Inflammation, Oxidative Stress, and Repair Capacity of the Vascular Endothelium in Obstructive Sleep Apnea

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Background—Indirect evidence implicates endothelial dysfunction in the pathogenesis of vascular diseases associated with obstructive sleep apnea (OSA). We investigated directly whether dysfunction and inflammation occur in vivo in the vascular endothelium of patients with OSA. The effects of continuous positive airway pressure (CPAP) therapy on endothelial function and repair capacity were assessed.

Methods and Results—Thirty-two patients with newly diagnosed OSA and 15 control subjects were studied. Proteins that regulate basal endothelial nitric oxide (NO) production (endothelial NO synthase [eNOS] and phosphorylated eNOS) and inflammation (cyclooxygenase-2 and inducible NOS) and markers of oxidative stress (nitrotyrosine) were quantified by immunofluorescence in freshly harvested venous endothelial cells before and after 4 weeks of CPAP therapy. Vascular reactivity was measured by flow-mediated dilation. Circulating endothelial progenitor cell levels were quantified to assess endothelial repair capacity. Baseline endothelial expression of eNOS and phosphorylated eNOS was reduced by 59% and 94%, respectively, in patients with OSA compared with control subjects. Expression of both nitrotyrosine and cyclooxygenase-2 was 5-fold greater in patients with OSA than in control subjects, whereas inducible NOS expression was 56% greater. Expression of eNOS and phosphorylated eNOS significantly increased, whereas expression of nitrotyrosine, cyclooxygenase-2, and inducible NOS significantly decreased in patients who adhered to CPAP ≥4 hours daily. Baseline flow-mediated dilation and endothelial progenitor cell levels were lower in patients than in control subjects, and both significantly increased in patients who adhered to CPAP ≥4 hours daily.

Conclusions—OSA directly affects the vascular endothelium by promoting inflammation and oxidative stress while decreasing NO availability and repair capacity. Effective CPAP therapy is associated with the reversal of these alterations. (Circulation. 2008;117:2270-2278.)

Key Words: endothelium • hypoxia • sleep

Obstructive sleep apnea (OSA) is strongly and independently associated with an increased risk for hypertension, ischemic stroke, and myocardial ischemia.1-3 The mechanisms underlying the increased prevalence of vascular conditions in patients with OSA remain poorly understood. Indirect evidence of reduced nitric oxide (NO) availability and elevated plasma levels of adhesion molecules suggests that vascular endothelial dysfunction and inflammation contribute to the development of vascular diseases in patients with OSA.4,5 However, dysfunction and inflammation have never been directly demonstrated in vivo in the vascular endothelium of patients with OSA.

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The present study aimed to ascertain whether dysfunction and inflammation occur in vivo in the vascular endothelium of patients with OSA and whether treatment of OSA affects the vascular endothelium. Proteins that regulate basal NO production and inflammation and markers of oxidative stress were quantified in freshly harvested venous endothelial cells. In addition, levels of circulating endothelial progenitor cells (EPCs) obtained from patients with OSA before and after treatment were measured because vascular endothelial function and repair capacity are known to be related.6 Reduced...
levels of bone marrow–derived EPCs, a marker of endothelial repair capacity, are associated with impaired vascular endothelial function and increased cardiovascular risk.6,7 To the best of our knowledge, endothelial repair capacity has never been assessed in patients with OSA.

We tested the hypothesis that endothelial oxidative stress and inflammation are increased and NO availability and repair capacity are reduced in patients with OSA compared with age-, gender-, and body mass index (BMI)–matched control subjects and that treatment with continuous positive airway pressure (CPAP) reverses these endothelial alterations.

Methods

Study Population

We conducted a prospective cohort study including patients with OSA and healthy control subjects.

