499)**	**Rhythm Abnormalities (n=236)**	**Conduction Abnormalities (n=263)**
Average SaO_2 REM (%)*‡	94.2±5.51	93.4±6.57	93.3±6.62	93.4±6.61
Average SaO_2 NREM (%)*	94.6±1.80	92.6±2.04	94.2±1.85	94.3±2.21
Min SaO_2 REM (%)*‡	86.9±7.46	85.5±8.30	85.6±8.33	85.5±8.32
Min SaO_2 NREM (%)*†	87.5±5.03	86.1±6.27	86.3±5.48	85.9±6.88

	Cardiac Arrhythmia (n=499)		Rhythm Abnormalities (n=236)		Conduction Abnormalities (n=263)	
	Univariate Unadjusted Model OR (95%CI)	**Age and Sex Adjusted Model OR (95%CI)**	**Univariate Unadjusted Model OR (95%CI)**	**Age and Sex Adjusted Model OR (95%CI)**	**Univariate Unadjusted Model OR (95%CI)**	**Age and Sex Adjusted Model OR (95%CI)**
% Time in REM						
≤17.5	1.53(1.2-1.9)	1.1(1.0-1.3)	1.1(0.8-1.5)	0.84(0.56-1.2)	2.1(1.5-2.9)	1.7(1.2-2.4)
17.6-22.5	1.36(1.1-1.7)	1.2 (0.92-1.8)	1.1(0.8-1.5)	0.94(0.67-1.3)	1.73(1.2-2.4)	1.5(1.1-2.2)
≥22.6	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)
% Time Stage 1 NREM						
≤3.3	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)
3.4-5.9	1.1(0.8-1.4)	1.1(0.87-1.4)	1.1(0.8-1.6)	1.1(0.80-1.6)	1.1(0.7-1.5)	1.1(0.78-1.5)
≥6	1.5(1.2-1.8)	1.2(0.94-1.5)	1.5(1.1-2.1)	1.3(0.89-1.7)	1.4(1.1-1.9)	1.1(0.84-1.6)
% Time Stage 2 NREM						
≤51.7	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)
51.8-61.6	0.9(0.7-1.2)	0.95(0.73-1.2)	1(0.7-1.4)	1.0(0.69-1.4)	0.9(0.7-1.3)	0.92(0.66-1.3)
≥61.7	1.45(1.2-1.8)	1.0(0.80-1.3)	1.6(1.2-2.2)	1.2(0.82-1.6)	1.31(1.1-1.7)	0.92(0.66-1.2)

% Time Stage 3/4 NREM						
≤11.9	1.4(1.1-1.7)	0.96(0.75-1.2)	1.6(1.2-2.1)	1.2(0.83-1.6)	1.1(0.84-1.6)	0.82(0.58-1.1)
12-22.1	0.9(0.7-1.1)	0.82(0.63-1.0)	0.8(0.5-1.1)	0.80(0.56-1.2)	0.87(0.71-1.2)	0.86(0.62-1.2)
≥22.2	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)
WASO (Minutes)						
≤34.9	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)
35-64.9	1.3(1-1.7)	1.0(0.79-1.3)1.	1.2(0.8-1.7)	0.90(0.61-1.3)	1.5(1.1-2.1)	1.1(0.81-1.5)
≥65	1.8(1.5-2.3)	1.1(0.85-1.4)	2.2(1.6-3.1)	1.4(1.0-1.9)	1.5(1.1-2.2)	0.88(0.63-1.2)
Sleep Efficiency (%)	1.9(1.5-2.3)	1.1(0.87-1.4)	2.2(1.6-3.1)	1.5(1.1-2)	1.6(1.2-2.2)	1.0(0.72-1.4)
≤80.9	1.2(0.9-1.5)	0.92(0.71-1.2)	1.2(0.8-1.7), .35	0.92(0.63-1.3)	1.2(0.9-1.7)	0.97(0.70-1.4)
81-89.9	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)
≥90						
Sleep Latency (Seconds)						
0	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)
1-14.5	1.0 (0.77-1.3)	1.1 (0.83-1.7)	0.91(0.73-1.3)	0.98 (0.69-1.4)	1.1(0.79-1.5)	1.2 (0.83-1.6)
≥14.6	1.2(0.91-1.5)	1.2(0.94-1.5)	1.2(0.81-1.5)	1.1(0.82-1.5)	1.2(0.93-1.6)	1.2(0.92-1.7)

Sleep to Awake Shift						
≤20.9	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)
21-30.9	1.1(0.84-1.3)	0.91(0.71-1.1)	0.91(0.58-1.3)	0.85(0.60-1.2)	1.1(0.82-1.5)	0.96(0.70-1.3)
≥31	1.3(1.0-1.6)	0.98(0.77-1.3)	1.3(0.88-1.6)	1.1(0.74-1.5)	1.3(0.91-1.8)	0.95(0.67-1.3)

Table 4: Sleep quality and percent time spent in different stages of sleep as predictor of Arrhythmia manifestation. All continuous variables were categorized into tertiles for analysis.

	Cardiac Arrhythmia (n=499)		Rhythm Abnormalities (n=236)		Conduction Abnormalities (n=263)	
	Univariate Unadjusted Model OR (95%CI)	**Age and Sex Adjusted Model OR (95%CI)**	**Univariate Unadjusted Model OR (95%CI)**	**Age and Sex Adjusted Model OR (95%CI)**	**Univariate Unadjusted Model OR (95%CI)**	**Age and Sex Adjusted Model OR (95%CI)**
Mean SaO_2 REM (%)						
≤93.8	2.1(1.7-2.7)	1.3(1-1.7)	2.3(1.6-3.1)	1.38(1.0-1.9)	2(1.4-2.8)	1.3(0.93-1.8)
93.9-95.6	1.5(1.1-1.9)	1.1(0.81-1.4)	1.1(0.8-1.6)	1.2(0.95-1.9)	1.9(1.3-2.6)	1.2(0.93-1.7)
≥95.7	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)
Mean SaO_2 NREM (%)						
≤93.9	1.6(1.3-2)	1.0(0.81-1.3)	1.7(1.2-2.3)	0.65(0.45-0.94)	1.5(1-2)	0.96(0.68-1.3)
94-95.4	1.1(0.8-1.4)	0.83(0.64-1.1)	1.5(1-2.1)	1.1(0.80-1.6)	1.4(0.9-1.6)	1.0(0.72-1.4)
≥95.5	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)
Min SaO_2 REM (%)						
≤85.9	1.7(1.3-2.1)	1.4(1.1-1.7)	1.7(1.2-2.4)	1.3(0.96-1.8)	1.7(1.2-2.3)	1.3(0.93-1.8)
86-89.9	1.5(1.2-1.9)	1.2(0.95-1.5)	1.5(1.2-2.1)	1.2(-.84-1.7)	1.6(1.1-2.1)	1.2(0.90-1.7)
≥90	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)

Min SaO_2 NREM (%)						
≤86.9	1.8(1.4-2.3)	1.3(0.94-1.6)	1.8(1.3-2.5)	1.3(0.93-1.8)	1.8(1.3-2.5)	1.3(0.92-1.7)
87-89.9	1.4(1.1-1.8)	1.1(0.86-1.4)	1.5(0.9-2.1)	1.2(0.83-1.7)	1.4(1-1.9)	1.1(0.78-1.5)
≥90	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)
% Time in Apnea						
≤0.2	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)
0.3-1.49	1.2(0.91-1.5)	1.0(0.80-1.6)	1.0(0.66-1.5)	0.90(0.62-1.3)	1.4(0.9-1.9)	1.2(0.83-1.6)
≥1.5	2.1(1.6-2.6)	1.2(0.96-1.6)	2.1(1.5-2.9)	1.3(0.90-1.8)	2.0(1.4-2.7)	1.2(0.84-1.6)
%Time in Hypopnea						
≤11.8	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)
11.9-19.3	1.2(0.9-1.5)	0.98(0.76-1.2)	1.3(0.9-1.8)	1.1(0.76-1.6)	1.1(0.8-1.5)	0.89(0.64-1.2)
≥19.4	1.5(1.2-1.9)	1.00(81-1.4)	1.7(1.2-2.4)	1.2(0.84-1.7)	1.4(1.1-1.9)	0.94(0.67-1.3)

Table 5: Oxygenation During various stages of sleep as predictor of Arrhythmia manifestation. All continuous variables were categorized into tertiles for analysis.

