



## Review Article

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# Prevalence and Impact of Patent Foramen Ovale in Patients with Obstructive Sleep Apnea

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## Abstract

**Background:** It is well known that obstructive sleep apnea (OSA) prevalence increases as body mass index (BMI) increases. Patients with OSA experience nocturnal apnea episodes which can result in hypoxemia, transient elevation of right atrial pressures, and a possible increase in right to left shunting. As such, OSA diagnosis and therapy may be tailored to address right-to-left shunting in these patients. Whether the prevalence of PFO in OSA patients is or is not increased, it may be appropriate to include transthoracic echocardiography (TTE) testing as a component of routine evaluation of patients with OSA.

**Objectives:** We hypothesize that patients with hypoxemia related to OSA are more likely to have a PFO than those patients with OSA without hypoxemia.

**Methods:** 80 patients with OSA verified by 4 different criteria were referred for TTE by the UNM Sleep Center. All patients underwent saline contrast TTE. The prevalence of PFO in our general echo population was calculated over the last year for comparison.

**Results:** Of 80 patients with varying degrees of OSA, ten (12.5%) had right to left shunting. PFO was not statistically associated with any AHI (Apnea Hypopnea Index). The only statistically significant association was between OSA and BMI ( $p < 0.001$ ). The prevalence of PFO in the control group was found to be 12.2%.

**Conclusions:** In contrast to previous studies, there was no association between OSA of any severity and PFO in our study population. There however was a statistically significant association between OSA and BMI.

**Abbreviations:** PFO: Patent Foramen Ovale; OSA: Obstructive Sleep Apnea; TTE: Transthoracic Echocardiogram; BMI: Body Mass Index; AHI: Apnea Hypopnea Index

## Introduction

The epidemic of obesity has been well documented. Over 65 percent of U.S. adults are either overweight or obese [1]. Twenty percent of those overweight with a mean body mass index (BMI) of 25 to 28 have been estimated to have mild obstructive sleep apnea (OSA), and 6 percent of the overweight have been estimated to have at least moderate OSA [2]. Further supporting the link between

obesity and OSA is the Wisconsin trial which showed that weight loss decreased the severity of OSA. However, not all patients with OSA are obese and it is estimated in the general population that 4% of middle aged men and 2% of middle aged women have OSA [3]. OSA has been demonstrated to produce significant adverse health consequences including development of systemic

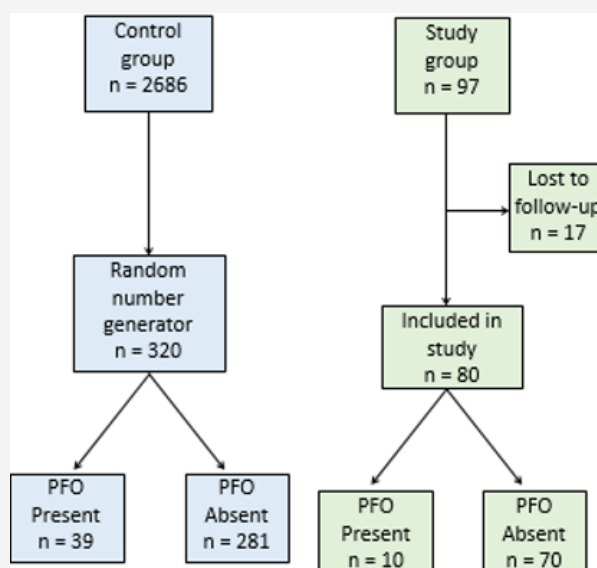
hypertension; increased risk of myocardial infarction; increased insulin resistance; and particularly relevant for the present study, an increased risk of stroke [4]. Patent foramen ovale (PFO) is a prevalent condition found in approximately 20 percent of adults on autopsy [5]. Shunting of venous blood across a PFO occurs when there is a higher right atrial than left atrial pressure and may result in paradoxical emboli [6,7]. Patients with OSA experience nocturnal apnea episodes which can result in systemic arterial oxyhemoglobin desaturation and transient elevation of right atrial pressures. In the presence of complicating cardiopulmonary conditions, there may be persistent pulmonary hypertension. Transesophageal echocardiography (TEE) is thought to be the gold standard for detection of PFO, however, it is semi-invasive and in the sedated patient makes detecting right-to-left shunting more difficult due to the lack of ability to perform the Valsalva maneuver [9]. A study by Lam, et al. in 2011 showed that there was no significant difference in sensitivities between TEE and TTE in detection of PFO when the Valsalva maneuver was employed [9]. Further supporting TTE in screening for PFO is a study which did not show any significant difference in detection of PFO between

TTE and TEE [10]. Our hypothesis is there is a correlation between OSA and PFO and that OSA diagnosis and therapy may be tailored to better address potential right-to-left shunting. We believe that available data support routine TTE evaluation of patients with OSA with high proportional desaturation for PFO.