Patients

Patients who were referred to the Sleep Disorders Center at the New York Presbyterian Hospital for evaluation of sleep-disordered breathing between September 2004 and January 2007 were prospectively screened for the study. Patients with newly diagnosed OSA defined as an apnea-hypopnea index (AHI) of ≥5 obstructive events per hour of sleep and free of conditions known to affect the vascular endothelium were eligible for the study. Patients with hypertension, coronary artery disease, heart failure, a history of stroke, diabetes mellitus, chronic obstructive or restrictive pulmonary disease, chronic renal disease, dyslipidemias, pharmacologically treated depression, or tobacco use within the past 10 years were ineligible for the study. Patients receiving medications or nutritional supplements and nightshift workers also were ineligible.

Control Subjects

We recruited control subjects from the community through advertising. Control subjects were nonsmoking healthy subjects who were not receiving medications or nutritional supplements. Control subjects were matched to patients for gender, age (within 4 years), and BMI (within 15%). Except for possible obesity, all control subjects had a normal physical examination and laboratory tests. All control subjects underwent polysomnography to exclude the presence of sleep-disordered breathing.

The Columbia University Committee on Human Research approved the study. All study participants gave written informed consent.

Study Protocol

All study participants underwent attended nocturnal polysomnography in the sleep center. Endothelial cell harvesting, blood sample collection, and flow-mediated dilatation (FMD) were performed between 9 and 11 AM within 48 hours of polysomnography while study participants were in a fasting state. All experimental procedures were repeated after a 4-week treatment period in all OSA patients.

Polysomnography and CPAP Therapy

Nocturnal polysomnography was performed as previously described.8 AHI was defined as the number of obstructive apnea plus hypopnea episodes per hour of sleep. (Details on polysomnography and CPAP titration can be found in the online-only Data Supplement.) Adherence to CPAP was defined as CPAP use for ≥4 hours daily.9 Adherence was assessed by use of a CPAP device with compliance software.

Vascular Endothelial Cell Harvesting

A 20-gauge angiocatheter was inserted into a forearm vein. Under sterile conditions, 3 J-shaped vascular guidewires (Arrow, Reading, Pa) were advanced sequentially into the vein up to 10 cm. Tips of the wires were removed and washed in endothelial cell dissociation buffer kept at 4°C. Each endothelial harvesting yielded 982±189 endothelial cells (mean±SD; range, 621 to 1267).

Immunohistochemistry for Protein Expression

Proteins that regulate basal endothelial NO production, including total endothelial NO synthase (eNOS) and activated eNOS (phosphorylated eNOS at serine 1177 [P-eNOS]), inflammation (cyclooxygenase-2 [COX-2] and inducible NOS [iNOS]), and markers of oxidative stress (nitrotyrosine) were quantified by immunofluorescence as previously described (Figure 1).9,10,11 Quantification by immunofluorescence has been validated repeatedly against immunoblotting in venous endothelial cells with coefficient correlations of 0.99 and 0.97.11,12 Reproducibility of quantitative immunofluorescence of protein expression in venous endothelial cells was assessed previously.11 The overall coefficient of variation and the mean measurement error for protein expression in venous endothelial cells (17 duplicate measurements) were 11% and 286 pixels, respectively.11 (Details on immunohistochemistry can be found in the online-only Data Supplement).

Brachial Artery FMD

Vascular reactivity of the brachial artery was assessed in the arm contralateral to the endothelial harvesting site by FMD according to the guidelines of the International Brachial Artery Reactivity Task Force.5,23 (Details on FMD can be found in the online-only Data Supplement).

Flow Cytometry for Circulating EPCs

EPCs were quantified in the venous blood by flow cytometry. EPCs were defined as cells positive for monoclonal antibodies against human kinase insert domain receptor, CD34, and CD133.7,14,15 (Details on flow cytometry can be found in the online-only Data Supplement).

Statistical Analysis

Continuous data are presented as mean±SD, median (interquartile range), or median (range). Categorical data are presented as percentage.