	Cardiac Arrhythmia (n=499)		Rhythm Abnormalities (n=236)		Conduction Abnormalities (n=263)	
	Univariate Unadjusted Model OR (95%CI)	**Age and Sex Adjusted Model OR (95%CI)**	**Univariate Unadjusted Model OR (95%CI)**	**Age and Sex Adjusted Model OR (95%CI)**	**Univariate Unadjusted Model OR (95%CI)**	**Age and Sex Adjusted Model OR (95%CI)**
Regular Afternoon Naps						
Never	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)
Sometimes	1(0.81-1.8)	1.3(0.98-1.7)	1.1(0.72-1.6)	1.4(0.95-2.0)	1.0(0.71-1.5)	1.3(0.86-1.8)
Often	1.2(0.76-1.4)	1.3(0.92-2.0)	1.1(0.60-1.9)	1.2(0.70-2.1)	1.3(0.79-2.2)	1.5(0.90-2.4)
Everyday	1.7(1.3-2.4)	1.6(1.2-2.2)	1.7(1.1-2.6)	1.5(1.0-2.4)	1.8(1.3-2.8)	1.7(1.1-2.6)
# of Naps Per week						
None	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)
1 or more	1.9(1.5-2.3)	1.25(1.0-1.6)	1.7(1.3-2.4)	1.2(0.87-1.6)	1.9(1.4-2.6)	1.3(0.96-1.7)

Table 6: Napping as predictor of Arrhythmia manifestation. All continues variables

REVIEW OF THE LITERATURE

Introduction

Cardiovascular Disease (CVD), which includes coronary artery disease, heart failure, and arrhythmias, is collectively one of the leading causes of morbidity and mortality worldwide. Although Cardiac Arrhythmia (CA) receives less attention that most other sub-types of CVD, the antecedents and future health complications of individuals with CA are becoming better known. Defined as any abnormality of the conduction system of the heart, CA is a condition which results in deviation from the normal sinus rhythm (NSR). Such pathologies could either affect the initiation, and propagation of the electrical current or the normal conduction pathway of the heart. Patients suffering from cardiac arrhythmias typically are more likely to have further complications such as stroke, heart failure, significant reduction in quality of life, and disability. The exact etiology of cardiac arrhythmias is not known; however, it is hypothesized that factors such as age, excess alcohol, tobacco, caffeine, and recreational drug consumption, overexertion, and genetics play a major role in its manifestation. A less explored, but emerging area of research relates to the risk of CA associated with poor sleep hygiene and consequent sleep deprivation and low sleep quality. Although there is clear evidence that obstructive sleep apnea can increase the risk of arrhythmia manifestation, such studies have failed to further investigate the relationship between variations in pre-clinical sleep and CA, which must be understood in order to enact primary prevention efforts in susceptible populations. In this study, we therefore sought to investigate the relationship between quality, quantity, and oxygenation during sleep using polysomnography data to cardiac arrhythmias.

Context for the Study of Sleep and Its Relationship to Health

Every human being sleeps an average of 25 to 30 years over its life span (Baumann, Strauch, Lehmann, Borbély, & Brandeis, 2003; Edwards et al., 2010; Ford & Cooper-Patrick, 2001; Harding & Feldman, 2008; Jike, Itani, Watanabe, Buysse, & Kaneita, 2018; Night, Antidote, & Epidemic, 2017). Indeed, sleep is one of the most important daily routines, as it is the period of time in which one's body rests and resets for another active day(Edwards et al., 2010). An adequate amount of sleep is therefore critical to survival and optimal everyday function(Baumann et al., 2003). To date, a number of studies have demonstrated the adverse outcome of insomnia(Ford & Cooper-Patrick, 2001; Harding & Feldman, 2008; Jike et al., 2018). Recently, the study of somnology – which describes the scientific and clinical study of sleep, quality, stages, and disorders – have also shown a marked decline in population sleep quality and quantity(Edwards et al., 2010; Shochat, 2012). This in part is a direct result of advancement and developments of information technology, the ubiquity of social media, and other popular online platforms(Cleveland, 2011). The exact mechanism of sleep initiation will be discussed in the following section, but in summary, the increased exposure to light emitting diodes, and unfiltered blue light has resulted in reduction of active melatonin in the brain which is responsible for proper sleep initiation(Cleveland, 2011). As such, sleep hygiene is one of the most important considerations in cardiovascular, neurological, and psychological health(Baumann et al., 2003; Bryant & Gómez, 2015; Edwards et al., 2010; Ford & Cooper-Patrick, 2001; Harding & Feldman, 2008; Jike et al., 2018; Night et al., 2017; Reite, Jackson, Cahoon, & Weil, 1975; R Stickgold, Hobson, Fosse, & Fosse, 2001).

Importance of Sleep

Sleep is important for efficient learning, memory formation, concentration and reaction-response situations(R Stickgold et al., 2001). The neural network of the brain is consistently remapping, and it is during sleep, that the majority of these reformations occur(Smith, 1985). Such networks and pathways are the roots of memory retention and learning. In particular, it is the Rapid Eye Movement stage of sleep that events stored in the short-term memory are often transferred and retained in the long-term memory(Smith, 1985, 1996; Smith & Rose, 1996) through a consolidation of procedural memory, however, the this does not hold true for declarative memory consolidation(Smith, 1985). Therefore, it is crucial for one to have adequate amount of high-quality sleep to learn and retain new memories. Sleep is also very crucial for maintaining a healthy cardiometabolic profile (Hoevenaar-Blom, Spijkerman, Kromhout, Van Den Berg, & Verschuren, 2011). During the period of sleep the cardiovascular system slows down allowing the heart muscles to rest and relax(Wolk, Gami, Garciatouchard, & Somers, 2005). Similarly, vasodilation (relaxation of blood vessels) during sleep allows for better blood delivery and subsequent oxygenation to all parts of the body(Wolk et al., 2005). Adequate sleep is therefore important for one's overall health and survival, as reductions in the quality and quantity of sleep have been implicated in an increased risk of hypertension, obesity, diabetes, and coronary artery disease(Jackson, Redline, & Emmons, 2015).

