Objectives: To assess the presence of right-to-left shunting (RLS) in patients with obstructive sleep apnea (OSA), and compare clinical characteristics and parameters of the sleep studies of patients with and without RLS.

Background: The most common cause of RLS is due to intermittent flow through a patent foramen ovale (PFO). PFO occurs more frequently in patients with OSA and may be involved in the exacerbation of OSA.

Methods: Patients with an abnormal polysomnogram seen at UCLA-Santa Monica Sleep Medicine Clinic were enrolled. A diagnosis of RLS was made using a transcranial Doppler (TCD) bubble study. Gender and age-matched controls were drawn from patients referred for cardiac catheterization who underwent a TCD. The frequency of RLS in OSA patients and the controls was evaluated. Clinical characteristics and polysomnogram parameters were compared between OSA patients with and without a RLS.

Results: A total of 100 OSA patients and 200 controls participated in the study. The prevalence of RLS was higher in patients with OSA compared to the control group (42% versus 19%; p < 0.0001). Patients with OSA and a RLS had a lower apnea-hypopnea index (AHI), less obstructive apnea, and fewer hypopnea episodes than patients with OSA without a RLS. The baseline and nadir SpO₂ were similar in both groups and did not correlate with the level of RLS assessed by TCD. The degree of desaturation for a given respiratory disturbance, as measured by oxygen desaturation index (ODI)/AHI ratio, was higher in OSA patients with RLS versus OSA patients without RLS (0.85 ± 0.07 versus 0.68 ± 0.04; p < 0.0001).

Conclusion: RLS, most commonly due to a PFO, occurs 2.2 times more frequently in OSA patients compared to a control population that was matched for age and gender. The severity of sleep apnea is not greater in OSA patients who have a PFO. However, patients with OSA and a PFO are more likely to become symptomatic at a younger age with an equivalent decrease in nocturnal SpO₂, and have greater arterial desaturation in proportion to the frequency of respiratory disturbances.

Keywords: sleep apnea, patent foramen ovale, right-to-left shunt

From January 2011 to September 2013, 100 sleep apnea subjects were enrolled in the study with the majority diagnosed with OSA (92%), and 8% diagnosed with mixed central sleep apnea and OSA. Of these subjects, 72% were using CPAP or bilevel positive airway pressure (BPAP). The mean age of the participants
was 55.1 ± 13.4 years, and 56% were male. Table 1 demonstrates the general characteristics of the study group and the control population. Of 100 patients in the study group, 42 had evidence of RLS on TCD, which was 2.2 times higher than the prevalence of RLS in the control group (42% versus 19%, p < 0.0001).

The Epworth Sleepiness Scale (ESS) was utilized to evaluate subjective symptoms of the OSA patients. The ESS scores were 8.9 ± 2.7 (range 3 to 18) and 8.1 ± 3.9 (range 3 to 24) in the OSA patients with and without RLS respectively, demonstrating no significant difference (p = 0.86). Table 2 presents the baseline clinical characteristics and Table 3 describes polysomnography parameters in sleep apnea patients with RLS compared to those without RLS. Patients with RLS were younger (mean age 51.1 ± 11.7 versus 58.1 ± 14.0 years, p = 0.01) and had a lower prevalence of hypertension. There was no significant difference in the BMI of patients with and without a RLS (p = 0.28). When assessing the severity of sleep apnea, those with RLS had a lower AHI and less obstructive apnea and hypopnea episodes (p = 0.028, p < 0.0001, and p = 0.008, respectively), although the baseline oxygen saturation and nadir of O2 between the two groups were similar. OSA patients with RLS had a lower ODI (p = 0.02); however, the ODI/AHI ratio was significantly higher when compared to the group without RLS (p < 0.0001). In the group of patients with sleep apnea and RLS, the magnitude of shunting on TCD (Spencer grade 3 versus Spencer grade 4 and 5) did not correlate with the nadir SaO2 (p = 0.46). The TCD Spencer grade correlated with the ODI/AHI ratio (rs = 0.523, p < 0.0001, Figure 1) demonstrating a higher ODI/AHI ratio with increased magnitude of RLS.

**DISCUSSION**

This large population of OSA subjects was studied to elucidate a possible association between OSA and RLS, most commonly due to a PFO. This study investigated the prevalence of RLS in patients diagnosed with OSA by means of a contrast TCD at rest and with Valsalva maneuver. A RLS was present in 42% of the patients with sleep apnea versus 19% of the control group, p < 0.0001.

