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RESEARCH ARTICLE

Cluster Analysis and Phenotyping Based on Association of Sleep Studies and Cardiovascular Comorbidities

John Arek Kileci[1,2], Derya Arkonac[2,3], Leslie Seijo[2,4] and Alfredo Astua[2,5]

[1]*Division of Pulmonary, Critical Care and Sleep Medicine, Department of Medicine, New York University Langone Medical Center, New York, USA*

[2]*Division of Pulmonary, Critical Care and Sleep Medicine, Department of Medicine, Mount Sinai Beth Israel, New York, USA*

[3]*Division of Cardiology, Mount Sinai Beth Israel, New York, USA*

[4]*Division of Pulmonary, Critical Care, Allergy and Sleep Medicine, University of California San Francisco, California, USA*

[5]*Division of Pulmonary, Critical Care and Sleep Medicine, Elmhurst Hospital Center of the Icahn School of Medicine, New York, USA*

***Corresponding author:** *John Arek Kileci, Division of Pulmonary, Critical Care and Sleep Medicine, Department of Medicine, New York University Langone Medical Center, New York, USA Bellevue Hospital,Room 7N24 (Bellevue Chest Office), 462 First Avenue, New York, NY 10016.*

Summary

Current knowledge/Study rationale: Phenotypes of sleep apnea in relation to cardiac comorbidities is not a well-studied topic. The rational of this study is to define phenotypes of sleep apnea and see the applicability of that information for future care of patients.

Study impact: We were able to demonstrate three major phenotypes. There needs to be more phenotypic studies in sleep apnea patients.

Abstract

Study objectives: Obstructive Sleep Apnea (OSA) is a complex disease process with a known significant association with cardiovascular diseases and the metabolic syndrome. This study aimed to define phenotypes of OSA based on sleep studies and cardiovascular comorbidities and to further investigate whether there would be any meaningful association between these disease processes. Defining phenotypes could assist in individual targeted treatments for patients with OSA.

Methods: We conducted a retrospective chart review on sleep studies between 12/6/2015 and 5/18/17 and identified 1056 adult patients. We documented all aspects of the sleep studies and then did a chart review on the identified patients in our Electronic Medical Record (EMR) to study cardiovascular disease processes of hypertension, atrial fibrillation, coronary artery bypass surgery, severity of diabetes and the presence of prior stroke.

Results: After comparing all our data, we found that lowest saturation, baseline saturation, N1, BMI, and N3 had strong correlations with AHI. Presence of diabetes and ESS number had no correlation. Hypertension and age had moderate while Rapid Eye Movement (REM) cycle, ECG abnormalities and sleep efficiency had small correlation with Apnea-Hypopnea Index (AHI).

Conclusions: Only hypertension had a significant effect on the clustering. The rest of the majority of the clusters were formed by differences in sleep stages, Respiratory Disturbance Index (RDI), lowest saturation points and sleep efficiencies. Based on these results, our study did not show a significant association between the cardiac comorbidities and sleep study outcomes as clustering.

Keywords

Sleep apnea, Cardiovascular disease, Cluster analysis, Sleep apnea phenotype

Abbreviations

OSA: Obstructive Sleep Apnea; AHI: Apnea-Hypopnea Index; IRB: Institutional Review Board; ESS: Epworth Sleepiness Scale; ECG: Electrocardiogram; EMR: Electronic Medical Record; BPV: Blood Pressure Variability; RDI: Respiratory Disturbance Index

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Introduction

Obstructive Sleep Apnea (OSA) is a common but complex sleep disorder characterized by sleep fragmentation and hypoxia, which if left untreated may cause harmful sequelae.

It is estimated that in the United States, the prevalence of moderate to severe OSA (Apnea-Hypopnea Index ≥ 15 per hour) may be as high as 10-17% in men and 3-9% in women [1]. This prevalence will likely continue to increase as the rate of obesity rises worldwide [1,2].

Patients with OSA have a higher risk of having cardiovascular comorbidities such as hypertension, diabetes and stroke which increase patients' morbidity and mortality. One of the most impactful sequelae of OSA is its effect on the cardiovascular system and the metabolic syndrome [3,4]. A proposed mechanism of the impact of OSA in the cardiovascular system is the repetitive cycles of hypoxia and arousals that cause swings in negative intrathoracic pressure, decrease in myocardial contractility, and decrease response from the parasympathetic nervous system. This leads to increase in blood pressure and heart rate, activation of oxidative stress and systemic inflammation, and impairment of endothelial function [3].