## Methods

### Study population

The study was reviewed and approved by the Institutional Review Board at the University Of New Mexico School Of Medicine in Albuquerque New Mexico. The sample included 97 patients (Figure 1). Patients were included if they had documented obstructive sleep apnea by overnight sleep study conducted at the University of New Mexico Sleep Center. Patients then underwent a saline agitated contrast transthoracic echocardiogram to evaluate for the presence of a PFO. Over the last year, 2,686 patients in the general population of patients were referred for TTE with saline bubble study. A random number generator was used (random.org) to select a frequency matched sample (4:1) to serve as the control group. The first 320 patients were selected in order of randomization.



**Figure 1:** Recruitment Diagram for Study and Control groups.

### Transthoracic echocardiography

Complete TTE with bubble contrast were performed during Valsalva and Mueller's maneuver (inhaling against a closed throat) at which time continuous pulse oximetry was measured. Complete TTE includes two-dimensional short and long axis parasternal, four-chamber, two-chamber, three-chamber, subcostal, and Inferior vena cava views. M-mode, pulse wave, continuous-wave, and color-flow Doppler studies were performed. The peak velocity of tricuspid regurgitant flow was recorded and the systolic pulmonary artery pressure was estimated using the modified Bernoulli equation.

### Assessment of presence of patent foramen ovale

The transthoracic four-chamber view was utilized to locate the thinnest portion of the interatrial septum and to interrogate for the presence of a PFO. Color flow and pulse Doppler was performed to assess flow patterns across the septum. Echocardiographic contrast was obtained by mixing 10 mL of normal saline solution with 1 mL of air in a syringe. Boluses (large doses of medication given over a short period of time) of agitated saline solution were rapidly injected into a peripheral vein and echogenic microbubbles, which dissipate within the pulmonary circulation, were imaged as they entered the right-sided chambers of the heart. In the presence of a

PFO, these microbubbles are seen to traverse the interatrial septum from right-to-left. The passage of these microbubbles is aided by the transient elevation of right atrial pressure produced by either forceful coughing or Valsalva maneuver for 15 seconds. The efficacy of cough or Valsalva maneuver was validated by observing a movement of the interatrial septum toward the left atrium following release of the Valsalva maneuver. At least three contrast injections were performed in each subject, one before, one during Valsalva maneuver, and one during Mueller's maneuver. Each patient was evaluated for the presence of an atrial septal defect other than a PFO by both color and spectral Doppler.

### Polysomnography

Sleep Studies were conducted at the University of New Mexico Health Sciences Sleep Disorders Center. Polysomnography was conducted according to established clinical protocols of the UNM Sleep Disorders Center, the New Mexico Sleep Society, and the American Academy of Sleep Medicine.

**Recording procedure:** Data was collected using Bio-logic digital monitoring systems or a similar upgraded system. EEG was recorded from frontal, central, and occipital scalp regions with simultaneous time-locked continuous recording of eye movements (EOG), cardiac rate and rhythm (EKG), submental EMG, right and left leg EMG (anterior tibialis), snoring, body position, arterial oxygen-hemoglobin saturation and synchronized digital video monitoring. A polysomnographic technologist was in attendance throughout this test. End-tidal or transcutaneous carbon dioxide monitoring was used when appropriate. Expanded but still limited EEG channels were added when indicated.

**Scoring criteria:** The study was manually scored, using sleep staging criteria of Rechtschaffen and Kales. The scoring of respiratory events, arousals, and leg movements was performed in accordance with standards recommended by the American Academy of Sleep Medicine and New Mexico Sleep Society.