To determine whether endothelial basal NO production, inflammation, oxidative stress, and repair capacity differ between OSA patients and control subjects, endothelial protein expression, FMD, and EPC levels were compared between groups. Bivariate analysis was performed with the unpaired Student t test, Wilcoxon rank-sum test, or χ² test as appropriate.

To determine whether severity of OSA affects endothelial function, linear regression with endothelial protein expression, FMD, and EPC levels as the dependent variables was performed. Bivariate analysis of the association between baseline measurements of dependent variables and AHI, arterial oxyhemoglobin desaturation ≥4% per hour of sleep [ODI4], arterial oxyhemoglobin saturation (SaO₂) nadir, and time spent below an SaO₂ of 90% during sleep [t< SaO₂ 90%] (independent variables) was performed with simple linear regression. We then adjusted for potential confounders (age, gender, and BMI) in multivariate linear regression.

To determine whether CPAP therapy affects endothelial protein expression, FMD, and EPC levels (dependent variables), we constructed linear mixed-effects regression models with CPAP adherence, age, gender, BMI, and time (baseline or follow-up) as fixed effects and subjects as random effects. These models account for intrasubject variability. An interaction term for CPAP adherence and time was included to evaluate the difference between the slopes of the 2 groups.

Because the results were virtually identical between the bivariate and multivariate linear regression analyses, we have provided only the adjusted least-square means (SEs). Statistical significance was assumed when the null hypothesis could be rejected at P<0.05. Statistical analysis was performed with STATA 7.0 software (Stata Corp, College Station, Tex).

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.
Results

Two hundred sixty-seven patients were newly diagnosed with OSA during the study period. Two hundred eighteen patients were not eligible for the study because of the presence of ≥1 exclusion criteria. We screened 49 eligible patients with OSA; 17 patients declined to participate in the study. Endothelial harvesting was unsuccessful in 2 of the remaining 32 eligible patients. Thus, 30 patients with OSA were available for analysis. Fifteen control subjects were studied. The clinical and laboratory characteristics of study participants are summarized in Table 1. Patients and control subjects were similar in age, gender, BMI, systemic blood pressure, fasting blood glucose, and total cholesterol levels. OSA patients had significantly lower SaO₂ nadir during sleep and had more daytime sleepiness as measured by the Epworth Sleepiness Scale than control subjects. Control subjects had an AHI <5 and spent no time during sleep with SaO₂ <90%.

Table 1. Baseline Characteristics of OSA Patients and Control Subjects

<table>
<thead>
<tr>
<th></th>
<th>OSA Patients (n=30)</th>
<th>Control Subjects (n=15)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>38±11</td>
<td>39±7</td>
<td>0.89</td>
</tr>
<tr>
<td>Gender, % female</td>
<td>33</td>
<td>40</td>
<td>0.66</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>34±8</td>
<td>30±6</td>
<td>0.27</td>
</tr>
<tr>
<td>AHI, events/h of sleep</td>
<td>25 (10–52)</td>
<td>0 (0–0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ODI4, events/h of sleep</td>
<td>12 (7–17)</td>
<td>0 (0–0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SaO₂ nadir, %</td>
<td>86 (60–89)</td>
<td>97 (96–98)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>t&lt;SaO₂ 90%, % of the total sleep time</td>
<td>2.5 (0.1–10)</td>
<td>0 (0–0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Epworth sleepiness scale score</td>
<td>15 (8–19)</td>
<td>8 (4–9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>120±17</td>
<td>118±19</td>
<td>0.52</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>74±6</td>
<td>77±11</td>
<td>0.37</td>
</tr>
<tr>
<td>Fasting glucose, mg/dL</td>
<td>93±18</td>
<td>83±17</td>
<td>0.18</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>175±37</td>
<td>181±35</td>
<td>0.70</td>
</tr>
</tbody>
</table>

Data are presented as mean±SD, median (interquartile range), or percentage.
Protein Expression in Venous Endothelial Cells at Baseline

Expression of eNOS, a main source of basal endothelial NO, and P-eNOS, the activated form of eNOS, was reduced by 59% and 94%, respectively, in patients with OSA compared with control subjects (Figures 2 and 3). Expression of both nitrotyrosine, a marker of oxidative stress, and COX-2, a marker of inflammation, was 5-fold greater in patients with OSA than in control subjects (Figures 2 and 3). Lastly, expression of iNOS, another marker of inflammation, was 56% greater in patients than in control subjects (Figures 2 and 3).