There have been several studies that have described the association between OSA and hypertension [5,6]. Patients with both hypertension and OSA have been found with increases in urine catecholamines, suggesting increased sympathetic activity in these patients [7].

Studies have also found a link between diabetes with OSA [8]. Patients with OSA have a higher risk of having diabetes and increasing OSA severity is associated with increased likelihood of having diabetes with worse diabetic control [8,9]. In patients with the metabolic syndrome, OSA is independently associated with increased glucose and triglyceride levels, as well as markers of inflammation, arterial stiffness, and atherosclerosis [2].

An observational study demonstrated that untreated patient with severe OSA had a higher incidence of fatal cardiovascular events which included myocardial infarction, acute coronary syndrome, and stroke, than untreated patients with mild-moderate OSA [10]. It is clear that OSA is a complex disease which affects other systems, predominantly the cardiovascular, yet, OSA continues to be classified simply with the Apnea-Hypopnea Index (AHI). Few studies have been done studying OSA and other comorbid conditions [11-13]. Given the importance of proper classification of OSA, we conducted a study aimed to better classify OSA taking into account several conditions associated with cardiovascular disease that abound in these patients.

Methods

We conducted a retrospective chart review on sleep studies performed at our hospital affiliated sleep center between 12/6/2015 and 5/18/17 and identified 1056adult patients. Our study was approved by the institutional review board (IRB). As seen in (Table 1), from the sleep studies we documented AHI, lowest saturation levels, Epworth Sleepiness Scale (ESS), Electrocardiogram (ECG) abnormalities, and percent saturation less than 90%. We then did a chart review on the identified patients in our Electronic Medical Record (EMR) and documented cardiovascular disease processes which were grouped into subgroups of hypertension, atrial fibrillation, and coronary artery bypass surgery.

We also documented the presence and severity of diabetes and the presence of prior stroke. Hypertension was classified based on the number of medications the patient was taking for control: 1 medication = mild, 2 medications = moderate, and 3 or more medications = severe (Table 2).

Other data collected included age, date of birth, gender, ethnicity, height, weight, and Body Mass Index (BMI). In preparing the data for analysis, variables with less than 10 cell counts were excluded from the analysis

Table 1: Retrospective chart review on sleep studies.

Classification of Data Points from Sleep Studies	Mild	Moderate	Severe
AHI Severity	15-May	15-30	≥ 03
Lowest Saturation	90%-80%	< 80%-70%	≤ 07%
Epworth Sleepiness Scale Score	0-12	13-18	➢ 18
ECG Abnormalities	1	2	≥ 3
Percentage Saturation of Less than 90%	0-1%	1%-5%	≥ 5%

Table 2: The presence and severity of diabetes and the presence of prior stroke.

Cardiovascular Comorbidities Group	Mild	Moderate	Severe
Hypertension	On 1 medication	On 2 medications	On 3 or more medications
Diabetes Mellitus	Hemoglobin A1C of 5.7-6.4%	Hemoglobin A1C of 6.5-8%	Hemoglobin A1C of greater than 8%

Table 3: How Candidate variables are correlated with AHI.

Variables	Correlation Coefficient	P-Value	Strength
Lowest Saturation	0.498	< 0.0001	Strong
RDI	0.456	< 0.0001	Strong
Baseline Saturation	-0.25	< 0.0001	Strong
N1	0.182	< 0.0001	Strong
BMI	0.171	< 0.0001	Strong
N3	-0.126	< 0.0001	Strong
HTN	0.112	0	Moderate
Age	0.104	0	Moderate
REM	-0.088	0	Small
ECG abnormalities	0.079	0.01	Small
Sleep Efficiency	0.078	0.01	Small
DM2	-0.053	0.08	None
ESS Score	0.025	0.42	None
N2	-0.024	0.43	None
DM1	0.022	0.48	None

leaving a total of 15 candidate variables. We then used correlation analysis and Chi square tests to examine which variables were related to AHI as outcome.

Given the categorical nature of the data, we adopted latent class analysis as a methodology to group patients into distinct groups based on the characteristics in (Table 3). The three cluster solution from the analysis is distributed as follows by AHI Category.

Results

After comparing all our data, we found that lowest saturation, RDI (Respiratory Disturbance Index), Baseline saturation, N1, BMI, and N3 had strong correlations with AHI. Presence of diabetes and ESS score had no correlation. Hypertension and age had moderate while REM cycle, ECG abnormalities and sleep efficiency had small correlation with AHI (Table 3).

