PATIENTS WITH VENOUS THROMBOEMBOLISM HAVE HIGHER PREVALENCE OF OBSTRUCTIVE SLEEP APNEA THAN THE GENERAL POPULATION

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APPROVAL PAGE

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ABSTRACT

Study Objectives

Obstructive sleep apnea (OSA) has been linked to a large number of cardiovascular diseases. However, the link between OSA and venous thromboembolic events (VTE) remains unclear. We sought to study the possible association between VTE and OSA.

Design

Retrospective study (August 1999 - April 2009).

Setting

University Tertiary Center.

Patients

We retrospectively collected data on patients with objectively confirmed VTE. Primary outcome was prevalence of OSA defined as an apnea-hypopnea index (AHI) $\geq 5$. Data on demographics and co-morbidities were recorded as well as body-mass index was calculated.
Measurements and Results

840 patients were identified as having VTE and analyzed for presence/absence of co-morbidities. Of 840 patients, 130 (15.5%) were also diagnosed with OSA. Compared to the control group (no OSA), those who had OSA were more obese (83.8% versus 43.8%) and had statistically higher prevalence of diabetes, coronary artery disease (CAD), and congestive heart failure (CHF). OSA patients had higher prevalence of pulmonary embolism but similar prevalence of deep vein thrombosis.

Conclusions

In this VTE cohort, the prevalence of OSA (15.5%) appears to be higher than that of the general population (2-10%). Our data suggest that patients with both OSA and VTE are more likely to be obese with diagnoses of CAD, CHF, and diabetes than their counterparts with VTE alone. OSA patients had higher prevalence of pulmonary embolism compared to controls. Although OSA has been clearly linked to arterial thrombosis, this study also suggests a link between OSA and venous thrombotic disorders.
ABBREVIATIONS

VTE – Venous Thromboembolic Event
PE – Pulmonary Embolism
DVT – Deep Vein Thrombosis
OSA – Obstructive Sleep Apnea
CHF – Congestive Heart Failure
CVA – Cerebrovascular Accident
BMI – Body Mass Index
CAD – Coronary Artery Disease
ROC – Receiver Operating Characteristics
AUC – Area Under the Curve
AHI – Apnea-Hypopnea Index
CHADS2 - clinical prediction tool for predicting risk of stroke in patients with atrial fibrillation
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INTRODUCTION

Venous thromboembolism (VTE), defined as deep vein thrombosis (DVT) and/or pulmonary embolism (PE), is a common and highly prevalent disease which affects an estimated 350,000 to 600,000 people in the United States every year and claims the lives of at least 100,000 [1]. Multiple risk factors increase the risk for DVT, including trauma, surgery, cancer, hormone therapy and others [1]. Obesity is one of the several conditions related to the development of VTE. Additionally, obesity is a known risk factor for Obstructive Sleep Apnea (OSA) and affects the disease severity [2]. The prevalence of OSA ranges between 2-10% of the general adult population in the United States [3], however this is likely underestimated due to under diagnosis of the disease [4].

OSA has been linked to many of cardiovascular diseases, including hypertension, ischemic heart disease, congestive heart failure (CHF), cerebrovascular accidents (CVA), pulmonary hypertension, cardiac arrhythmias, end-stage renal disease and overall cardiovascular mortality [5-7]. Conversely, the link of OSA to VTE, another cardiovascular disease, is not well established. At least two
published reports have suggested a relationship between OSA and VTE. However, both studies suffered from low sample size and design limitations [8-9]. Due to the unclear association between OSA and VTE, we sought to study the potential relationship and estimate the prevalence of OSA among patients with VTE.
BACKGROUND

Venous Thromboembolism

Venous thromboembolism (VTE) is a common and highly prevalent disease with high morbidity and mortality. VTE affects an estimated 350,000 to 600,000 people in the United States every year and claims the lives of at least 100,000 [1]. VTE encompasses both deep vein thrombosis (DVT) and pulmonary embolism (PE). DVT refers to a blood clot in one of the “deep” or large veins of the body. DVTs usually begin in the lower leg or calf or distal upper extremity, then propagate proximally [10]. PE occurs when a portion of the proximal clot in one of the large veins breaks off and travels through the heart into the pulmonary arteries. PE occurs in over one-third of patients with DVTs and is a life-threatening complication [10].

Over 50 percent of DVTs are asymptomatic [11]. However, DVTs can lead to pain, swelling, warmth, tenderness, discoloration, and/or erythema of the area [1]. PE symptoms include tachypnea, tachycardia, diaphoresis, pleuritic chest pain and/or hemoptysis [1].
Approximately 15 percent of PEs are fatal with 10 percent being rapidly fatal [10]. Death due to PE results from right ventricular failure [12].