Adherence to CPAP Therapy

Eighteen patients used CPAP for 4 weeks, and 12 patients declined CPAP therapy because of discomfort. The average daily use of CPAP was 5.2±2.1 hours (range, 2 to 8 hours). Fourteen patients used CPAP ≥4 hours daily for an average of 6.1±1.5 hours. The 4 remaining patients used CPAP <4 hours daily for an average of 2.2±0.5 hours. Women were more likely to decline CPAP than men. Otherwise, age, BMI, AHI, SaO2 nadir, ODI4, t<90%, daytime sleepiness, blood pressure, fasting glucose, and total cholesterol levels, as well as baseline endothelial protein expression, FMD, and EPC levels, were similar in patients who accepted CPAP and patients who declined CPAP. Body weight and systolic and diastolic blood pressures remained unchanged during CPAP therapy.

Effects of CPAP Therapy on Protein Expression in Venous Endothelial Cells

CPAP therapy significantly increased eNOS and P-eNOS expression and significantly decreased nitrotyrosine, COX-2, and iNOS expression (Figure 4A). Expression of eNOS,
Nitrotyrosine, COX-2, and iNOS was similar to that of control subjects when patients adhered to CPAP ≥ 4 hours daily \((P = 0.18 \text{ to } 1.0)\). Expression of P-eNOS remained lower than in control subjects despite adherence to CPAP ≥ 4 hours daily \((P = 0.03)\). In contrast, protein expression did not change in patients who used CPAP < 4 hours daily or declined CPAP (Figure 4B).

Flow-Mediated Dilation
Brachial artery FMD, an indirect marker of endothelial NO-mediated reactivity, was measured in 22 patients with OSA and the 15 control subjects. No differences in the resting brachial diameter and percent reactive hyperemia after cuff deflation were observed between patients with OSA and control subjects. Baseline FMD was lower in patients with OSA compared with control subjects: 4.01 \text{ ± } 2.79\% \text{} (\text{} \text{} \text{}0.001). CPAP therapy significantly increased FMD in patients who adhered to CPAP ≥ 4 hours daily \((7.24 \pm 4.24\% \text{} \text{} vs. 3.71 \pm 3.44\%; \text{} \text{} \text{}P = 0.004), whereas it did not affect FMD in patients who used CPAP < 4 hours daily or declined CPAP \((5.0 \pm 2.38\% \text{} \text{} vs. 4.30 \pm 2.60\%; \text{} \text{} \text{}P = 0.06).

Circulating EPC Levels
Circulating EPC levels, a marker of endothelial repair capacity, were measured in 22 patients with OSA and the 15 control subjects. At baseline, EPC levels were lower in patients with OSA than in control subjects: 0.013 \text{ ± } 0.006\% \text{} vs. 0.049 \text{ ± } 0.022\% \text{} (\text{} \text{} \text{}P < 0.001). CPAP therapy increased EPC levels to that of control subjects when patients adhered to CPAP ≥ 4 hours daily: 0.037 ± 0.020\% \text{} vs. 0.049 ± 0.022\% \text{} (\text{} \text{} \text{}P = 0.15). EPC levels remained unchanged when patients used CPAP < 4 hours daily or declined CPAP: 0.015 ± 0.009\% \text{} vs. 0.014 ± 0.008\% \text{} (\text{} \text{} \text{}P = 0.32).