In (Table 4), we have a chi square analysis on all the studies.

Based on the results from correlations and chi-

Table 4: Chi-square analysis on candidate variables.

Characteristic	AHI						
	Mild	Moderate	None	Severe	Total	Chi Square	Pvalue
Age							
< 30	34	16	8	9	67		
30-39	71	50	21	20	162		
40-49	76	66	28	30	200		
50-59	86	92	59	41	278		
60-69	73	80	38	42	233		
70+	37	33	29	14	113		
Total	377	337	183	156	1053	27.2	0.027
Baseline Saturation							
< = 95	72	101	63	57	293		
96	60	69	52	34	215		
97	85	83	50	39	257		
98+	154	84	18	23	279		
Total	371	337	183	153	1044	85.9	< 0.0001
BMI							
Class I	71	73	40	34	218		
Class II	68	66	40	32	206		
Class III	74	96	58	49	277		
Normal	71	37	12	8	128		
Overweight	94	65	33	33	225		
Total	378	337	183	156	1054	41.7	< 0.0001
DM1							
Mild	20	24	12	13	69		
Missing	315	278	148	126	867		
Moderate	31	23	11	7	72		
Severe	14	12	12	10	48		
Total	380	337	183	156	1056	8.6	0.478

DM2							
No	282	244	125	107	758		
Yes	97	93	58	49	297		
Total	379	337	183	156	1055	3.2	0.357
ECG							
Mild	126	115	75	62	378		
Moderate/Severe	17	18	10	12	57		
None	237	204	98	82	621		
Total	380	337	183	156	1056	8.1	0.233
ESS Score							
0 - 3	90	68	40	26	224		
11 to 15	104	67	41	42	254		
15+	34	40	11	21	106		
4 to 6	61	73	37	23	194		
7 to 10	89	88	53	44	274		
Total	378	336	182	156	1052	20.5	0.058
HTN							
Mild	99	99	47	39	284		
Moderate	41	38	30	25	134		
Severe	20	17	15	21	73		
Unknown Meds	215	174	88	68	545		
Total	375	328	180	153	1036	23.6	0.005
Lowest Saturation							
Mild	356	260	89	45	750		
Moderate	10	55	70	67	202		
Severe	12	22	24	44	102		
Total	378	337	183	156	1054	295.8	< 0.0001
N1(%)							
< 3	13	16	5	6	40		
12+	91	96	70	83	340		
3 to 5	66	51	25	10	152		
6 to 12	208	173	82	54	517		
Total	378	336	182	153	1049	54.4	< 0.0001
N2(%)							
< 60	102	90	56	56	304		
60 - 69	105	95	36	36	272		
70 - 79	121	110	62	37	330		
80+	50	42	29	24	145		
Total	378	337	183	153	1051	13.2	0.153
N3(%)							
0	166	170	111	89	536		
1+	212	167	72	63	514		
Total	378	337	183	152	1050	17.9	0.001
RDI							
< 20	316	277	53	4	650		
0	61	49	29	27	166		
20+	2	11	101	124	238		
Total	379	337	183	155	1054	621.9	< 0.0001
REM							

< 10	77	56	45	63	241		
10 to 15	84	73	23	34	214		
15 to 20	86	84	46	24	240		
20 to 25	78	68	42	12	200		
25+	53	56	27	20	156		
Total	378	337	183	153	1051	54	< 0.0001
Sleep							
Mild	56	68	30	32	186		
Normal	239	207	110	73	629		
Severe	83	62	43	47	235		
Total	378	337	183	152	1050	16	0.014

Table 5: Final variables selected for cluster analysis.

Age	**Code**
< 30	1
30-39	2
40-49	3
50-59	4
60-69	5
70+	6
Baseline Saturation	**Code**
< = 95	1
96	2
97	3
98+	4
BMI	**Code**
Normal	1
Over weight/under weight	2
Class I	3
Class II	4
Class III	5
ECG	**Code**
None	1
Mild	2
Moderate/Severe	3
HTN	**Code**
Unknown Medication	1
Mild	2
Moderate	3
Severe	4
Lowest Saturation	**Code**
Mild	1
Moderate	2
Severe	3
N1(%)	**Code**
< 3	1
3 to 5	2
6 to 12	3
12+	4
N3(%)	**Code**
0	1
1+	2
RDI	**Code**
< 20	0
0	1
20+	2
REM(%)	**Code**
< 10	1
10 to 15	2
15 to 20	3
20 to 25	4
25+	5
Sleep Efficiency	Code
Normal	1
Mild	2
Severe	3

Table 6: 3 Cluster solution distributions by AHI Category.