Physiology of Sleep

Sleep is a highly controlled process that is defined by a set schedule of sleep and awake cycles (Roehrs, 2000) that are referred to as the circadian rhythm - a process which is dictated by the availability of, and lack of light (Depner, Stothard, & Wright, 2014). Controlled by the hypothalamus, a group of cells known as suprachiasmatic nucleus (SCN)(Carley & Farabi, 2016) are responsible for setting the biological clock (i.e. circadian rhythm), based on availability of

light. The process of sleep regulation has been studied extensively and thus far the two-process model has served as a major framework in understanding regulation of sleep-wake cycles(Carley & Farabi, 2016). Within this model, the S Phase refers to homeostatic process, which includes the signals received by the SCN from the body to regulate hemostasis and initiate sleep(Ephron & Carrington, 1966). On the other hand, the C process refers to circadian rhythm signalling(Borbély, Daan, Wirz-Justice, & Deboer, 2016; Ephron & Carrington, 1966). This process refers to the light and dark cycles, and its effects on sleep regulation. It is therefore the combination of the C and S phase signals that results in proper sleep regulation and initiation. While the exact mechanism of sleep is complex, in lower light conditions, the SCN sends signal to the pineal gland, which in turns releases a melatonin(Lewy, Ahmed, Jackson, & Sack, 1992). This hormone is responsible for initiation of sleep and is photosensitive, which means it will be destroyed if exposed to light(Akerstedt & Nilsson, 2003; Depner et al., 2014; Edwards et al., 2010; Irwin, Olmstead, & Carroll, 2016; Lewy et al., 1992; Luyster, Strollo, Zee, & Walsh, 2012; Rangaraj & Knutson, 2016; Roehrs, 2000). At the same time, the brain stem communicates with the hypothalamus, causing the sleep promoting cells to secrete GABA, a neurotransmitter which is responsible for reducing the state of arousal to help with sleep initiation(Pace-Schott & Hobson, 2002). The signals for sleep initiation are received from both the S process and C process. As a result, the S process signals when the body is in a state known as sleep debt(VAN DONGEN, ROGERS, & DINGES, 2003), a state wherein an individual is sleep deprived and physiologically needs sleep to be able to function.

Stages of Sleep

Number of different physiological changes are observed during sleep. Such changes have been extensively studied and are broadly defined as major sleep stages: i) the Rapid Eye Movement (REM), and; ii) Non-Rapid Eye Movement (NREM) stage. The NREM stage is further subdivided to four additional stages, each of which corresponds to a specific state of brain and cardiovascular activity(Loomis, Harvey, & Hobart, 1937). These substages are characterized by the depth of sleep, with NREM stage 4 being the deepest sleep. The REM-NREM stages are cyclical and occur in a particular order(Loomis et al., 1937; ROSS, JOHNSON, & WALTER, 1966). At the sleep onset, individuals typically exhibit characteristics for NREM 1, and gradually progress to stages 2, 3, 4, before finally entering REM. Any disruption to the length, or percentage of each stage contribution may contribute to the development of a sleep disorder(Carskadon & Dement, 2017; Horner, 2017; McGinty & Szymusiak, 2017; Peever & Shiromani, 2017). A healthy individual spends on average 75%-80% of overall sleep in NREM stages while the other 20%-25% is spent in REM. Every NREM-REM cycle is typically 90-120 minutes in length, although this duration increases as the number of cycles increase throughout the night(McGinty & Szymusiak, 2017).

Non-Rapid Eye Movement Sleep

Within NREM sleep, stage 1 is typically described as the lightest sleep(Carskadon & Dement, 2017) and is known as a transitional stage from the state of wakefulness to sleep. Indeed, electroencephalograms during this stage of sleep reveal alpha waves that are similar to those observed in the wakefulness relaxation state, meaning that environmental disturbances can easily cause disruption to this stage of sleep(Carskadon & Dement, 2017). It is at this stage that the muscles relax, and respiration and heart rate begin to slow; nonetheless, individuals in this stage may experience the phenomenon of “hypnic jerk”, which is defined as sudden spasm of large muscles, sometimes experiencing the sensation of rapid fall(Carskadon & Dement, 2017). This is

one of the shortest stages of sleep, lasting up to 7 minutes, or 2%-5% of overall sleep time(Carskadon & Dement, 2017). On the other hand, the second stage of NREM sleep is typically the longest, contributing to 45%-55% of overall sleep time. This second stage of sleep is characterized by a manifestation of K- complexes and sleep spindles in the EEG tracing(Carskadon & Dement, 2017; Gais, Mölle, Helms, & Born, 2002). These forms are thought to play a major role in memory reconciliation and motor skill learning(Gais et al., 2002). K-complex are characterized by a single large spike in the EEG recordings, while sleep spindles are smaller in amplitude but higher in frequency(Forget, Morin, & Bastien, 2011). Previous studies have shown that brain spindles represent the transfer of information from hippocampus to neocortex which contributes to memory reconciliation; as a result, they been interpreted as a physiological index of intelligence(Anderer et al., 2001; Carskadon & Dement, 2017; Gais et al., 2002; Loomis et al., 1937; McGinty & Szymusiak, 2017; ROSS et al., 1966), and a marker for schizophrenia (ROSS et al., 1966), restless leg syndrome, narcolepsy, and obstructive sleep apnea(Carskadon & Dement, 2017; Lavigne & Montplaisir, 1994). The spindles and complexes in the stage 2 of NREM sleep also act as guardian, and protectors of sleep(McGinty & Szymusiak, 2017) as they allow the individual to be less reactive to external stimuli and maintain the sleep state(Forget et al., 2011). At this stage of sleep the core body temperature begins to decrease and further bradycardic response is observed(Carskadon & Dement, 2017). Finally, the third and fourth stages of NREM sleep are typically categorized together as they present very similar EEG tracings. Collectively, stage 3/4 sleep is considered the deepest sleep stage and as such slow wave sleep patterns as well as delta waveforms can be observed in the EEG tracing(Carskadon & Dement, 2017).

Rapid Eye Movement Sleep

One of the most studied stages of sleep is the rapid eye movement (REM) sleep. As the name suggests there is an increased frequency of the ocular muscles contraction resulting in rapid eye movement. This is the last stage of sleep in a sleep cycle and is typically characterized by large deviation from regular homeostasis state. Notably, EEG recording during REM sleep exhibit similar characteristics as the awake state, exhibiting desynchronized brain wave activity and theta waves also known as "sawtooth" pattern. This stage is also known as the stage of autonomic instability, due to increased fluctuations between sympathetic and parasympathetic nervous signals(Lanfranchi, Pépin, & Somers, 2017).

Beyond the patterns described above, REM sleep is most well-known for muscle atonia (i.e. muscle paralysis), as this is the stage when most dreams occur, and this muscle paralysis will prevent against any potential acting out of one's dreams(Solms, 2000; Robert Stickgold & Wamsley, 2017). Dreaming is defined as auditory, visual, and in some cases tactile hallucinations, in addition to increased heart rate, eye movement and emotional response(Nir & Tononi, 2010; Solms, 2000; Robert Stickgold, 2017; Robert Stickgold & Wamsley, 2017). These responses are similar to those seen during alert wakefulness state(Robert Stickgold & Wamsley, 2017). Auditory, visual and tactile experiences as a result of dreaming is typically stored in the short-term memory and are forgotten prior to or short after awakening(Nir & Tononi, 2010). Despite the ease by which a person can be awoken during REM sleep, maintenance of the awake state can be very difficult and short lived(Nir & Tononi, 2010). Of note, a number of studies have shown adverse cardiovascular outcomes as a result of disturbances to this stage of sleep(Nisha Aurora, Crainiceanu, Gottlieb, Kim, & Punjabi, 2018). Increased heart rate variability and unorganized breathing patterns are some of the mechanisms that allow adequate oxygenation and cardiovascular health at this stage (Nisha Aurora et al., 2018). As such, reduction in this stage of

sleep is correlated with higher risk of atherosclerosis, hypertension, hyperlipidemia, obesity, and other cardiometabolic disorders(Brown, Basheer, McKenna, Strecker, & McCarley, 2012; Irwin et al., 2016; Solms, 2000). By the same token, obstructive sleep apnea has the most pronounced adverse effect on this stage of sleep(Irwin et al., 2016). Epidemiological studies have shown that lack of proper oxygenation during this stage of sleep is also correlated with a higher incidence of cardiovascular diseases(Marin-Oto, Vicente, & Marin, 2019). Similar trends were not observed for NREM stages(Irwin et al., 2016). Fluctuations in blood pressure and heart rate are typically influenced by the autonomic nervous system during REM; therefore, there is an increased risk of myocardial infarction in the morning due to higher than normal blood pressure and heart rate(Pierdomenico et al., 2015). In summary, proper oxygenation and length of REM sleep is crucial for cardiometabolic health.