While the most dreaded complication of a DVT is a PE, DVTs can also lead to additional complications. Approximately 30 percent of patients that develop a DVT deal with subsequent problems encompassed by the term post-phlebitic syndrome. These include chronic leg swelling and pain, skin breakdown and ulceration, chronic thromboembolic disease, and pulmonary hypertension [13]. Further, after the first episode of DVT, a patient remains at higher risk for additional DVTs in the future [13]. Of those that deal with a first episode of DVT, 30 percent will suffer from another DVT in the following 10 years, with the highest risk in the first 2 years [14]. Multiple risk factors increase the risk for DVT, including obesity, trauma, surgery, cancer, hormone therapy, cancer and others [1]. Obstructive Sleep Apnea (OSA) shares many risk factors with VTE, most notably, obesity. Obesity also affects OSA disease severity [2, 15].
Obstructive Sleep Apnea

OSA is a disorder in which repetitive interruptions of ventilation occur during sleep by obstruction of the pharyngeal airway due to loss of muscle tone [16]. The disease is characterized by signs of disturbed sleep, sleepiness or fatigue and abnormal sleep breathing patterns [16]. OSA was first believed to be described by Charles Dickens in 1837 when he coined the term “Pickwickian.” This term was then adapted and used by Sir William Osler in the early 20th century and by Dr. Burwell in the 1950s. In 1965, Gastault et al noted that patients with this syndrome had apneic events during sleep. In 1969, Kuhlo et al noted that patients with this syndrome were successfully treated with tracheostomy. In 1978, Remmers et al studied the mechanisms by which the upper airway collapsed during sleep, which began the term “obstructive sleep apnea.” Finally in 1981, Sullivan et al published a paper on successful treatment of OSA with continuous positive airway pressure [17-18].
OSA is estimated to affect at least 2-10% of the general adult population in the United States and continues to increase in prevalence due to the obesity epidemic [3]. Obesity is thought to contribute to OSA by increasing the volume of pharyngeal soft tissue and reducing the airway diameter, thus increasing likelihood of airway collapse. Normally, reflex-driven muscle activation is required to maintain patency in the upper airway in OSA prone individuals. This reflex is compromised during sleep leading to apneic or hypopnic events [15]. Furthermore, there is evidence that OSA is under-diagnosed. For example, in a subset of surgical patients, less than 20% of the patients with clinically significant OSA had previously been diagnosed with the condition [4]. Other studies claim that >85% of patients with OSA have never been diagnosed and would benefit from treatment [19].

OSA is defined by an Apnea-Hypopnea Index (AHI) >5 in a symptomatic patient [16]. OSA is diagnosed after an overnight sleep study where the AHI is determined, with apnea defined as a >10 sec pause in breathing and hypopnea defined as decreases in breathing that lead to a fall in oxygen saturation or arousal [15]. The total number apnic and hypopnic events are totaled and divided over the
hours of sleep to yield the AHI index which is used to categorize severity of OSA.

OSA results in secondary disease by a number of mechanisms including increased cytokine levels, hypoxia and hypercarbia. In healthy subjects, sleep deprivation alone has been shown to increase levels of C-reactive peptide, interleukin-6 and tumor necrosis factor-alpha [20-23]. OSA leads to subsequent hypoxia and hypercarbia, which activates the sympathetic nervous system and diminishes cardiovascular variability [15]. Oxygen saturations have been documented as low as 60% during these events and this disrupts the normal "autonomic and hemodynamic responses to sleep" [24].

OSA also leads to the release of vasoactive substances (endothelin and aldosterone), inflammatory and oxidative stress markers (plasma cytokines, adhesion molecules, C-reactive protein, superoxide, nitrotyrosine) and leads to endothelial dysfunction (resistance to vessel relaxation with acetylcholine), insulin resistance, intrathoracic pressure changes, and thrombosis (increased platelet activation and fibrinogen) [15, 25-26]. Furthermore, reactive oxygen species are more abundant with OSA (specifically superoxide) and have been shown to destabilize the endothelial nitric oxide synthase
messenger RNA and decrease nitric oxide production by over 60% [26-29].

Endothelial damage and oxidative stress markers have been shown to resolve after initiation of treatment for OSA (continuous positive airway pressure), providing further proof that OSA is directly related to these findings [26]. In addition, prolonged hypoxia has been shown to induce the transcription factor hypoxia-inducible factor-1 that subsequently leads to erythropoietin and vascular endothelial growth factor production [30-31]. In sum, OSA seems to contribute to a microvascular inflammatory state, similar to that of hypertension and diabetes mellitus.