	AHI Category				
Cluster	**Mild**	**Moderate**	**None**	**Severe**	**Total**
1	102	71	62	100	335
2	73	67	19	114	273
3	233	32	164	19	448
Total	408	170	245	233	1056

square tests, the final variables selected for clustering are listed below along with their categories. All variables are ordinal in nature (Table 5).

We performed a cluster analysis using latent class analysis (Table 6).

The (Table 7) blow provides the probabilities of belonging to a given category for each cluster.

Based on this, we have 3 clusters with descriptions below (Table 8).

Cluster Seperation (Figure 1).

Discussion

Our study demonstrates the difficult and intricate relationship between cardiovascular comorbidities and

Table 7: Estimated Probabilities and Standard Errors.

		Probabilities			Standard Errors		
Response Category	**Code**	**Cluster 1**	**Cluster 2**	**Cluster 3**	**Cluster 1**	**Cluster 2**	**Cluster 3**
Age	**Code**						
< 30	1	2%	4%	11%	1.0%	1.3%	1.7%
30-39	2	3%	15%	25%	1.4%	2.5%	2.4%
40-49	3	14%	21%	21%	2.4%	2.8%	2.3%
50-59	4	24%	32%	24%	2.9%	3.3%	2.5%
60-69	5	32%	20%	16%	3.1%	3.1%	2.1%
70+	6	25%	8%	2%	2.7%	2.0%	1.0%
BMI							
Normal	1	11%	0%	21%	2.0%	0.1%	2.3%
Overweight	2	25%	12%	24%	2.8%	2.4%	2.4%
Class I	3	21%	22%	19%	2.7%	3.0%	2.2%
Class II	4	19%	26%	16%	2.6%	3.1%	2.1%
Class III	5	24%	40%	19%	2.8%	3.5%	2.3%
Baseline Saturation							
< = 95	1	26%	59%	9%	3.3%	3.9%	2.6%
96	2	25%	22%	17%	2.7%	3.0%	2.2%
97	3	29%	16%	27%	2.9%	2.8%	2.5%
98+	4	20%	4%	48%	2.8%	1.8%	3.4%
HTN							
Mild	1	38%	42%	71%	3.5%	3.9%	2.8%
Moderate	2	32%	28%	24%	3.0%	3.2%	2.4%
Severe	3	19%	17%	5%	2.5%	2.7%	1.6%
None	4	11%	12%	0%	2.0%	2.4%	0.4%
Lowest Saturation							
Mild	1	72%	31%	98%	3.4%	5.8%	1.4%
Moderate	2	22%	41%	2%	2.9%	4.3%	1.4%
Severe	3	6%	28%	0%	1.6%	3.6%	0.1%
N1							
< 3	1	1%	7%	4%	0.9%	1.7%	1.0%
3 to 5	2	0%	23%	20%	0.5%	3.0%	2.2%
6 to 12	3	29%	55%	62%	3.8%	3.6%	2.8%
12+	4	70%	15%	15%	4.0%	3.1%	2.5%
N3							
0	1	65%	49%	42%	3.2%	3.6%	2.7%
1+	2	35%	51%	58%	3.2%	3.6%	2.7%
RDI							
< 20	1	11%	17%	19%	2.2%	2.6%	2.1%
0	2	49%	51%	78%	3.4%	4.1%	2.4%
20+	3	39%	33%	3%	3.3%	3.8%	1.3%
REM							
< 10	1	41%	20%	11%	3.3%	2.9%	1.8%
10 to 15	2	18%	21%	22%	2.5%	2.8%	2.2%
15 to 20	3	21%	24%	24%	2.9%	3.2%	2.3%
20 to 25	4	13%	15%	27%	2.3%	2.5%	2.4%
25+	5	7%	21%	17%	1.7%	2.9%	2.1%
Sleep Efficiency							
Normal	1	19%	81%	77%	3.4%	3.9%	2.8%
Mild	2	27%	15%	13%	3.1%	3.0%	2.0%
Severe	3	55%	4%	10%	3.9%	2.1%	2.1%

Table 8: Cluster descriptions.