### Table 2. Relations Between Markers of Endothelial Reactivity, Inflammation, and Oxidative Stress and Severity of OSA

<table>
<thead>
<tr>
<th>AHI, Events per h of Sleep</th>
<th>n</th>
<th>Tertile 1, 0 (0 – 4)</th>
<th>Tertile 2, 10 (6 – 20)</th>
<th>Tertile 3, 52 (21–109)</th>
<th>P for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>eNOS, au</td>
<td>45</td>
<td>0.66 (0.09)</td>
<td>0.34 (0.09)*</td>
<td>0.11 (0.10)†</td>
<td>0.001</td>
</tr>
<tr>
<td>P-eNOS, au</td>
<td>45</td>
<td>0.54 (0.07)</td>
<td>0.01 (0.07)*</td>
<td>0.02 (0.07)*</td>
<td>0.001</td>
</tr>
<tr>
<td>Nitrotyrosine, au</td>
<td>45</td>
<td>0.24 (0.24)</td>
<td>1.39 (0.25)*</td>
<td>1.83 (0.27)*</td>
<td>0.001</td>
</tr>
<tr>
<td>COX-2, au</td>
<td>45</td>
<td>0.0 (0.33)</td>
<td>0.75 (0.31)*</td>
<td>0.92 (0.33)*</td>
<td>0.007</td>
</tr>
<tr>
<td>iNOS, au</td>
<td>45</td>
<td>0.17 (0.10)</td>
<td>0.16 (0.10)</td>
<td>0.43 (0.11)†</td>
<td>0.047</td>
</tr>
<tr>
<td>FMD, %</td>
<td>37</td>
<td>9.6 (1.0)</td>
<td>4.3 (1.1)*</td>
<td>3.5 (1.3)*</td>
<td>0.001</td>
</tr>
<tr>
<td>EPCs, %</td>
<td>37</td>
<td>0.05 (0.01)</td>
<td>0.01 (0.01)*</td>
<td>0.0 (0.01)*</td>
<td>0.001</td>
</tr>
</tbody>
</table>

au indicates arbitrary units. Data are presented as mean (SE) or median (range) adjusted for age, gender, and BMI.

* \(P < 0.05\) vs tertile 1 (control subjects); † \(P < 0.05\) vs tertile 2.
Sao2, nadir, and ODI4 after adjustment for age, gender, and BMI (Tables I through III of the online-only Data Supplement). Daytime sleepiness was not associated with baseline protein expression, FMD, and EPC levels (data not shown).

**Relations Between Adherence With CPAP Therapy and Markers of Endothelial Reactivity, Inflammation, and Oxidative Stress**

After adjustment for age, gender, and BMI, expression of eNOS and P-eNOS, FMD, and EPC levels remained significantly greater whereas expression of nitrotyrosine, COX-2, and iNOS remained significantly lower in patients who adhered to CPAP ≥4 hours daily compared with patients who used CPAP <4 hours daily or declined CPAP (Table 3). Further adjustment for AHI, Sao2 nadir, ODI4, t<90%, fasting glucose levels, or total cholesterol did not significantly affect the results (data not shown).

**Discussion**

The present data provide direct evidence of vascular endothelial dysfunction and inflammation in OSA patients without clinical evidence of cardiovascular disease and the first clue that endothelial repair capacity is impaired in these patients. Furthermore, the data indicate that effective CPAP therapy reverses vascular endothelial dysfunction and inflammation and enhances endothelial repair capacity in patients with OSA. Endothelial dysfunction and inflammation in patients with OSA who are free of overt cardiovascular disease may underlie the development of vascular conditions such as hypertension, ischemic stroke, and myocardial ischemia in these patients.