Sleep Study and Pathologies

To investigate qualitative and quantitative properties of sleep, individuals at higher risk of sleep disorders undergo an investigation known as polysomnography(Douglas, Thomas, & Jan, 1992; Kushida et al., 2005, 2006), the study of physiological, neural, and cardiovascular changes during different stages of sleep(Kushida et al., 2006). This technique allows healthcare professionals to properly monitor and diagnose sleep disorders. This test is typically administered in a clinic overnight with the patient sleeping while attached to an electrocardiogram, electroencephalogram, electro-oculography, electromyography, blood pressure machine, pulse oximeter, and finally a microphone(Douglas et al., 1992). Throughout the night, the machines measure all physiological changes as well as noises made by the patient during sleep, such as snoring, as well as any talking(Kushida et al., 2005). Collectively, polysomnographic techniques allows for proper diagnosis of number of disorders (e.g. central sleep apnea, narcolepsy, restless

leg syndrome, night terrors, insomnia, and nightmare disorder)(Coleman et al., 1982) though inspection of a hypnogram of the physiological changes at each stage of sleep(Douglas et al., 1992).

Obstructed sleep apnea (OSA) is one of the most important risk factors for number of cardiovascular diseases(Koo, Patel, Strohl, & Hoffstein, 2008b; Marin-Oto et al., 2019). Characterized by a reduction, or in some severe cases, a complete cessation of oxygen delivery during the various stages of sleep, individuals with suspected OSA will undergo polysomnography to determine the presence or absence of the disease(Kushida et al., 2006). Among the many complications of OSA, it is usually linked to early onset of coronary artery disease, hypertension, heart failure, and arrhythmias(Nisha Aurora et al., 2018) as a result of poor oxygen delivery during sleep and resulting hypoxia in major organs (Nisha Aurora et al., 2018). The effects of sleep apnea on the development and progression of arrhythmias has been well-studied and will be discussed in the following sections. Lastly, patients suffering from OSA have lower blood oxygen saturation throughout the night, which in some cases forces a person to wake up in order to catch their breath(Guilleminault, Tilkian, & Dement, 1976). This disturbance in sleep results in disruption of proper sleep stage progression, resulting in less restful sleep. Lifestyle modifications such as weight loss, exercise, smoking cessation, and reduction in alcohol consumption, as well as use of a Continuous Positive Airway Pressure (CPAP) ventilator, are some the treatments for OSA(Guilleminault et al., 1976). In a randomized controlled trial investigating over 2,700 participants, those with moderate to severe OSA who were randomized to usual care and CPAP therapy had higher quality of life improvement compared to those with just usual care, with no difference in recurrent cardiovascular events(McEvoy et al., 2016). Therefore, the effect of such therapy is still a subject of great debate (Marin-Oto et al., 2019; McEvoy et al., 2016; Nsair, Hupin,

Chomette, Barthélémy, & Roche, 2019; Randerath, Bonsignore, & Herkenrath, 2019). Moreover, most studies to date have investigated the simple correlation between blood oxygenation state and risk of cardiovascular events, with relatively little work on the relationship between sleep quality and stage progression and CVD.

Physiology and Pathologies of the Conduction system

Collectively, CVD represents one of the major causes of morbidity and mortality in older population internationally(Verrier & Josephson, 2009). Such disorders can range from coronary artery disease, which can ultimately result in myocardial infarction, to rhythm and functional abnormalities of the cardiac system(Verrier & Josephson, 2009). Cardiac Arrhythmia is defined as any disturbance to the normal rhythm and conduction pathway of the cardiac system(Kenny, 2014). In short, an electrical impulse is generated at the pacemaker cells of the Sinoatrial (SA) node in the right atrium of the heart. These electrical currents are propagated throughout the atrium resulting in atrial contraction and emptying of blood from atrium to the ventricles. The electrical current then travels to the atrioventricular junction, where it is briefly slowed to allow atrium to empty. Once the electrical current passes through the AV node, it travels down the bundle of his, ultimately branching into the right and left bundle branches and purkinje fibres(Kenny, 2014). The electrical current travelling down the bundle branches results in the contraction of the right and left atrium, causing blood to travel to the pulmonary and systemic circulations, respectively(Kenny, 2014).

Normal Sinus Rhythm (NSR) refers to the regular initiation, and propagation of electrical rhythms of the heart. Any deviation from the regular process of the conduction system results in pathologies known as cardiac arrhythmia (CA). Generally, arrhythmias are described as either

rhythm (i.e. improper initiation and depolarization of the cardiomyocytes in either atrium, ventricle, or both) or conduction abnormalities (i.e. improper propagation of electrical signals throughout the heart). Rhythm abnormalities can further be classified as those of the upper chambers - known as atrial tachyarrhythmia, or those of the bottom chambers of the heart - ventricular tachycardias.(Ottoboni, Lee, & Zei, 2011) One further type of arrhythmia, known as supraventricular tachycardia, refers to an inappropriate circuit re-entry resulting in fast and unorganized heartbeat originating above the ventricular tissues(Buescher & Asirvatham, 2011; Ottoboni et al., 2011). To date, a number of studies have investigated the origin, cellular pathology, and etiology of these diseases, yet the exact cause of arrhythmia manifestation remains unknown(Kenny, 2014; Ottoboni et al., 2011; Tracy et al., 2013).

Some of the most common rhythm abnormalities include atrial fibrillation, ventricular tachycardia, atrioventricular nodal re-entry, and atrial flutter(Beheiry, Al-Ahmed, & Natale, 2011; Buescher & Asirvatham, 2011; Kenny, 2014). By the same token, major types of conduction abnormalities are left and right bundle branch block, first, second, or third atriovencular block, as well as fascicular block(Guettler et al., 2019; Kenny, 2014). These pathologies prevent the proper propagation of electrical current, thereby resulting in cardiac arrhythmias(Guettler et al., 2019). The arrhythmias of the upper chambers are rarely life threatening, but commonly result in diminished quality of life(Beheiry et al., 2011; Buescher & Asirvatham, 2011; Cook & Hsia, 2011; Guettler et al., 2019; Ottoboni et al., 2011). By contrast, ventricular tachycardias such as ventricular tachycardia and ventricular fibrillation are life threatening if not adequately treated(Cook & Hsia, 2011). Because treatments are not completely effective and recurrences are frequent, primary prevention efforts are sorely needed.

OBJECTIVES

The objectives of this thesis are therefore two-fold:

1. To evaluate the differences in objective and subjective sleep measures amongst those with and without different types of cardiac arrhythmias.
2. To determine the predictors of Cardiac Arrhythmias including rhythm and conduction abnormalities.