Several factors influence the development of OSA. Age and obesity are noted to increase risk of OSA and the severity of disease can be linked with BMI [2, 15]. Race seems to play a role, as the risk for blacks exceeds that for whites [32]. Gender has also been shown to affect the prevalence of OSA. Men appear to have 2-3 times the risk of developing OSA as compared to females [33]. Pre-menopausal women or post-menopausal women on hormone replacement therapy have a significantly lower risk in the development of OSA as compared
to post-menopausal women not on hormone replacement therapy [34].

Due to the increasing prevalence and under-diagnosis of OSA, the co-morbidities associated with this disease continue to expand. OSA has been linked to a large number of cardiovascular diseases, including hypertension (30-83%) [35-36], ischemic heart disease (30-58%) [37-38], congestive heart failure (CHF) (12-53%) [39-41], cerebrovascular accidents (CVA) (43-91%) [42-44], pulmonary hypertension, cardiac arrhythmias, end-stage renal disease and overall cardiovascular mortality [5-7]. OSA has also been linked to type II diabetes [45]. OSA patients that are not treated for their disease clearly have increased mortality from cardiovascular events [46].

The link of OSA to VTE events, another cardiovascular disease, is not well established. At least two published reports have suggested a potential relationship between OSA and VTE. However, both reports suffered from low sample size and design limitations [8-9]. Nevertheless, many studies have investigated the link between OSA and a thrombotic phenotype.
Obstructive Sleep Apnea and Thrombosis

Multiple studies have confirmed that OSA induces an inflammatory phenotype and a prothrombotic state [47-48]. Patients with OSA have increases in plasma cytokines, adhesion molecules, leukocyte activation and TNF-alpha [15]. OSA also leads to alterations in the levels of vasoactive substances, including increases in endothelin [49], and aldosterone [50], and decreases in nitric oxide [51]. Recent studies have established the association between OSA, endothelial dysfunction/apoptosis [26, 52-54], and elevated C-reactive peptide levels [55]. In patients with OSA, microvascular endothelial function (tested by relaxation to acetylcholine) has been shown to be impaired. In addition, this impairment is reversed with proper OSA treatment [56]. Regarding hypercoagulability, von Kanel et al. has shown that patients with OSA have elevations in prothrombotic factors. These include increased plasma fibrinogen, reductions in fibrinolytic capacity, activation of clotting factors, and heightened platelet activity [47-48].
Since the late 1800s from Dr. Virchow’s epidemiological studies, Virchow’s triad has been studied as the foundation for thrombosis and VTEs. Virchow’s triad includes alterations in blood (hypercoagulability), alterations in vessels (endothelial damage), and alterations in blood flow (stasis). OSA has been shown to induce an inflammatory phenotype with endothelial damage and a hypercoagulable state, consistent with Virchow’s triad. With the addition of stasis, which is found in many medical conditions (including hospitalization itself), there is a large increase in the risk for VTE. Although OSA has been linked with arterial thrombosis, the goal of this study is to link OSA with the venous thrombotic disorders.
Venous Thromboembolism and Obstructive Sleep Apnea

In summary, VTE is a disease that carries high morbidity and mortality. The list of risk factors for the development of VTE continues to expand. OSA is one such disease that appears to be a logical fit for inclusion as a risk factor for VTE. OSA has been linked to multiple cardiovascular diseases, diseases of arterial thrombosis, and a prothrombotic phenotype. OSA, by itself or its downstream mediators, affects all three corners of Virchow’s triad. A relationship between OSA and VTE seems a logical conclusion, but the link remains unclear.

The following study is designed to examine if patients with VTE have a higher prevalence of OSA than the general population. We hypothesize that OSA leads to a prothrombotic phenotype that increases the risk of developing VTEs. In the same line, we hypothesize that patients that have developed previous VTEs will have a higher percentage of patients (prevalence) with OSA. As OSA and VTE carry that same risk factor of obesity, we hope to be able to discern if VTE and OSA are linked independent of adiposity. Furthermore, due to the concurrence of OSA and multiple other
medical conditions (diabetes, CAD, CHF and stroke), we expect that patients with both VTE and OSA will have a higher prevalence of these medical conditions.