Right to left flow of blood through a PFO occurs intermittently after straining, such as with the Valsalva maneuver, and during everyday events like coughing, exercise, or heavy lifting. RLS has also been observed using TCD in patients with OSA during episodes of nocturnal apnea.8,25 Hypoxemia increases pulmonary vasoconstriction leading to pulmonary hypertension.26 Even without RLS, episodes of apnea induce hypoxemia, which can result in an increase in
pulmonary arteriolar resistance causing transient elevation in pulmonary pressures. In the presence of a PFO, the increase in right-sided pressure may exaggerate any underlying RLS and exacerbate hypoxemia. This feedback loop increases the likelihood of right-to-left shunting across a PFO with progressive hypoxemia ultimately leading to arousal. It has been demonstrated that treatment with continuous positive airway pressure (CPAP) can reverse shunting in these patients. It is hypothesized that patients with OSA who have a PFO with RLS are more likely to become symptomatic earlier due to more prominent oxygen desaturation at a similar level of sleep apnea dysfunction compared with a person with OSA who does not have a RLS.

This study revealed a 2.2 fold higher frequency of RLS in patients with sleep apnea compared with a control group, which is consistent with previous reports. In contrast, using both contrast TCD and transthoracic echocardiography, Shaikh et al. reported no significant difference in the prevalence of PFO in 100 OSA patients compared to 50 controls matched for age and gender. They reported a PFO prevalence of 43% in the OSA patients compared to 30% in the control subjects, which did not reach statistical significance (p = 0.16). Their data are

### Table 2—Comparison of baseline characteristics in sleep apnea patients with vs. without RLS.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Sleep Apnea with RLS</th>
<th>Sleep Apnea without RLS</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>51.1 ± 11.7</td>
<td>58.1 ± 14.0</td>
<td>0.01</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>21 (50%)</td>
<td>35 (60.3%)</td>
<td>0.32</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.7 ± 1.28</td>
<td>27.5 ± 12.8</td>
<td>0.28</td>
</tr>
<tr>
<td>Neck circumference (cm)</td>
<td>38.6 ± 3.9</td>
<td>40.7 ± 5.7</td>
<td>0.3</td>
</tr>
<tr>
<td>TCD at rest (Spencer grade)</td>
<td>2.7 ± 1.6</td>
<td>1 ± 0.2</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>TCD on Valsalva (Spencer grade)</td>
<td>4.2 ± 0.8</td>
<td>2 ± 0.4</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>ESS Score</td>
<td>8.9 ± 2.7</td>
<td>8.1 ± 3.9</td>
<td>0.86</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± standard deviation except as noted. Hypercoagulability states include: use of oral contraceptive pills/hormone replacement therapy, pregnancy, factor V Leiden, prothrombin G20210A mutation, antiphospholipid antibodies, homocysteinemia, protein S deficiency, protein C deficiency, elevated lipoprotein A, antithrombin III deficiency, anticardiolipin AB, factor VIII activity, B2-glycoprotein-1 AB and thrombocytosis. HTN, hypertension; DM, diabetes mellitus; RLS, right-to-left shunting of blood; TCD, transcranial Doppler; BMI, body mass index; ESS, Epworth Sleepiness Scale.