Cluster 1	Cluster 2	Cluster 3
• 72% probability of having mild lowest saturation • 70% probability of having 12+ NI • 65% probability of having 0 N3 • 55% probability of having severe sleep efficiency	• 59% probability of having < = 95 Baseline Saturation • 51% probability of having 1+ N3 • 51% probability of having 0 RDI • 55% probability of having 6 to 12 N1 • 81% probability of having normal sleep efficiency	• 75% probability of having mild HTN • 98% probability of having mild lowest saturation • 62% probability of having 6 to 12 N1 • 58% probability of having 1+ N3 • 78% probability of having 0 RDI • 77% probability of having normal sleep efficiency

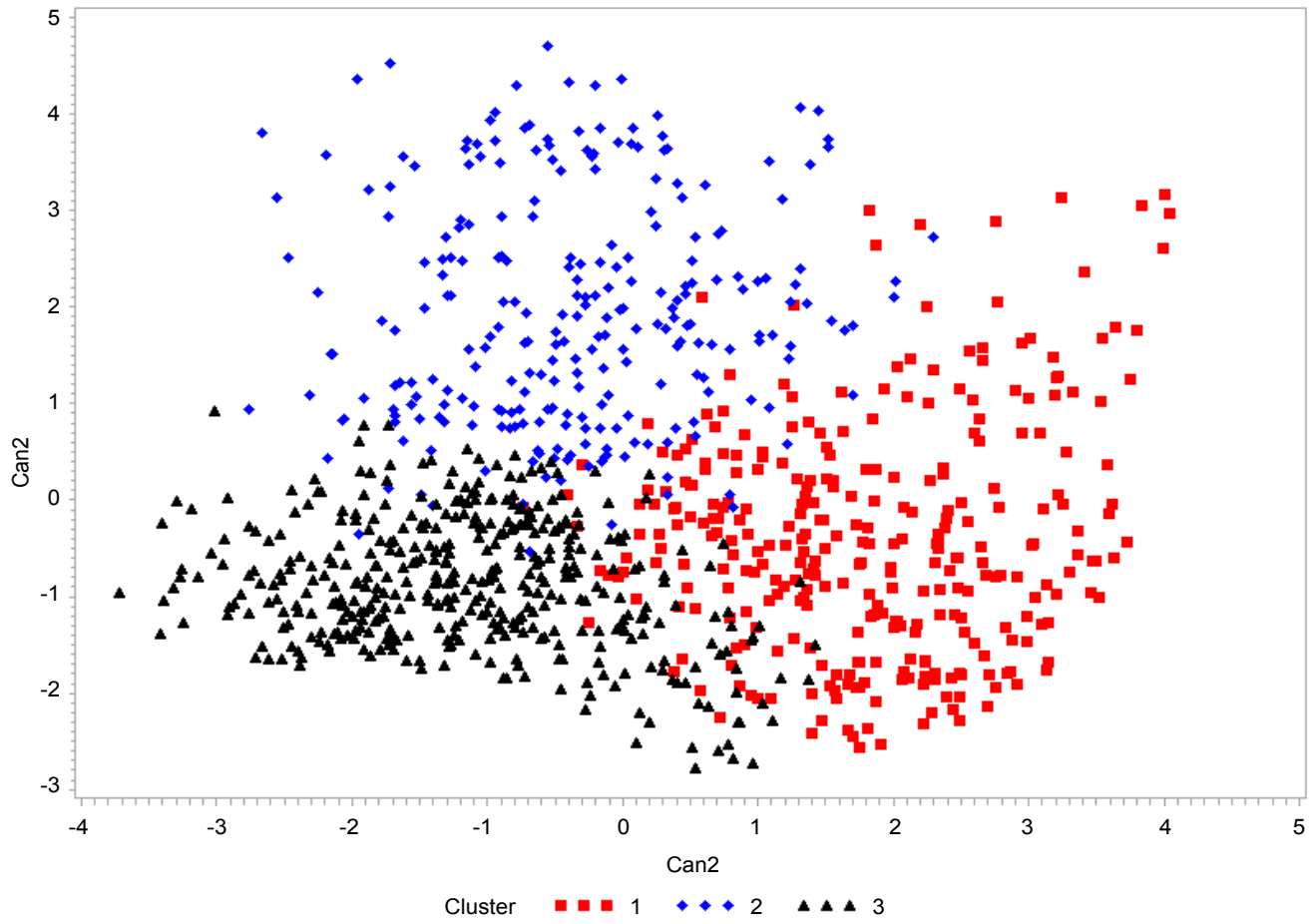

Figure 1: Cluster Separation.