Being able to discern a patient population that carries a higher risk of VTE would be invaluable in prevention and treatment of this disorder. As the CHADS score (and other risk stratifying scoring systems) is currently used to predict the risk of stroke in patients with atrial fibrillation, the existence of OSA could be added as a factor in predicting the risk of VTE in patients. Currently the prevention of VTE applies mostly to hospitalized patients, however, some clinicians are even questioning if VTE prophylaxis should be applied to selected patients in the outpatient setting. Nevertheless, discerning if OSA induces a pro-VTE phenotype would alter the current recommendations for prophylaxis. Regarding treatment, recommendations for the length of anticoagulation are variable. If OSA is found to be a risk factor for VTE, a longer duration of anticoagulation might benefit patients with OSA.

The primary hypothesis of this study is that patients with VTE have a higher prevalence of OSA than the general population. If this hypothesis holds true, clinicians may want to question their patients
with VTE for the risk factors of OSA and consider a polysomnogram. As mentioned above, OSA is a treatable disease and treatment alters the disease outcome. This study has the potential to alter clinical practice and help to draw attention to the association of VTE and OSA.
Design and Setting

A retrospective study was conducted at the University of Missouri Hospitals and Clinics from August 1999 to April 2009. This center is a tertiary university hospital and is equipped with 8 beds for polysomnography. The Institutional Review Board from the University of Missouri approved the study under the exempt category. The study was registered at clinicaltrials.gov (NCT01051297).

Patients

All adult patients (>18 years of age) with ICD-9 coding indicative of VTE were included. The initial search contained all of the following ICD-9 codes: 415.11, 415.12, 415.19, 453.4, 453.9, 453.41, 453.42, 671.33, 671.44. The study investigators then reviewed the charts extensively to verify the clinical diagnosis of VTE. The study investigators did not independently adjudicate any of the clinical findings. VTE was defined as the objective diagnosis of pulmonary
embolism (PE) or deep vein thrombosis (DVT). VTE was confirmed by extremity venous-doppler ultrasonography (abnormal compression ultrasound), venography, spiral CT of the chest (a new intraluminal filling defect in segmental or more proximal branches on spiral CT scan), high probability ventilation-perfusion VQ scan (a new perfusion defect of at least 75% of a segment with a local normal ventilation result), or pulmonary angiography (a new intraluminal filling defect, or an extension of an existing defect, or a new sudden cutoff of vessels more than 2.5 mm in diameter on the pulmonary angiogram). Only confirmed VTE patients (as listed in past medical history or per available records of radiographic testing) were included in the study. Patients without objective confirmation of VTE were excluded. If the status of OSA or height and weight could not be ascertained, then such patients were also excluded.

**Measurements**

Patient charts were reviewed and the following data was collected: age, race, smoking status, and presence of diabetes mellitus, CHF, CVA, and coronary artery disease (CAD). Height and weight data, which allowed calculation of the BMI (Body Mass Index), was also collected. Patients were classified into five groups according
the WHO classification [57-58]: Normal (BMI < 25.0), overweight (BMI 25.0 to 29.9), and obesity (BMI ≥ 30) was subdivided into grade 1 (BMI 30 to 34.9), grade 2 (BMI 35 to 39.9), and grade 3 (morbid, BMI ≥ 40) [57]. Primary outcome for this study was the prevalence of OSA among this group of patients with VTE. OSA was defined as an apnea-hypopnea index (AHI) of ≥ 5 by overnight polysomnography or the presence of OSA in the patient’s medical history confirmed by a sleep study in an outside laboratory not available for our review. Please see the results section for demographics of this study population (may also see Table 1).

**Statistical analysis**

Data were entered into a database (Microsoft Excel, Microsoft Corporation, Redmond, WA, 2007). The cohort was then divided into groups according to presence or absence of OSA. The two groups (OSA and No-OSA) were then compared. Continuous data were expressed as means or medians according to normality testing using Kolmogorov-Smirnov tests and compared using the student T or the Mann-Whitney tests whichever applicable. Categorical variables were expressed as percentages and compared using the chi-square or Fisher exact tests. For statistical analysis, parametric or non-parametric
tests were used according to normality testing. Furthermore, the prevalence of OSA was estimated according to classes of BMI. Statistical significance was defined as $p < 0.05$ and all tests were two-sided.

Receiver operating characteristics (ROC) analysis was used to evaluate the performance of BMI in the prediction of OSA among patients with VTE. Area under the curve with 95% confidence interval was estimated. According to the curve we defined the cut-off value with best combination of sensitivity and specificity.
Results

From August 1999 - April 2009, 1239 patients were found to have the included ICD-9 codes and were screened. Of those 1239 patients, 840 patients were included in the study and 399 were excluded. Most patients were excluded due to the inability to confirm VTE or BMI. Figure 1 illustrates the consort diagram for study inclusion and exclusion. Of the 840 patients with VTE, 130 were also diagnosed with OSA yielding a prevalence of 15.5% of OSA in the cohort.