### Definition of Terms

Apnea is a cessation of nasal/oral airflow despite continued respiratory effort for a minimum duration of 10 seconds.<sup>11</sup> Hypo-

pnea is defined as a 30% or greater reduction in thoraco-abdominal movement or airflow lasting at least 10 seconds terminated by either an arousal or awaking.<sup>11</sup> AHI (apnea hypopnea index) is the average number of apneas and hypopneas per hour of sleep with significance determined by both the American Academy of Sleep Medicine and by the Centers for Medicaid and Medicare Services [11]. The oxygen desaturation index (ODI) is defined as the number of desaturation episodes with a reduction in saturation of >4% from baseline per hour of sleep [11]. Proportional desaturation can thus be expressed as the ratio of ODI (desaturations/hour) divided by the AHI (respiratory events/hour), that is, desaturations/event. High proportional desaturation will be defined as ODI/AHI > 0.70 desaturations/event. In addition, prior to lights out (the initiation of the sleep study), pulse oximetry (pulse and oxygen saturation levels) will be measured during intentional breath hold and Valsalva. A patent foramen ovale was considered present if a minimum of five microbubbles were seen in the left atrium within three cardiac cycles after opacification of the right atrium following peripheral echocontrast injection. An atrial septal defect was considered present if a consistent discontinuity of the septum was observed in different echocardiographic views and a left to right Doppler flow signal across the septum was recorded. All studies were interpreted separately by two independent observers who had no prior information about the patient's clinical status.

### Statistical Analysis

Continuous variables are summarized as mean  $\pm$  SD. Categorical variables are summarized as counts or percentages. Unpaired t tests were used for comparison of continuous variables between defined groups. Chi square tests were used to compare categorical variables between defined groups and to test for bivariate associations. Univariable and multivariable logistic regression was used to test the association between PFO presence and selected independent variables. Statistical significance was defined when  $p < 0.05$ . Using a control PFO rate of 12.5%, as observed in our pilot investigations, a sample size of 400 patients with a 4:1 ratio of control to OSA (320 control patients and 80 OSA patients) would be necessary to identify a minimal clinically important difference of 12.5% between OSA and control groups with 5% confidence and 80% power.

### Result

**Table 1:** Patient Characteristics.

Characteristics	Patients with OSA N, (%)	Control Subjects, N (%)
Mean Age, years	51	61
Number of Male, % male	35, 44%	159, 50%
Mean BMI	36	29.59
Mean AHI, by CMS criteria	31.5	N/A
Mean AHI, AASM	38.7	N/A
Hypertension, %	58, 59.8%	179, 55.9%
Coronary artery disease	8, 8.2%	49, 15.3%
History of cerebrovascular accident	5, 5.15%	98, 30.6%
Hypoxemia	3, 3.1%	70, 21.9%
OSA	80, 100%	49, 15.3%

**Table 2:** Indications for Referral for TTE in Control Group.

Indication Listed	Number of Patients
Cerebrovascular accident	100
Pulmonary Hypertension	46
Arrhythmia	16
Infection/Vegetation	16
Heart Failure	53
Coronary Artery Disease	39
Murmur	9
Pre-operative	3
Dyspnea	13
Valve Disease	10
Syncope	18
Thrombosis	8
Miscellaneous	5

Of the 97 patients initially enrolled in the study, 17 were lost to follow because they did not receive a complete echocardiogram with bubble study. The baseline characteristics of the 97 initially enrolled patients are in (Table 1). The control subjects had higher rates of hypoxemia, coronary artery disease and stroke, similar rate of hypertension and lower BMIs. All of the study patients had OSA in varying degrees of severity while the control group incidence of OSA was 15.3%. (Table 2) lists the different indications for referral in the control group, the vast majority being cerebrovascular acci-

dent (100/320 patients) and hypertension (46/320 patients). Any degree of right to left shunting was present in 10 (12.5%) of the 80 patients compared with 39 (12.2%) of the 320 controls ( $p=0.939$ ). There were statistically significant associations between OSA and BMI ( $p<0.05$ ), BMI and DI ( $p=0.017$ ), AASM AHI ( $p=0.022$ ) and CMS AHI ( $p=0.005$ ) (Table 3). There was no association between PFO and OSA ( $p=0.939$ ), BMI ( $p=0.876$ ), age ( $p=0.572$ ), DI ( $p=0.302$ ), AASM AHI ( $p=0.193$ ) or CMS AHI ( $p=0.212$ ) (Table 3).