INTRODUCTION

Almost one third of every human's life is spent sleeping(Luyster et al., 2012). The importance of sleep as a process crucial to memory reconciliation, neurological health, and proper cardiovascular functioning (Edwards et al., 2010; Smith, 1996; R Stickgold et al., 2001) is now well known.(Depner et al., 2014; Ford & Cooper-Patrick, 2001; Knutson et al., 2009; Luyster et al., 2012) Sleep is a protected period for the cardiovascular system to rest and prepare for the functioning of the coming day,(Verrier & Josephson, 2009) but it is also a very dangerous time for the cardiovascular system as 20% of myocardial infarctions and 15% of overall sudden cardiac deaths occur during sleep(Pavwoski & Shelgikar, 2017). Obstructive sleep apnea (OSA) is purported to be the main culprit for such occurrences(Porto, Sakamoto, & Salles, 2017), as a lack of proper oxygenation due to OSA results in reduction of blood oxygen saturation. The resulting transient ischemia can result in myocardial infarction and disruption of normal sinus rhythm of the heart(Guilleminault et al., 1976; Porto et al., 2017; Verrier & Josephson, 2009). If left untreated, OSA can result in cardiac remodelling which will further complicate the rhythm of the heart and cause manifestation of novel arrhythmias(Dimitri et al., 2012; Linz et al., 2018). Therefore, proper oxygenation during sleep is of utmost importance. Although a number of studies have investigated the relationship between OSA and cardiac arrhythmias (Verrier & Josephson, 2009), the impact of sleep on arrhythmogenesis is not well known. In this study, we therefore sought to investigate the relationship between various measures of objectively measured sleep and cardiac tachyarrhythmias in order to better understand opportunities for risk reduction.

METHODS

Study Design

Data for this analysis was derived from the Sleep Heart Health Study (SHHS) which was obtained through a limited access request to the U.S. National Heart, Lung, and Blood Institute (NHLBI). The SHHS is a harmonized dataset of four cohort studies with self-perceived and directly assessed measures of sleep quality and quantity on which to examine patterns of sleep and arrhythmia. Physical, physiological, and sleep data for all consented participants were collected and utilized in the analysis of this study. Objective sleep measure variables were obtained via a polysomnography study of participants. During this time heart rate, continuous ECG, breathing rate, and blood pressure data were also collected.

Sleep Heart Health Study

Sponsored by the National Heart, Lung, and Blood Institute (NHLBI) in the United States of America (USA), the Sleep Heart Health Study (SHHS), was one the largest studies investigating the effects of sleep breathing on cardiovascular health. This was a longitudinal study which was divided into two phases. Phase 1 (SHHS1) and phase 2 (SHHS2) of this study enrolled and collected general, cardiovascular, and family history, along with anthropometric, electrophysiologic, and polysomnographic data from 6,441 participants older than 40 years of age in in 1995-1998 and 2001-2003 respectively. All participants were subsequently followed up until 2010, and any manifestation of cardiovascular disease outcome was recorded.

Outcomes

On the basis of previous literature(B.J. et al., 2016), participants were divided into subgroups without any history of arrhythmia (NSR) or those with evidence of arrhythmia (CA).

Participants within the CA group were further divided into those with Rhythm Abnormalities (RA) and Conduction Abnormalities (CAb) based on their ECG findings. Participants were assigned to RA and CAb subgroups depending on whether the ECGs trace found abnormal rhythm or conduction morphologies. The primary outcome of interest was any CA, while secondary outcomes include subgroups of CA during second visit of Sleep Heart Health Study.

Cardiac Arrhythmia

Upon inspection of ECG data, those with first, second, and third degree atrioventricular block, left bundle branch block, right bundle branch block, incomplete left bundle branch block, incomplete right bundle branch block, nonspecific intraventricular conduction delay, Wolff-Parkinson-White syndrome (WPW), atrial fibrillation, atrial flutter, premature atrial contraction, premature ventricular contraction, left or right atrial hypertrophy were considered to have a CA(B.J. et al., 2016).

Rhythm Abnormalities

Of those participants within the CA group, those with left or right atrial hypertrophy, atrial fibrillation, atrial flutter, WPW, premature atrial contraction, or premature ventricular contraction were further sub-categorized to RA.

Conduction Abnormalities

Lastly, participants with first, second, and third-degree atrioventricular block, left bundle branch block, right bundle branch block, incomplete left bundle branch block, incomplete right bundle branch block, and nonspecific intraventricular conduction delay were subcategorized to conduction abnormality (CAb) (B.J. et al., 2016).

Objective Sleep Variables (Polysomnography)

All participants underwent a polysomnography study which included continuous EEG and ECG recording, as well as blood pressure, and oxygen saturation measurements. All sleep-related

data was then categorized into: i) sleep stage and progression variables; ii) quantity and quality of sleep measures, and; iii) measures of arterial blood oxygenation at various stages of sleep.

Sleep Stages and progression

In addition to total sleep time, we obtained the percentage of time each participant spent in each stage of sleep [% time in Rapid Eye movement sleep (REM), % Time in Stage 1 Non-Rapid Eye movement Stage (NREM-1), % Time in Stage 2 Non-Rapid Eye Movement (NREM-2), and % Time in Non Rapid Eye Movement stage 3 and 4 combined (NREM-3/4)].

Quantity and Quality of Sleep Measures

Total sleep time, obtained by polysomnography, represents the total number of minutes that participants were sleeping, whereas quality of sleep was assessed by four separate but related measures.

Wake After Sleep Onset (WASO)

Wake After Sleep Onset (WASO) is one of the most widely used measurements of sleep quantity. It measures the number of minutes that participants wake up post nocturnal cycle initiation. These wake episodes can be as pronounced as participants waking up to use the bathroom, or as minimal as a momentarily wake, which is typically not remembered by participants. This variable is represented as sum of all minutes spent awake after the participant falls asleep.

Sleep Efficiency

Similar to WASO, sleep efficiency computes the percentage of time that a person was asleep while in bed, and is obtained by dividing the number of minutes slept by total minutes in bed. This variable is expressed as a percentage of overall time spent in bed.

Sleep Latency

By contrast, sleep latency represents the length of time (in minutes) it takes to transition from a state of wakefulness to the first and lightest stage of non-rapid eye movement (NREM-1) sleep. This latency variable is typically measured in minutes and demonstrates the ease of falling asleep.

Sleep to awake shift (SWS)

Sleep to awake shift (SWS) measures the number of times that a person wakes up after sleep initiation. Specifically, SWS is measured by number of times that a person experiences sleep rhythm disruption (i.e. NREM-1 sleep is disrupted). In contrast with WASO, which measures the total number of minutes that participants are awake after the first instance of sleep initiation, SWS, measures the number of times that a person was awoken after sleep initiation.

Arterial Oxygen Saturation During Various Stages of Sleep

Sleep apnea results in reduced oxygenation during sleep, which can present as rhythm and conduction abnormalities. Average and minimum blood oxygen saturation rate during REM and NREM sleep were therefore retained for further analysis.

Subjective Sleep Variable

The SHHS collected numerous questionnaire-based (subjective) sleep measure variables. For the purposes of this analysis, we focused on habits that can interfere with normal night sleep quality such as afternoon naps and the total number of naps per week, on the basis of the following: *"During a usual week, how many times do you nap for 5 minutes or more?"*. Response options included none or one or more. Afternoon naps were assessed by the question: *"Do you try to "make time" in your schedule for a regular nap or "siesta" in the afternoon?"*. Response options included the four following options: "Never", "Sometimes", "Often", or "Always", and was recoded to "Regular Afternoon Naps" (Sometimes/Often/Always vs Never) in the current analysis.

Sample Selection

Inclusion Criteria

All participants with complete and available history, ECG, Polysomnography, and demographics data were included in the study.

Exclusion Criteria

Participants with missing sleep data were excluded from the analysis. Additionally, in order to reduce bias in our sample, participants with existing cardiac pacemaker, or implantable cardioverter defibrillator (ICD) were excluded from the study analysis.