### Table 3—Comparison of clinical polysomnography parameters in sleep apnea patients with vs. without RLS.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Sleep Apnea with RLS</th>
<th>Sleep Apnea without RLS</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline O₂ saturation (%)</td>
<td>94.5–96.8</td>
<td>94.1–96.5</td>
<td>0.15</td>
</tr>
<tr>
<td>Nadir O₂ saturation (%)</td>
<td>86.2 ± 4.0</td>
<td>84.9 ± 7.2</td>
<td>0.29</td>
</tr>
<tr>
<td>Obstructive apneas (per hour)</td>
<td>3.5 ± 1.5</td>
<td>15.7 ± 7.0</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Hypopneas (total)</td>
<td>36.3 ± 21.3</td>
<td>54.6 ± 39.6</td>
<td>0.008</td>
</tr>
<tr>
<td>Central apneas (total)</td>
<td>0</td>
<td>0.67 ± 1.2</td>
<td>N/A</td>
</tr>
<tr>
<td>Mixed apneas (total)</td>
<td>1.38 ± 0.39</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>AHI events/h</td>
<td>16.4 ± 20.7</td>
<td>28.0 ± 28.6</td>
<td>0.028</td>
</tr>
<tr>
<td>Arousal Index (per hour)</td>
<td>34.5 ± 22.4</td>
<td>36.6 ± 27.10</td>
<td>0.68</td>
</tr>
<tr>
<td>ODI events/h</td>
<td>14 ± 1.7</td>
<td>19 ± 1.3</td>
<td>0.02</td>
</tr>
<tr>
<td>ODI/AHI</td>
<td>0.85 ± 0.07</td>
<td>0.68 ± 0.04</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Time in bed (min)</td>
<td>428.3 ± 34.3</td>
<td>430.8 ± 46.6</td>
<td>0.77</td>
</tr>
<tr>
<td>Time asleep (min)</td>
<td>318.9 ± 47.0</td>
<td>328.3 ± 62.0</td>
<td>0.41</td>
</tr>
<tr>
<td>Stage 1 (min)</td>
<td>64.6 ± 23.6</td>
<td>52.98 ± 28.3</td>
<td>0.03</td>
</tr>
<tr>
<td>Stage 2 (min)</td>
<td>203.7 ± 36.3</td>
<td>212.83 ± 60.0</td>
<td>0.38</td>
</tr>
<tr>
<td>Stage3 (min)</td>
<td>10.7 ± 11.6</td>
<td>9.02 ± 14.4</td>
<td>0.53</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± standard deviation except as noted. AHI, apnea-hypopnea index; ODI, oxygen desaturation index; RLS, right-to-left shunting of blood.
limited by a small control group with possible confounders resulting in a higher PFO frequency in the control group than the expected 20% to 25% reported prevalence in the general population.\textsuperscript{5–7} Additionally, the study only included patients with severe OSA. They did observe a significantly higher prevalence of PFO with large shunts in their OSA group versus controls. In our control group of 200 subjects, a history of sleep apnea was present in 5.5% and RLS was discovered in 19%, both of which are within the expected prevalence in the general population. Of the 11 control patients with OSA, 4 (36%) had a PFO. The study and control groups were well matched for age, gender, and other clinical risk factors.

There were several unexpected differences in the group of sleep apnea patients with or without RLS. The sleep apnea group with RLS was significantly younger, with a trend towards a lower BMI, lower neck circumference, and lower cardiovascular risk factors than those without RLS. The AHI and obstructive apneas were lower in the sleep apnea with RLS subgroup (p = 0.028 and p = 0.001, respectively). However, this group still had recorded low oxygen saturations (86% ± 4.0%), and they were just as symptomatic based on their ESS scores, which is consistent with findings by Shaikh et al.\textsuperscript{11} These observations describe a subgroup of patients with sleep apnea and RLS without the high frequency of expected risk factors (high BMI, large neck circumference, or high rate of obstructive apneas) who still have hypoxemia and significant frequency of arousals. This suggests that the RLS contributes to producing hypoxemia and symptoms at a lower level of obstruction to airflow resulting in presentation at a younger age. RLS may contribute to the hypoxemia independent of the apnea and hypopnea episodes.

To objectively discriminate between desaturation caused by shunting of blood versus hypopnea-apnea induced alveolar hypoventilation, Johansson et al. utilized the ODI/AHI ratio as a marker of the amount of desaturation for a given level of respiratory disturbance. Right to left shunting of blood can cause a reduction in arterial oxygen saturation and an increase in the ODI/AHI ratio. Their study revealed that the group of OSA patients with a high ODI/AHI ratio (≥ 0.66) had a significantly higher PFO prevalence of 60% compared to 13% in OSA patients with a low ODI/AHI ratio.\textsuperscript{12} Shaikh and colleagues also demonstrated lower AHI and higher ODI/AHI ratio (p = 0.004) in OSA patients with clinically significant shunts.\textsuperscript{13} Our study corroborates these results with a significantly higher ODI/AHI ratio in OSA patients with RLS versus OSA patients without RLS (0.85 ± 0.07 versus 0.68 ± 0.04, respectively; p < 0.0001). Despite the similarity of symptoms by the ESS score, the ODI/AHI difference suggests that there is more hypoxemia for a given level of hypopnea in those subjects with a RLS. Additionally, the TCD Spencer grade correlated with the ODI/AHI ratio (r = 0.52, p < 0.0001) demonstrating a higher ODI/AHI ratio with increased magnitude of RLS. Concordant with prior studies, this depicts a level of hypoxemia out of proportion to the observed respiratory disturbance highlighting the likely role of RLS in the resultant nocturnal desaturation.