OSA. To our knowledge this is the most comprehensive study to date that includes many cardiac comorbidities. Multiple studies [13-17] have demonstrated a relationship between obstructive sleep apnea and cardiac comorbidities but have not been able to investigate the same number of studies combined with the number of variables in our study. There are very limited number of prospective studies in the literature and one large prospective observational study with a mean follow up of 10.1 years found that when comparing healthy controls matched for age, sex and weight those with severe untreated OSA had more fatal and non-fatal cardiovascular events whereas those treated by CPAP did not differ-

ent significantly from the controls [10].

Cluster analysis has also been used to help differentiate comorbidities found in obese patients; Reategui, et al. looked at 14 obesity comorbidities from 1237 discharge summaries from the i2b2 2008 Obesity dataset and found relationships between obesity, hypertension and OSA [18]. A small prospective study of 45 patients analyzed OSA's association with cardiovascular disease finding associations with severe OSA and moderate to severe coronary artery [19]. With a similar goal to our study Sweed, et al. retrospectively studied 244 patients diagnosed with OSA to assess the prevalence of associated comorbidities and the most common comorbid-

ities they identified were obesity, hypertension, and diabetes mellitus [20]. Hypertension is a well-studied disease process that has been shown to be better controlled with CPAP [21] and our study also demonstrated moderate correlation of the severity of hypertension and AHI. Some studies have attempted to treat hypertension in OSA patients by using beta blockers instead of diuretics given the OSA triggered excessive sympathetic nervous system response [22]. Interestingly, OSA was found to increase 24 h diastolic blood pressure variability (BPV) in hypertensive patients and night time systolic in multiple studies [23-26]. High AHI, was associated with elevated diastolic blood pressure in the morning and was postulated as one symptom that could be diagnostic for OSA [27].

Finding well defined clusters in a population as big and diverse as OSA is difficult but if noted could prove fruitful. The best scenario would be to have groups of the population that could be treated in an individual manner for focused care creating a targeted algorithm that may in the long turn achieve better control and higher compliance with improved outcomes.

The strength of our study is the number of sleep studies that were looked at in detail and the multiple EMRs used within our health system. The limitation of the cluster study is that we were not able to reach a unified clustering based on differences in the levels of comorbidities. We aimed for clusters to form based on comorbidity severity and in correlation to the AHI severity, however there were comorbidities that had no association with the AHI and therefore not included in the cluster. We only used Age, baseline saturation, BMI, ECG abnormalities, hypertension, lowest sat, N1 sleep stage, N3 sleep stage, RDI, REM and sleep efficiency. Based on these variables, our study resulted in three major clusters. When all clusters are compared, we were able to demonstrate different characteristics of sleep studies but only hypertension had a significant effect on the clustering. The rest of the majority of the clusters were formed by differences in sleep stages, RDI, lowest saturation points and sleep efficiencies. Based on these results, our study did not show a significant association between the cardiac comorbidities and sleep study outcomes as clustering.

This study demonstrates how severity of sleep apnea has a direct relationship with hypertension and perhaps sleep efficiency. Nocturnal hypoxia has already been an established cause of hypertension [28] and prospective studies have been also performed to establish this phenomenon [6-10]. It is thought that the cause of systemic hypertension in patients are due to persistently elevated sympathetic nerve activity due to hypoxemia, with associated increased blood pressure and heart rate. This happens even during wakefulness and muscle sympathetic nerve activity is attenuated during apnea under hypoxic conditions [29,30] pointing out to a direct link with hypoxemia.

Baroreflex sensitivity is diminished in OSA and this leads to intermittent hypoxemia [31,32] that has also been shown to be reduced with CPAP use.

We are not fully confident that a larger study would be able to demonstrate better clustering with these disease processes. We believe that one of the explanations why we were not able to show associations between the cardiovascular disease processes and severity of sleep study is the heterogeneity of each cardiovascular disease process and we were simply looking at a cross section of the disease in whatever time frame was available in our EMR. The uncontrolled or undiagnosed diseases prior to the recording in the EMR or not recording might account for the clustering issues we faced. We believe that a prospective study with these diseases aiming at a controlled way of collecting the data might yield more uniform results. It might also yield better clustering that may yield individualized treatment algorithms for patients suffering from OSA and its associated comorbidities.

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