Vascular endothelial function is commonly assessed indirectly by the flow-mediated technique as the relative increase in brachial artery diameter in response to peak reactive hyperemia. The technical challenge of accurately measuring brachial artery diameter in patients notwithstanding, a reactive hyperemia-induced increase in brachial artery diameter depends on both the magnitude of the hyperemic response and the functional state of the vascular endothelium. In contrast to the FMD technique, quantification of eNOS and P-eNOS expression in freshly harvested endothelial cells provides direct insight into in vivo endothelial NO production and activity. The inverse relationship between expression of eNOS and P-eNOS in venous endothelial cells and OSA severity (as assessed by AHI and the degree of arterial oxyhemoglobin desaturation) and the reversal of these alterations with CPAP therapy directly demonstrate that OSA reduces endothelial NO availability.

Repetitive episodes of hypoxia/reoxygenation, similar to those associated with transient cessation of breathing in OSA, reduce endothelial NO production at the transcriptional and posttranscriptional levels while increasing production of reactive oxygen species. Increased oxidative stress, in turn, reduces and destabilizes eNOS mRNA while limiting the availability of cofactors required for NO production. In contrast to short-term exposure to oxidative stress, prolonged oxidative stress such as that observed in untreated OSA reduces eNOS enzymatic activity by suppressing eNOS phosphorylation at S1179. Endothelial oxidative stress increases and fewer cofactors are available for NO synthesis, eNOS preferentially promotes superoxide production, which hastens NO degradation and thereby reduces NO availability. Reduced NO availability results in endothelial dysfunction and thereby increases the risk for vascular diseases in patients with OSA.

Levels of circulating free nitrotyrosine have been reported to be similar in otherwise healthy OSA patients and BMI-matched control subjects. However, the in vivo half-life of nitrotyrosine is short, and its volume of distribution is 20-fold greater than the plasma volume, indicating its extensive distribution in the extravascular compartment. Endothelial expression of nitrotyrosine more closely reflects endothelial oxidative stress in OSA than levels of circulating free nitrotyrosine. The improvement in endothelium-dependent vasodilatation after antioxidant therapy is further evidence of increased endothelial oxidative stress in OSA. Increased levels of C-reactive protein, leukocyte superoxide, and soluble circulating adhesion molecules suggest vascular endothelial activation and inflammation in patients with OSA. Upregulation of COX-2 and iNOS in venous endothelial cells harvested from patients with untreated OSA provides direct evidence of vascular inflammation in OSA.
iNOS plays an essential role in vascular inflammation and oxidative stress. Endothelial COX-2 upregulation may have dual pathogenic implications in patients with OSA. It may contribute to oxidative stress buildup by promoting superoxide generation and endothelial activation via increased production of vasoconstricting and inflammatory prostanoids. Alternatively, COX-2 upregulation may be an attempt to defend against repetitive episodes of hypoxemia/reoxygenation. The return of endothelial expression of COX-2 and iNOS to control levels after effective CPAP therapy underlines the role of OSA in the vascular inflammation.

As occurs in patients with coronary artery disease, vascular endothelial dysfunction is associated with reduced levels of circulating EPCs in OSA patients without overt cardiovascular disease. EPCs are bone marrow–derived cells that enter the systemic circulation to replace defective or injured mature endothelial cells. Impaired recruitment of EPCs from the bone marrow is likely to be related to depressed NO production and activity in patients with OSA. Reduced EPC levels may exacerbate endothelial dysfunction in patients with OSA because EPCs are the major repository of eNOS at the site of ischemia/reperfusion-induced endothelial injury. Reduced EPC levels compromise endothelial repair capacity and are likely to contribute to the OSA-related increase in cardiovascular risk.

Although CPAP therapy appears to reduce and/or reverse increased cardiovascular risk in patients with OSA, adherence to CPAP therapy remains a major obstacle. When CPAP therapy is monitored objectively, only 46% of patients have been shown to adhere to CPAP. In the present study, 47% of patients adhered to CPAP ≥4 hours daily. Adherence to CPAP for 4 weeks reversed the downregulation of eNOS and P-eNOS and the upregulation of markers of oxidative stress and inflammation. These findings support previous reports that CPAP therapy normalizes circulating and exhaled markers of oxidative stress in patients with OSA. CPAP therapy was not allocated randomly to our patients. Although our findings remained unchanged after adjustment for demographics and baseline vascular measures, a randomized trial is required to definitively ascertain the beneficial effects of CPAP therapy on endothelial function in OSA. Reversal of vascular endothelial dysfunction and inflammation and enhancement of endothelial repair capacity as shown in the present study may mediate the beneficial effects of CPAP therapy on clinical outcome in patients with OSA.