Table 1 (and Figure 2) illustrates the demographics and Table 2 (and Figure 3 and 4) illustrates the co-existing medical conditions and outcomes of the patients included in the study. 453 (53.9%) patients were females and the median age was 55 (18-94). Figure 3 illustrates the breakdown of VTE by the presence or absence of OSA. Of the 840 patients, 619 (73.8%) had DVT with 524 (73.9%) in the No-OSA group and 95 (73.1%) in the OSA group (p = 0.843). 530 (63.3%) of the patients had PE with 439 (61.9%) in the No-OSA and 91 (71.7%) in the OSA group (p = 0.047). 309 (36.8%) had both DVT and PE
with 253 (35.6%) in the No-OSA group and 56 (43.1%) in the OSA group (p=0.106).

When comparing the two groups (OSA, No-OSA), there was no difference in age, race, gender or rates of CVA events (p > 0.05 - see Table 1, 2 and Figure 2 for details). Compared to the control group (No-OSA), those who had OSA were more obese (83.8% versus 43.8%) and had higher rates of diabetes, CAD, and CHF (p-values: <0.0001, <0.0001, 0.028, and <0.0001, respectively - see Table 2 or Figure 4 for details).

As obesity was associated with OSA in this study, OSA prevalence was divided into obesity categories. Figure 5 illustrates prevalence of OSA according to grade 1 (BMI 30-34.9), 2 (BMI 35-39.9), and 3 (BMI >40) BMI categories. There was a clear trend of increasing prevalence of OSA based on BMI. Both the normal and overweight groups had rates comparable to the general population but the three obese (grade 1, grade 2 and grade 3 - morbid) had much higher prevalence with rates reaching 50% in the morbidly obese (grade 3) group.
In order to provide numbers to assist in clinical decision making, ROC analysis was performed. Figure 6 depicts the ROC curve according to BMI. The analysis had good performance with area under the curve (AUC) of 0.797 [95% confidence intervals (0.753-0.840), p <0.0001]. The best cut-off value for diagnosis of OSA in patients with VTE was a BMI of 34. This yielded a sensitivity of 78% and specificity of 75%. If a primary care provider has a patient present with a new VTE, the ROC analysis suggests a BMI of 34 or greater as the best cut-off to consider a polysomnogram.
Discussion

In this population of patients with confirmed VTE, the prevalence of OSA (15.5%) is higher than the general population (2-10%) [3]. Our data also suggests that patients with prior diagnoses of OSA and VTE are more likely to be obese with higher rates of CAD, CHF and diabetes (Figure 4). Remarkably, there was no difference in age between the two groups although age is clearly listed as a risk factor for VTE in the literature. Interestingly, the OSA group had higher prevalence of PE (71.7% vs. 61.9%; p=0.047) but similar rates of DVT (see Figure 3). This latter finding may, in part, explain the higher overall cardiovascular mortality in OSA patients noted by other studies [5]. Although OSA has been clearly linked to arterial thrombosis, this study suggests a link between OSA and the venous thrombotic disorders. However, obesity could be an underlying association between OSA and VTE.

Our findings are consistent with previous studies that have also noted a relationship between OSA and VTE. Ambrosetti et al. have shown through a limited sample size study (N=89) that OSA patients
appear to be at increased risk of VTE [8]. Of 89 patients with OSA, 2 developed proximal DVTs and one of those patients developed PE over a 3 year follow-up. Another study by Arnulf et al. showed that in patients (N=68) admitted to the hospital with a VTEs, 82.4% (56/68) had an AHI ≥ 5 and 63% (43/68) had an AHI > 15 [9].

Obesity appears to be a common factor between OSA and VTE. In our OSA group, 83.8% of the patients were obese with a median BMI of 40.69 (versus 43.8% and a BMI of 29.09 in the No-OSA cohort), although the causal relationship is unclear. Obesity has been shown to effect hemostasis by many of the same mechanisms as OSA. As summarized by Stein and Goldman, obesity has been shown to effect fibrinolysis, plasminogen activator inhibitor-1 levels and platelet aggregability [59].

In our study we found a clear trend of higher prevalence rates of OSA with increasing BMI (see Figure 5). The morbidly obese group (BMI ≥ 40) had a prevalence rate of about 50% indicating that one-half of the patients in this group had OSA. ROC analysis showed that a BMI of 34 was the best cut-off value. Our data suggests that sleep evaluation may be necessary in those patients with prior VTE and obesity grades 1, 2 or 3 as these three groups had much higher
prevalence of OSA. In the other 2 groups (normal and overweight) OSA was comparable to general population, thus sleep evaluation might be based on other suggestive signs and symptoms rather than BMI.