Participant Screening and Outcome Assignment

Overall, total 3,984 participants (Control: 3,469, CA: 515) were initially assessed and screened for eligibility. Participants within CA group were further divided to those with rhythm abnormalities (n=240), or conduction abnormalities (n=275). Overall, a total of 531 participants were excluded due to missing critical data points (NSR: 515, CA: 18 (RA:4, CAb: 12)). As such, the final sample size yielded 3,453 participants, of which 2,945 were in NSR and 499 others in CA group (RA:236, CAb: 263). A summary of the derivation of the final analytic sample is displayed in **Figure 1**.

Statistical Analysis

Baseline characteristics of study participants were described by mean and standard deviation for continuous measures, and with frequency and % for categorical variables. Group-based differences in baseline characteristics (arrhythmia, rhythm abnormalities, and conduction abnormalities) were compared to those in normorhythmic category using an independent t-test for continuous variables and chi-square for categorical variables. The relationship between established arrythmia risk factors and emerging sleep parameters were assessed in univariate logistic regression. Tertiles of each sleep parameter with arrhythmia and each arrhythmia subcategory was then assessed using unadjusted and age- and sex-adjusted logistic regression, with normorhythmic

participants as the referent. First-order interactions for age- and sex- with all sleep parameters was assessed, and because no effect modification was found, only overall pooled estimates were presented. All analyses were conducted in SPSS v23 with statistical significance set at an alpha of 0.05.

Ethics

This secondary analysis was subsequently approved by the Human Participants Research Committee of York University.

RESULTS

Study Population

Sample Selection

A total of 3,984 participants from the SHHS were assessed for eligibility. Cardiac Arrhythmia (CA) was present in 515 participants and absent from the remainder of the sample (Normorhythmic (NSR): 3,469). Of those with CA, 240 participants had rhythm abnormalities tachyarrhythmia (RA), and 275 suffered from conduction abnormalities (CAb). After excluding participants with missing sleep data (n=515 from the NSR, n=4 RA, and n=12 Cab) a final sample of 3,453 [2,954 in the NSR group and 499 in the CA group (RA: n=236, CAb: n=263)] was available for analysis (**Figure 1**).

Demographic and Clinical Characteristics

Within the complete sample, participants were 68.1± 10.6 years of age (Control: 67±10.5, CA: 74.4±9.2, NSR: 67±10.5), with higher mean ages among the RA and CAb subgroups (NSR: 67±10.5 vs RA: 74.6±9.3, P<0.0001, and NSR: 67±10.5 vs CAb: 74.1±9.1, P<0.0001). Overall, a small majority of participants were male (total: 54%; NSR: 55.8% vs CA: 56.3%, P=0.02) with a modestly higher percentage of male participants in the CA (vs NSR) groups (RA: 55.1%, and CAb,: 57.4% vs NSR: 55.8%, both p<0.0001). SHHS participants were also largely of white European ancestry and married, with no notable subgroup variation. By contrast, the prevalence of hypertension (HTN), and history of myocardial infarction (MI) and coronary artery bypass graft procedures (CABG) were higher in the CA group and its sub-groups compared to normorhythmic participants (HTN: NSR: 53% vs CA: 72.9%, P<0.0001, MI: NSR: 4.9% vs CA: 12.2%, P=0.003, CABG: NSR: 2.3% vs CA: 8.4%, P<0.0001); however, there were no differences in BMI or history of stroke. Complete demographics and comorbidity data are presented in **Table1**.

Sleep Quality Measures

A total of five sleep quality measures and their relationship to cardiac arrhythmia were investigated in this study (**Table 2**). In general, individuals with CA had lower overall sleep time when compared to normorhythmic individuals (581.3±107.1 vs. 603.4±99.23 minutes, $p<0.0001$), a finding that persisted when compared within the RA and Cab subgroups (603.4±99.21 vs 575.4±107 and 586.6±108 respectively, $P<0.0001$ in both cases). Furthermore, those with CA had more sleep-to-awake shifts, and total WASO minutes (30.4±16.6 vs. 27.9±13.1 times, $P<0.0001$, and 69.9±47.8 vs. 58±40.1 minutes, $P<0.0001$, respectively). Similarly, those with normal conduction anatomy had more efficient sleep compared to those with pathology (83.9%±9.5% vs. 80.8%±11.1%, $P<0.0001$), despite no differences in sleep latency. These findings held true for participants in both the rhythm and conduction abnormality subgroups.

Oxygenation at Various sleep stages

In terms of sleep, normorhythmic participants had higher blood oxygen saturation at all sleep stages compared to those in CA group, an effect that was accounted for by lower average and minimum oxygen saturation during REM sleep in the CAb subgroup only (Average SaO_2 REM: CAb: 93.4%±6.6% vs NSR: 94.2%±5.5%, $P<0.05$, Minimum SaO_2 REM: CAb: 85.5%±8.3% vs. 86.9%±7.5%, $P<0.05$). Conversely, the difference in minimum and average blood oxygen saturation during NREM was lower only among those in the RA (but not CAb) subgroup (Average SaO_2 NREM: RA: 91.2%±1.8% vs NSR: 94.6%±1.8%, $P<0.05$, Minimum SaO_2 NREM: RA: 85.9%±6.9% vs. 87.5%±5%, $P<0.05$). Finally, while participants with CA and the RA and CAb subgroups spent more time in sleep apnea (CA: 4.8±8.8 vs. NSR: 2.7±6.1, $P<0.05$) and hypopnea, only differences for time in hypopnea persisted within the RA and CAb subgroups (**Table 3**).

Sleep Progression and Stages

Beyond the findings presented above, polysomnography data allowed us to further examine the percent of time participants spend in each sleep stage. Here again, those in CA and its subgroups tended to have poorer sleep quality in that they spent less time in REM sleep compared to those who were normorhythmic (CA: 18.8±6.1 vs NSR: 20.4±6 minutes, P<0.0001). On the other hand, with the exception of the CAb group for Stage 3/4 sleep, no differences in time spent in non-REM sleep stage were observed for any other group. (**Table 4**).

Napping Habits

A number of other self-reported measures of sleep patterns provides new insight into the relationship with CA pathology. Specifically, taking a regular afternoon nap, defined as regular or everyday naps, were higher amongst those in CA patients and its subgroups (NSR:14.8%, vs CA: 22.9%, and RA: 21.9%, and CAb: 23.7% respectively, P<0.0001). It is also noteworthy that most of the participants in NSR group did not nap during the week, while this was not true for the CA group, yielding a higher prevalence of individuals who took 1 or more naps per week in CA group compared to NSR (**Table 5**).

Sleep Related Predictors of Cardiac Arrhythmia manifestation

To test and determine the sleep-related predictors of CA, all continuous variables were divided into tertiles and categorized accordingly. The tertiles for each variable are found in tables 5 through 9.

Sleep Quality Measures

Sleep Time

Unadjusted logistic regressions revealed that compared to 8 to 10 hour a night sleepers, those who slept between 6-8 hours (OR: 1.4, 95%CI: 1.1-1.2, p=0.02) and 6 or less hours (OR: 2.6, 95%CI: 1.5-4.3, p<0.0001) had higher odds of arrhythmia. After adjustment for age and sex, those who slept less than 6 hours per night remained twice as likely to report a cardiac arrhythmias (OR_{adj}: 2.1, 1.2-3.5, p=0.008; RA: OR_{adj}: 2.2, 1.1-4.4, p=0.03, and; CAb: OR_{adj}: 1.9, 1-3.9, p=0.05).