The molecular mechanisms that mediate atherosclerosis in patients with OSA cannot be ascertained from the study of the venous endothelium. Our primary aim was to investigate whether OSA directly affects the vascular endothelium. Venous and arterial endothelial cells clearly exhibit differential gene expression. However, veins are functionally abnormal in OSA. Veins and arteries are chronically exposed to the same circulating levels of proinflammatory factors. Production of reactive oxygen species is similar in venous and arterial segments harvested from patients with atherosclerosis. Basal eNOS levels are comparable in human venous and arterial endothelial cells. Levels of eNOS decrease similarly when cells are cultured at reduced oxygen tension. In healthy subjects, protein expression is similar when endothelial cells are harvested simultaneously from a vein and an artery. Although vascular reactivity may differ among vascular beds, venous endothelial markers of NO production and FMD, an indirect marker of arterial endothelial NO-mediated reactivity, are decreased in untreated OSA and increase with effective CPAP therapy.

The concomitant improvement in arterial FMD and venous endothelial NO availability and reduction in oxidative stress and inflammation with CPAP therapy strongly support a vascular inflammatory state in OSA. In contrast to arterial cell harvesting, venous sampling can be performed serially with minimal hazard and discomfort to patients. Independently of differences in venous and arterial endothelial cell phenotypes, our data unequivocally demonstrate that like tobacco toxins, elevated cholesterol, and/or glucose, OSA directly affects the vascular endothelial environment.

Obesity is associated with vascular endothelial dysfunction and inflammation and thus may have contributed to endothelial alterations in our patients. Reversal of vascular endothelial dysfunction and inflammation associated with CPAP therapy in the absence of concomitant change in body weight strongly argues that endothelial alterations were overwhelmingly related to OSA in our patients.

Conclusions

OSA is clearly associated with vascular endothelial dysfunction and inflammation, and impaired endothelial repair capacity that can be reversed by effective CPAP therapy. Whether antiinflammatory and antioxidant therapy has an adjunctive role in the treatment of OSA remains to be investigated.

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Disclosures

None.

References


CLINICAL PERSPECTIVE

Alterations in multiple vascular endothelial pathways promote the development of hypertension, ischemic stroke, and myocardial ischemia. However, reduced nitric oxide availability, as indirectly assessed by flow-mediated dilatation, is for practical purposes the only endothelial pathway considered in patients with vascular conditions. Quantification of proteins regulating nitric oxide production and activity, inflammation, and oxidative stress in freshly harvested venous endothelial cells shows that, in addition to reducing nitric oxide production and activity, repetitive episodes of hypoxia/reoxygenation associated with transient cessation of breathing are responsible for vascular inflammation and oxidative stress buildup in patients with obstructive sleep apnea (OSA) free of overt cardiovascular diseases. Similar to what has been reported in patients with coronary disease, impaired endothelial repair capacity, as evidenced by reduced endothelial progenitor cell count, accompanies vascular endothelial dysfunction in patients with OSA. Adherence to continuous positive airway pressure therapy substantially enhances nitric oxide production and activity and completely reverses endothelial inflammation and oxidative stress buildup while normalizing endothelial repair capacity in patients with OSA. The reversal of endothelial dysfunction with continuous positive airway pressure therapy emphasizes the importance of early recognition and treatment of OSA. The present findings account for the well-documented increased risk for hypertension, ischemic stroke, and myocardial ischemia in OSA.
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Figure 1 (Online Data Supplement)

Gated Events: 20000

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<td>KDR+ cells</td>
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