Our study has limitations. The retrospective design limits our conclusions with the inherent weakness included in this design. ICD-9 coding was initially used to identify patients although complete chart reviews were performed to confirm included data. We found that many patients that were labeled by ICD-9 code as VTE, did not actually have the disease. Although unexpected, we consider this as a strength for our study as it required data to be confirmed for every patient. Another limitation is that we could not consistently ascertain whether OSA preceded VTE or vice versa, and thus, we expressed the percentage of OSA patients as a prevalence rather than incidence. In addition, we did not have access to all the sleep studies as many of them were performed in outside laboratories. In these instances, we chose not classify the patient as sleep apnea unless we found objective evidence in the chart that the patient carried this disorder. We excluded patients that were described as high risk or potentially having OSA, without evidence of sleep study. Many patients may have had OSA without a clear medical record or proper testing and
diagnosis; these were not included in our study. These uncertainties may have led to underestimation of the prevalence of OSA in this cohort.

Additional study limitations include the inability to have a true control group due to study design. Examining a cohort of patients with similar BMIs without obstructive sleep apnea would allow additional conclusions and analysis of data. Further studies would benefit from having an established control group of patients with comparable comorbidities without OSA.

Our study also has many strengths. This is the largest cohort in the literature that investigates the relationship between OSA and VTE. Further, the previous two other reports had 157 patients combined [8-9]. We confirmed the diagnoses of VTE and OSA and also studied baseline characteristics to discern if the relationship is independent or confounded by obesity, a common factor between these two disorders.
**Conclusion**

Patients with VTE do have a higher prevalence of OSA (15.5%) as compared to the general population. CAD, CHF, and diabetes also appear to be more prevalent in patients with both VTE and OSA as compared to patients with VTE alone. Obesity continues to be one of the confounding variables and obesity also increases the risk of VTE, OSA, and many other medical conditions. Of particular interest, in a cohort of patients with VTE, we found similar prevalence of DVT but increased prevalence of PE in patients with OSA. Although OSA has been clearly linked to arterial thrombosis, this study suggests a link between OSA and VTE. Further studies are necessary to clarify the possible association between these disorders.
**Further Studies**

Due to the high prevalence of obesity and OSA, further studies of the development of VTE in OSA patients would be helpful to clarify the causal relationship between these diseases. Current plans include a retrospective study looking at patients diagnosed with OSA and two prospective studies. The studies have been registered with clinicaltrials.gov. In the retrospective study, comparable methods will be used to examine the prevalence of VTE in patients diagnosed with OSA. In this study, attempts will be made to establish a time-line of the diagnoses of VTE and OSA. Establishing a time-line between the onset of OSA and development of VTEs may be helpful in elucidating the relationship between the two diseases.

In the first prospective study, inclusion criteria will be patients greater than 18 years of age that have current or previous VTEs. Patients will be located through the Thromboembolic Clinic at the University of Missouri and/or through admission at the University of Missouri Hospital. This study was approved through the University IRB under waiver of documentation of consent. After verbal consent is obtained, patients will be given a sleep questionnaire including the
Epworth Sleepiness Scale [60]. The Epworth Sleepiness Scale is a measure of the degree of patient sleepiness in imaginary situations. The sleep questionnaire will also include information on demographics, height, weight, sleep hygiene, and medical co-morbidities. Furthermore, if the patient is found to score high on the Epworth Sleepiness Scale (>8), they will be encouraged to discuss the prospect of a sleep study with their primary care physician. These patients will then be followed for a year and monitored for the diagnosis of OSA. Currently 25 patients have been enrolled in this study.

In the second prospective study, inclusion criteria will be patients greater than 18 years of age that are admitted to the University or Columbia-Regional sleep labs. This study was also approved by the University of Missouri IRB under waiver of documentation of consent. After verbal consent is obtained, these patients will be offered a questionnaire to evaluate for a past medical history of VTE. Sleep study results will be viewed after the sleep study for the diagnosis of OSA. Also, a thorough review of the patients medical record will be performed for demographics and medical co-morbidities. These patients will then be followed for the next year to monitor for the development of VTE by the means of a phone call to the patient and medical records. This study will allow the estimation
of incidence of symptomatic VTE (both PE and DVT) in patients with OSA. Currently approximately 100 patients have been enrolled in this section of the study.