**Table 3:** Correlation matrix for present study and associated p values from chi square analysis.

	OSA	BMI	DI	AHI	PHO
OSA		<0.001			0.936
BMI	<0.001		0.017	0.005	0.809
DI		0.017		0.189	0.302
AHI		0.005	0.189		0.193
PHO	0.936	0.809	0.302	0.193	

**Table 4:** Comparison of echocardiography findings and severity of OSA.

	Severity of Obstructive Sleep Apnea		
	Mild	Moderate	Severe
Pulmonary Hypertension by Echo	4	5	7
Hypertension	10	11	34
CAD	2	0	6
CVA	1	2	1
RV dilated	3	3	7
LVH	1	0	1
Diastolic Dysfunction	5	5	14

(Table 4) shows the number of patients with different echocardiography findings in relation to severity of OSA. As would be expected severe OSA has a higher number of patients with hypertension, coronary artery disease, right ventricular dilation and diastolic dysfunction. The number of patients with cerebrovascular accident was however not higher in the group OSA.

(Figure 2) is a scatter plot showing the range of hypoxemia during polysomnography and the degree of OSA by CMS and AASM criteria. The trendline shows what would be expected; that more severe OSA is generally associated with worse hypoxemia.

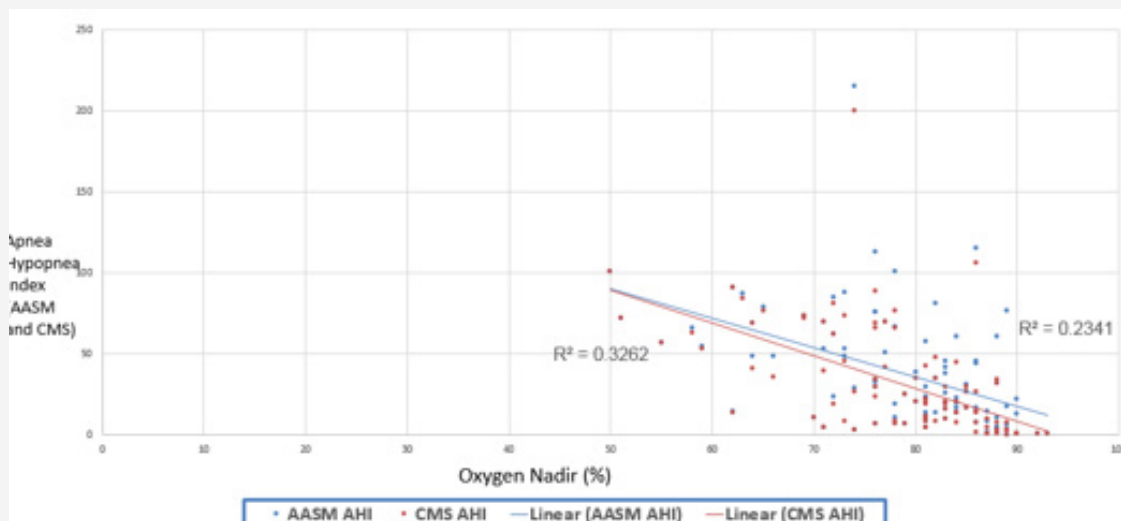


Figure 2: Scatter plot comparing severity of hypoxemia and OSA.

### Discussion

Table 5: Prior studies of association between PFO and OSA.

Study Authors	Number of patients with OSA included	Number of controls	Number of controls with PFO, percent	Number Studied with PFO, percent	P value
Shanoudy, et al. [12]	48	24	4, 17%	33, 69%	P<0.0001
Johansson, et al. [13]	15	15	2, 13%	9, 60%	P=0.02
Beelke, et al. [14]	78	89	13, 15%	21, 27%	P<0.05
Guchlerner, et al. [15]	100	n/a	n/a	72, 72% (PFO or other right to left shunting)	
Lau, et al. [16]	102	50	13, 26%	48, 47.1%	P=0.014
Shaikh, et al. [17]	100	50	15, 30% 3, 6% (large shunts)	43, 43% 18, 18% (large shunts)	P=0.16 P=0.049
Camp, et al. (current study)	80	320	39, 12.2%	10, 12.5%	P=0.939