There are several case reports which describe that PFO closure in patients with sleep apnea may lead to improvement of symptoms including higher oxygen saturation levels and improvement of daytime fatigue.\textsuperscript{29–31} In addition, sleep polysomnographic data suggest that there are fewer episodes of hypopnea and apnea after PFO closure.\textsuperscript{30,31} Recently, Rimoldi et al. investigated 40 patients with new OSA, 14 of which (35%) had a PFO. OSA patients with a PFO underwent closure in this nonrandomized observational study. Patients who underwent PFO closure demonstrated a significant improvement in ODI/AHI, nocturnal systolic blood pressure, right-ventricular to right-atrial systolic blood pressure gradient and left ventricular diastolic function.\textsuperscript{32} However, Shaikh et al. did not demonstrate any significant improvement in objective or qualitative parameters in the subgroup of 6 patients with large shunts who underwent percutaneous PFO closure.\textsuperscript{11} However, 3 of the 6 patients who underwent PFO closure had residual shunts at 12 months. Their reported residual shunting is significantly higher than what is reported in the literature and may be secondary to the utilization of the BioSTAR (NMT Medical Inc.) PFO closure device which has been associated with increased residual shunting after PFO closure and is no longer manufactured.\textsuperscript{33,34} More cases of PFO closure in OSA patients would need to be studied to better evaluate this intriguing association.

The observation of a higher than expected frequency of RLS in patients with OSA does not prove a cause-and-effect relationship. Only a randomized prospective trial of PFO closure compared with non-closure in OSA patients who have a PFO could confirm that PFO is causally related to OSA severity. However, observational studies are useful to support the hypothesis that the presence of a RLS from a PFO exacerbates sleep apnea symptoms. OSA remains a significant health concern with increased morbidity and is difficult to treat. Even though CPAP provides an effective means of improving OSA symptoms, it requires consistent, long-term commitment by patients and is often plagued by noncompliance. Further studies that compare OSA patients with and without a RLS are needed to help determine if improvement in RLS will provide significant symptomatic and objective benefits in oxygen saturation and sleep disturbance.

**Limitations**

The current study has several limitations. Our control group was composed of 200 patients who did not undergo polysomnography for detection of OSA. However, the only purpose of the control group was to determine the frequency of RLS in a population that was matched for age and gender. The prevalence of PFO in our control group was 19%, which is consistent with other reports that determined the frequency of PFO in the general population. The frequency of OSA by history in the control group was 5.5%, which is typical for the general population and it is unlikely that performing a sleep study in the control group would have affected the prevalence of RLS.

We utilized TCD with contrast because it is a noninvasive bedside procedure with well documented sensitivity and specificity for PFO detection. TCD is limited by its inability to identify the location of the shunt; however, almost all right-to-left shunts are due to PFOs or small ASDs since other etiologies, such as large trans-pulmonary shunting from pulmonary AVMs, are rare (1% of TCD exams).\textsuperscript{15–20} Compared with heart catheterization for PFO detection, TCD is more sensitive than TEE since there is a 10% false negative rate with TEE because patients cannot perform a Valsalva maneuver with a TEE probe down their esophagus.\textsuperscript{20,22–24} The patients in our study
with OSA and PFO did not undergo PFO closure, which would be needed to evaluate a cause and effect relationship.

CONCLUSION

Our study is in agreement with other reports that reveal a higher than expected prevalence of RLS in patients with OSA. It also suggests an underlying mechanism by which the RLS of a PFO may produce symptoms of hypoxemia earlier in the course of the condition. The presence of a RLS as assessed by TCD in patients with sleep apnea was found to be 2.2-fold higher than in the general population. The patients with RLS were younger and despite having a lower AHI, they had a higher ODI/AHI ratio and were just as symptomatic with greater nocturnal desaturations with respect to the frequency of respiratory disturbance.

ABBREVIATIONS

AHI, apnea-hypopnea index
ODI, oxygen desaturation index
OSA, obstructive sleep apnea
PFO, patent foramen ovale
RLS, right to left shunt
TCD, transcranial doppler

REFERENCES


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Address correspondence to: Jonathan Tobis, MD, Director of Interventional Cardiology Research, UCLA, B-976 Factor Building CHS, 10833 Le Conte Avenue, Los Angeles, CA 90095, Email: Jtobis@mednet.ucla.edu

DISCLOSURE STATEMENT

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