The second study will also have the benefit of a control group. Patients that undergo sleep studies and do not qualify as OSA patients will provide a proper control group. This will allow proper comparisons and proper controls for obesity and other confounders. This current study was unable to benefit from a true control group as there was no set criteria for what a "control" patient would be. The ICD-9 search included patients coded for VTE and to analyze data for the patients that do not have a coding for VTE (all the other patients in the University health system) would be unfeasible. Set criteria for control patients would need to have been set from the beginning and set criteria for control patients would have their own limitations by inherent design.
Clinical Implications

This is the largest study to examine the relationship between VTE and OSA. In this study, we found that patients diagnosed with VTE have a higher prevalence of OSA than the general population. This suggests that patients who are found to have VTE should be considered for evaluation for OSA by overnight polysomnogram. However, further studies are necessary to confirm these findings. Furthermore, after breaking down the prevalence of OSA by BMI, we found that above a BMI of 34 in patients with VTE confers a sensitivity of 78% and specificity of 75% for OSA. This study does have the confounder of obesity, so this limits the clinical implications.

In future studies, we hope to further investigate the link between OSA and VTE. If our hypothesis is correct, patients that are found to have VTE should be investigated for OSA and patients found to have OSA should be considered a higher risk for thrombosis. Currently OSA has been linked to multiple cardiovascular diseases, but not specifically to VTE. If OSA does induce a hypercoagulable state, it would be of interest to study the treatment of continuous positive airway pressure and its effect on this state. Also, there potentially
could be implications on the length and/or initiation of anticoagulation in patients with OSA and/or VTE.

Healthcare workers should be aware of the association between OSA and VTE particularly since both of these diseases by themselves are associated with high morbidity and mortality.
Bibliography


Tables, Figures, and Legends

Titles

**Figure 1.** Consort Diagram for Study Population.

**Table 1.** Demographics of the study patients and those with or without obstructive sleep apnea.

**Table 2.** Co-existing medical conditions and outcomes for the study population.

**Figure 2.** Baseline demographics of the study population.

**Figure 3.** VTE outcomes separated by study groups (OSA vs No-OSA).

**Figure 4.** Co-morbid conditions in the study population separated by the presence or absence of OSA.

**Figure 5.** Prevalence of OSA among patients with VTE according to BMI categories.
Figure 6. Receiver operating characteristics (ROC) curve for BMI predicting the status of OSA.
Legends

Figure 1.

1239 patients with ICD-9 coding for venous thromboembolic events (VTE) were enrolled in the study. 840 were included and 399 were excluded for various reasons. Of the 840, 130 were also diagnosed with obstructive sleep apnea (OSA) for a prevalence of 15.5%.

Table 1.

Demographics for the study population. There was no difference in age, race or sex. Patients with higher body-mass indices (BMI) had a higher prevalence of OSA.

Table 2.

Co-existing medical conditions and outcomes for the study population. Venous thromboembolic event (VTE) patients that were found to have obstructive sleep apnea (OSA) had a higher prevalence of obesity, coronary artery disease (CAD), congestive heart failure (CHF), and type 2 diabetes (DM 2). There was a trend towards a higher prevalence of strokes and smoking. The patients with OSA also had more pulmonary embolisms (PE).
Figure 2.
No difference was found in gender, race or age between the OSA and No-OSA groups.

Figure 3.
When comparing the study population separated by the presence or absence of OSA, no difference was found between prevalence of DVT. The OSA group has a significantly higher prevalence of PE and a trend towards higher prevalence of the combination of DVT and PE.

Figure 4.
When comparing the study population separated by the presence or absence of OSA, there were significantly more OSA patients with type 2 diabetes (DM 2), congestive heart failure (CHF), and coronary artery disease (CAD). Also, there was a trend towards increased stroke and patients that were smokers in the OSA subset of patients.

Figure 5.
OSA prevalence increased with higher BMI (body-mass index) in patients with VTE. The morbidly obese group (BMI ≥ 40) had an obstructive sleep apnea (OSA) prevalence rate of about 50%.
**Figure 6.**

Best Cut-Off value was found to be a BMI of 34 with a sensitivity of 78% and specificity of 75%. In patients with venous thromboembolism (VTE) and a body-mass index (BMI) greater than 34, the sensitivity is 78% and specificity 75% for obstructive sleep apnea (OSA).
Figure 1. Study Flowchart

Assessed for eligibility (n=1239)

Enrollment

840 enrolled

Excluded (n=399)
- No VTE
  (n=314)
- OSA status could not be ascertained
  (n=6)
- BMI data not available
  (n=79)

OSA
130

Analysis

No OSA
710
## Table 1.