In this study we did not find that PFO is more prevalent in patients with OSA compared to the general population. The main finding in this study is contrary to our hypothesis and contrary to the majority of prior studies looking at the association between OSA and PFO. Multiple studies have evaluated the prevalence and impact of PFOs in patients with OSA and their key findings are found below in (Table 5). The first study followed 48 Veteran’s Affairs patients prospectively using TEE and found 69 percent had a PFO compared

to 17 percent of matched controls [12]. This study documented significant hypoxemia after Valsalva maneuver (attempting to forcibly exhale while keeping the glottus closed) in subjects with a PFO. This study included a relatively small number of patients and employed TEE which is a semi-invasive procedure compared to TTE. A similar case control study found that 60 percent of 15 patients with prominent oxyhemoglobin desaturation characterized by proportional desaturation (as defined by a ratio of oxygen desaturation index/

apnea-hypopnea index greater than 0.66) had a PFO as opposed to 15 percent of 15 controls with less desaturation (ODI/AHI<0.33) [13]. This latter study similarly had a small number of patients included compared to our study. Another recent prospective study of 78 OSA patients using transcranial Doppler (TCD) found 27 percent had a PFO compared to 15 percent of matched controls [14]. Two studies in 2011 and 2012 used transcranial Doppler to look for right to left shunting in OSA and found 47.1% and 72% prevalence, respectively [15,16]. It should be noted that TCD cannot distinguish between a PFO and the rarer intra-pulmonary shunt. The most recent study examined 100 patients and compared them with 50 healthy controls using transthoracic echocardiography and found a non-significant difference of 43% compared to 30% prevalence, although they did find that patients with severe OSA had a higher prevalence of PFO with large shunts [17]. Our study included a larger number of controls and the prevalence of PFO in the two groups was much closer, 12.2% compared to 12.5%. More recently there have been studies looking at the efficacy of PFO closure, including the recently mentioned paper by Sheikh, et al. which did not recommend PFO closure. All of these studies reported a correlation between obstructive sleep apnea and PFO with different hypothesis regarding pathophysiology. One hypothesis presented in the previously mentioned studies is that increased intrathoracic pressure as the patient inhales against a closed airway increases the intrathoracic pressure thereby increasing right sided heart pressure. Another theory is that apneic episodes increase pulmonary artery pressure thereby also increasing right sided heart pressures [16]. These increases in right sided heart pressures translate to increased right atrial pressure which can in theory lead to right to left shunting. Our study found no correlation between PFO and even the most severe cases of OSA, and additionally found no correlation between PFO and obesity or the apnea hypopnea indices, all of which argue against each hypothesis.

Given the known potential harms of over testing, we cannot recommend routine screening with echocardiography for the detection of PFO in patients with obstructive sleep apnea as there does not appear to be any correlation between PFO and OSA. The impact of our study is that in the absence of a correlation, other etiologies for increased prevalence of stroke in OSA patients should be evaluated and that desaturation in OSA is not likely related to PFO. This is relevant as new technologies for PFO closure become more frequently employed as a tactic to reduce the incidence of stroke and reduce nocturnal desaturations. The incidence of PFO in OSA is the same as the general population undergoing routine echocardiography in our laboratory.

### Study Limitations

This study has several limitations; the first being that patients were recruited over many years, and over that time period techniques in echocardiography and imaging modalities have changed. There is of course variation in the quality of the images obtained

due to body habitus as well as technique. The demographics of our control patients were also slightly different, including an increased age and lower BMI, as these factors may have a theoretical contribution to the prevalence of PFO. Our study was powered to identify a 12.5% difference in PFO prevalence rates between control subjects and OSA patients. The observed difference of 0.3% (95% CI, -6.6% to 9.9%) provides assurance that there can be no more than a 10% higher difference in PFO prevalence between OSA and controls under the conditions of this study. A much larger study would be necessary to demonstrate a difference in PFO prevalence less than 10%.

### Conclusion

Our results are contrary to previously published articles which document a significant association between OSA and PFO. We found no association between the two, and the incidence of PFO was very similar to the general population of patients studied with TTE at our institution. This is clinically important as percutaneous closure procedures are becoming more common in patients with cryptogenic stroke and a PFO. There is a hypothetical risk of stroke with PFO, but no increasingly identified independent risk with OSA. However, CVA rates were low in both arms and the study was clearly underpowered to look at this different question. Therefore, with no increased association of PFO in OSA, the indication for closure is questionable and may place the patient at greater risk of morbidity and mortality.

### Acknowledgment

None.

### Conflicts of Interest

No conflict of interest.

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