WASO

For wake-after-sleep onset, the findings were less consistent. Whereas the initial unadjusted models revealed that waking after more than 35 minutes of sleep onset was a significant predictor of cardiac arrhythmia, no significant effect was found for conduction abnormalities, and only WASO above 65 minutes was related to rhythm abnormalities. Nonetheless, once the models were adjusted for age and sex, WASO more than or equal to 65 remained a significant predictor of rhythm (OR_{adj}:1.4, 95%CI:1.1-1.9, p=0.03), but not conduction abnormalities or CA overall (CA: OR_{adj}:1.1, 95%CI: 0.85-1.4, p=0.14, CAb: OR_{adj}:0.88, 95%CI: 0.63-1.2, p=0.29).

Sleep Efficiency

Finally, our preliminary analyses revealed that sleep efficiency less than or equal to 80.9% was a significant predictor of CA, RA, and CAb, a finding that persisted once adjusted for age and sex (CA: OR_{adj}:1.95%CI: 1.1-2, p=0.01). Notwithstanding the above, sleep latency, and the number of sleep-to-wake shifts per night were not significant predictors of cardiac arrhythmia, rhythm or conduction abnormalities in the crude or adjusted models.

Oxygenation at Various sleep stages

Minimum Arterial Blood Saturation

In an effort to build upon the findings of the sleep stage analysis presented above, additional analyses were undertaken to examine whether minimum and average arterial blood saturation during REM and NREM sleep were significant predictors of CA. At the bivariate level, minimum oxygen saturation less than 89.9% and 86.9% were significant predictors of cardiac arrhythmia during REM and NREM sleep, respectively (Min SaO_2 REM: OR:1.5, 95%CI: 1.2-1.9, p=0.001, and Min SaO_2 NREM: OR:1.8, 95%CI: 1.4-2.3, P<0.0001), a finding that persisted within RA and CAb subgroups (**Table 7**). Once adjusted for age and sex, however, only minimum arterial blood oxygen saturation during REM sleep remained a significant predictor of CA (OR_{adj}:1.4, 95%CI: 1.1-1.7, p=0.02).

Mean Arterial Blood Saturation

Similar trends were observed for average arterial blood oxygen saturation. At the bivariate level, average SaO_2 of 93.9% or less during NREM sleep, and 95.6% or less during REM sleep was related to CA (Average SaO_2 REM: OR:1.5, 95%CI: 1.1-1.9, p=0.002, and Average SaO_2 NREM: OR:1.6, 95%CI: 1.3-2.0, P<0.0001), only a minimum oxygen saturation of 93.8% or less during REM sleep was a significant predictor of CA (OR_{adj}:1.3, 95%CI: 1-1.7, p=0.05) and rhythm (OR_{adj}:1.75, 95%CI: 1.3-2.4, p=0.001), but not conduction abnormalities, once adjusted for age and sex.

Disturbances to Regular Blood Oxygenation

To examine whether previous findings on sleep apnea and cardiac health extend to CA and its subtypes, we undertook a further analysis of disturbances to regular oxygenation. At the bivariate level, spending 1.5% or more of total sleep time in apnea was significantly related to CA, RA, and Cab; however, once adjusted for age and sex, only the relationship with rhythm abnormalities (OR_{adj}:1.4, 95%CI: 1-1.9, p=0.04) remained. Similarly, while percent time spent in

hypopnea (19.4% or more) was related to CA and its subcategories, this effect was abolished after further adjustment.

Sleep Stage Progression

The final polysomnographic measure utilized in this study was the percent time spent in each stage of sleep. Findings from the crude analysis revealed that spending less than 22.5%, 6% and 61.7% in REM, NREM 1, and NREM 2, respectively, were associated with elevated odds of CA. Once adjusted for age and sex, spending less than 17.5% and 22.5% of overall sleep in REM predicted CA and conduction abnormalities respectively (CA: OR_{adj}:1.1, 95%CI: 1-1.3, p=0.05, and CAb: OR_{adj}:1.5, 95%CI: 1.1-2.2, p=0.01) (Table 4).

Subjective Measures of sleep: Naps

As with the descriptive findings discussed above, age- and sex-adjusted models revealed that everyday napping was associated with a 40-70% greater odds of CA and its subtypes (CA: OR_{adj}:1.4, 95%CI: 1-1.8, p=0.05, RA: OR_{adj}:1.5, 95%CI: 1-2.4, p=0.05 and CAb: OR_{adj}:1.7, 95%CI: 1.1-2.6 p=0.01), whereas less frequent napping (1 nap per week) was only associated with a greater likelihood of CA (OR_{adj}:1.25, 95%CI: 1-1.6, p=0.05).

DISCUSSIONS

Main Findings

In this study we sought to determine the relationship between sleep and cardiac arrhythmias through the use of polysomnography and ECG-derived heart rhythm data to characterize sleep across a host of objective (e.g. sleep quantity, quality, stage progression, and oxygenation) and subjective measures. In general, individuals with cardiac arrhythmias had lower sleep quality and quantity as illustrated by WASO, sleep time, sleep efficiency and number of sleep-to-awake shifts. This was also true for participants in the CA subcategories. Furthermore, REM sleep measures

were significantly different between normorhythmic and arrhythmia groups. After adjustment for age and sex, taking regular afternoons, sleep time less than or equal to 6 hours, as well as percent time spent in REM and oxygenation during REM sleep were significant predictors of CA. Finally, in all cases, subjective measures of sleep – most notably a napping frequency more than once a week or regular afternoon naps – were significant predictor of arrhythmias.

Within subgroups of CA, rhythm, and conduction abnormalities, being in apnea for more than 1.5% of the overall sleep time and average blood oxygen saturation of less than or equal to 93.8% during REM were significant predictors of rhythm abnormalities such atrial fibrillation and flutter. Additionally, sleep quality measures such as WASO more than 65 minutes, sleep efficiency less than 80.9%, and sleep time less than 6 hours were also significantly related to RA. Finally, sleeping for less than 6 hours a night and spending less than 22.5% of overall sleep in REM were also significantly related to conduction abnormalities, even after adjusting for age and sex. Thus, our outcomes demonstrate that while oxygenation during sleep is potentially a protector against arrhythmias, it is REM sleep that plays a major role in regulating heart rhythm. By the same token, the overall sleep quantity is an extremely important contributor to CA, RA, and CAb. This is while that quality of sleep measures such as wake after sleep onset, and sleep efficiency were only significant in predicting pathologies associated solely with rhythm abnormalities.

Sleep Quantity and Deprivation

Previous studies have provided detailed insight into the relationship between cardiovascular disease and sleep, most notably sleep quantity (Ayas et al., 2003; Cappuccio, D'Elia, Strazzullo, & Miller, 2010; Jackson et al., 2015; Knutson, 2010; Knutson, Spiegel, Penev, & Van Cauter, 2007; Knutson et al., 2009; Leung & Douglas Bradley, 2001; Luyster et al., 2012; Spiegel, Tasali, Leproult, & Van Cauter, 2009; Wolk et al., 2005), quality(Hoevenaar-Blom et al.,

2011), oxygenation, and potential apneas(Depner et al., 2014). Consistent with previous literature on cardiometabolic health (e.g. higher BMI, type 2 diabetes, hypertension(Knutson, 2010), coronary artery disease(Ayas et al., 2003), and heart attack and stroke(Knutson, 2010; Knutson et al., 2007, 2009; Spiegel et al., 2009)), we found that sleeping less than 6 hours a night was a significant predictor of rhythm and conduction abnormalities. Similarly, in a study by Genuardi et al. each hour reduction in sleep resulted in 17% increased risk of developing atrial fibrillation (Genuardi et al., 2019). These findings are consistent with the results of our study; however, we found that sleep duration of 6 hours or less was associated with a 2.2-fold greater likelihood of having a rhythm abnormality. Therefore, it is important to maintain a healthy sleep habits in order to reduce the risk of developing arrhythmias as well as other metabolic disorders(Irwin et al., 2016). The MORGEN study clearly demonstrated that with lower sleep duration and quality have a much higher risk of CVD and CHD specifically(Hoevenaar-Blom et al., 2011), however, this study did not investigate cardiac electrical abnormalities, and thus, we add to this literature with our finding that decline in sleep measures especially during REM is associated with CA manifestation regardless of age and sex.