<table>
<thead>
<tr>
<th>Groups</th>
<th>No-OSA</th>
<th>OSA</th>
<th>Total</th>
<th>P-values</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>710 (84.5%)</td>
<td>130 (15.5%)</td>
<td>840 (100%)</td>
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<tr>
<td><strong>Female Gender</strong></td>
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<tr>
<td>n (%)</td>
<td>390 (54.9)</td>
<td>63 (48.5)</td>
<td>453 (53.9)</td>
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<td>130 (15.5%)</td>
<td>53 (41.5)</td>
<td>183 (21.8%)</td>
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<tr>
<td><strong>Age</strong></td>
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<tr>
<td>median (range)</td>
<td>55 (18-94)</td>
<td>53.5 (29-84)</td>
<td>55 (18-94)</td>
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<tr>
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<td>130 (15.5%)</td>
<td>53 (41.5)</td>
<td>183 (21.8%)</td>
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<tr>
<td><strong>BMI</strong></td>
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<tr>
<td>median (range)</td>
<td>29.09 (15.40-119.6)</td>
<td>40.69 (20.90-169.75)</td>
<td>31.49 (15.4-169.75)</td>
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<tr>
<td></td>
<td>130 (15.5%)</td>
<td>53 (41.5)</td>
<td>183 (21.8%)</td>
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<td><strong>BMI – Normal</strong></td>
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<tr>
<td>n (%)</td>
<td>194 (27.3)</td>
<td>8 (6.2)</td>
<td>202 (24)</td>
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<td>130 (15.5%)</td>
<td>53 (41.5)</td>
<td>183 (21.8%)</td>
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<tr>
<td><strong>BMI – Overweight</strong></td>
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<tr>
<td>n (%)</td>
<td>205 (28.9)</td>
<td>13 (10)</td>
<td>218 (26)</td>
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<td>130 (15.5%)</td>
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<td>183 (21.8%)</td>
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<td><strong>BMI – Obesity</strong></td>
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<td>n (%)</td>
<td>311 (43.8)</td>
<td>109 (83.8)</td>
<td>420 (50)</td>
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<td>130 (15.5%)</td>
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<td><strong>Grade 1</strong></td>
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<tr>
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<td>140 (19.7)</td>
<td>15 (11.5)</td>
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<td>130 (15.5%)</td>
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<td>130 (15.5%)</td>
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<td><strong>Grade 3 (morbid)</strong></td>
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<td>78 (11)</td>
<td>71 (54.6)</td>
<td>149 (17.7)</td>
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<tr>
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<td>130 (15.5%)</td>
<td>53 (41.5)</td>
<td>183 (21.8%)</td>
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<td><strong>Race</strong></td>
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<td>Black</td>
<td>86 (12.2)</td>
<td>18 (14.2)</td>
<td>104 (12.5)</td>
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Table 2.

<table>
<thead>
<tr>
<th>Groups</th>
<th>No-OSA</th>
<th>OSA</th>
<th>Total</th>
<th>P-values</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>710 (84.5%)</td>
<td>130 (15.5%)</td>
<td>840 (100%)</td>
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<tr>
<td>DVT n (%)</td>
<td>524 (73.9)</td>
<td>95 (73.1)</td>
<td>619 (73.8)</td>
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<td>PE n (%)</td>
<td>439 (61.9)</td>
<td>91 (71.7)</td>
<td>530 (63.3)</td>
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<td>DVT and PE n (%)</td>
<td>253 (35.6)</td>
<td>56 (43.1)</td>
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<td>Smoking n (%)</td>
<td>319 (44.9)</td>
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<td>Diabetes</td>
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<td>Type 1 n (%)</td>
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<td>7 (5.4)</td>
<td>50 (6)</td>
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<td>Type 2 n (%)</td>
<td>107 (15.1)</td>
<td>44 (33.8)</td>
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<td>CHF n (%)</td>
<td>60 (8.5)</td>
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<td>86 (10.2)</td>
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<td>STROKE n (%)</td>
<td>71 (10)</td>
<td>19 (14.6)</td>
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<td>CAD n (%)</td>
<td>109 (15.4)</td>
<td>32 (24.6)</td>
<td>141 (16.8)</td>
<td>0.028</td>
</tr>
</tbody>
</table>
Figure 2.

Percentage of Patients

- Females (%)
- White (%)
- Black (%)
- Age (years)

Categories:
- No-OSA
- OSA
Figure 3.

[Bar chart showing the percentage of patients with DVT, PE, and both with and without OSA.]
Figure 4.
Figure 5.
Figure 6.