Wake after sleep onset (WASO) and Sleep Efficiency

Quality of sleep is as an important indicator of proper nocturnal cycle progression (Hoevenaar-Blom et al., 2011). In a systematic review by Aziz et al. (2017), reductions in the quality and quantity of sleep were strongly associated with clinical and subclinical cardiovascular disease(Aziz et al., 2017). The health consequences of two measures of sleep quality – namely sleep efficiency and WASO – have been examined at length(Quan et al., 1997). For example, in a cross-sectional study of 270 female shift workers, half of whom were hospital shift workers while the other half had regular 8-hour a day jobs, found that shift workers had significantly lower sleep

quality as well as higher incidences of CVD(Lajoie, Aronson, Day, & Tranmer, 2015). While these findings are in general consistent with our study, we also found that sleep quality measures such as WASO and sleep efficiency were strong predictors of rhythm abnormalities.

Rapid Eye Movement Sleep and Oxygenation

While separate, the findings that sleep efficiency and WASO are related to CA are consistent with our finding of a major role of REM sleep in arrhythmias, as REM sleep is thought to be integral for cardiovascular relaxation and longer-term cardiac health(Koo, Patel, Strohl, & Hoffstein, 2008a; Leung & Douglas Bradley, 2001), (Choi, Park, Yu, Ryu, & Ha, 2016). Indeed, using the SHHS dataset, Aurora et al. have previously reported a relationship between apnea and lack of oxygenation during REM sleep with CVD endpoints (Nisha Aurora et al., 2018). Furthermore, Aurora et al. (Nisha Aurora et al., 2018) utilized the apnea-hypopnea index (AHI) to classify the oxygenation during REM and found that those with high AHI had a significantly higher prevalence of cardiovascular disease(Nisha Aurora et al., 2018). These findings are consistent with the results of our study which demonstrated that reduced arterial blood oxygenation during REM was associated with a 30% greater likelihood of arrhythmias. Unsurprisingly, there is typically a higher chance of apnea and hypopnea during REM sleep compared to the other stages(Grace, Hughes, & Horner, 2013), as it is during this stage that muscles are relaxed and paralyzed. The neurotransmitters involved in REM-mediated paralysis can therefore cause paralysis of the epiglottis, which in turn contribute to a blocking of the larynx and a subsequent reduction in, or complete blockage, of oxygen transmission(Grace et al., 2013). This is also supported by a study by Choi et al. wherein individuals with sleep apnea were found to have more severe reductions in oxygenation during REM sleep compared to the other stages(Choi et al., 2016). Moreover, because

the amount of time one spends in REM sleep is independently related to cardiometabolic health(Calandra-Buonaura, Provini, Guaraldi, Plazzi, & Cortelli, 2016), disruption in the quality of sleep in this stage supports a role for pathology in the autonomic regulation pathway(Calandra-Buonaura et al., 2016). One further explanation for the importance of REM sleep to arrhythmia development is that some, but not all, homeostasis processes are suspended(Ephron & Carrington, 1966). Of note, there is a large fluctuation in heart rate, breathing, and blood pressure that does not occur in any of the other stages of sleep or even wakefulness(Ephron & Carrington, 1966).

Sleep Apnea and Arrhythmia

A considerable body of research now supports a relationship between sleep apnea and atrial fibrillation(Ravi et al., 2003; S. et al., 2004), and several of these studies can be drawn upon to provide context to findings from the current investigation. In an earlier analysis of the SHHS by Tung et al. central sleep apnea was found to be associated with a higher prevalence of AF(Tung et al., 2017). In the present analysis, being in apnea for 1.5% or more of overall sleep time was associated with a higher prevalence of rhythm abnormalities, to the extent that apnea during sleep was associated with a 1.42 greater odds of rhythm abnormalities as compared to those with no sleep apnea. This finding is further supported by an analysis of 8,256 participants by Kendzersak et al. which found that having 30 AHI events per hour (Kendzerska, Gershon, Atzema, Hawker, & Leung, 2017) and spending more than 10 minutes of sleep with arterial blood saturation below 90 percent increases the risk of AF hospitalization by 92% and 281%, respectively. This means the minimum blood oxygen saturation below 90 percent can nearly triple the likelihood of

hospitalization for atrial fibrillation, which is consistent with the findings of the current study(Kendzerska et al., 2017). However, unlike the current study, Kendzersak et al. (REF) did not investigate deoxygenation in each particular stage of sleep. As a result, the current study provides much needed insight into the relative importance of apnea and desaturation in the various sleep stages

Afternoon Naps and Prevalence of Arrhythmia

Accumulating evidence now suggests that regular daytime napping may contribute to a higher risk of CVD, and increased morbidity and mortality amongst older adults(Ancoli-Israel & Martin, 2006). Within our sample of middle-aged adults, our study demonstrated that regular naps were associated with a 70% greater likelihood of CAb, and a 50% greater likelihood of rhythm abnormalities. There are a number of possible explanations for the aforementioned findings, including sleep fragmentation, pre-existing disease, and overall poorer sleep quality (Ancoli-Israel & Martin, 2006; Carskadon, Brown, & Dement, 1982; Goldman et al., 2008). In a cross-sectional study of 235 middle aged adults, Goldman et al. found that those with regular naps during the day had higher fragmented and lower quality sleep overall(Goldman et al., 2008), as fragmentation is known to reduce nocturnal sleep efficiency and quality(Carskadon et al., 1982). It stands to reason that this is one of the explanations for why we observe a higher likelihood of arrhythmia in those with regular daily naps, and is consistent with emerging literature that lower quantity and quality of sleep is associated with a higher likelihood of arrhythmia(Cappuccio et al., 2010; Hoevenaar-Blom et al., 2011; Knutson et al., 2007; Leung & Douglas Bradley, 2001; Parthasarathy et al., 2015). As such, factors that contribute to a reduction in these sleep parameters may contribute to the development of arrhythmia and represent a suitable target for intervention. (Ancoli-Israel &

Martin, 2006). More research is however necessary, as these findings are in contrast to earlier studies that recommended regular afternoon naps for improved daily function and overall health(Dinges, 1992).

Strengths and Limitations

This study was done using data obtained by the SHHS. As such, the cross-sectional nature of the analysis, and lack of a matched control design prevents casual inference. Furthermore, some pre-existing conditions, as well as self-reported measures of napping may have introduced response bias in the outcomes. On the other hand, this study had a large sample with objectively assessed measures of sleep, which ensures a high level of internal and external validity.

CONCLUSION

Cardiac arrhythmias, comprising of rhythm and conduction abnormalities, are one of the major causes of morbidity and mortality in adults. Analyzing self-report, electrocardiogram, and polysomnography data from over two thousand SHHS participants we found that oxygenation and sleep stage progression - particularly the amount of time one spends in REM, apnea, and minimum arterial blood oxygenation during different stages - are important predictors of arrhythmia. Prospective studies are needed to further investigate the effects of sleep habits on cardiac arrhythmias; however, findings from this study serve as a starting point for future work to examine the sleep related behaviors with arrhythmias, work that may ultimately provide a more comprehensive understanding of primary and secondary prevention of these conditions.

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