The renal resistance index is increased in mild-to-moderate obstructive sleep apnoea and is reduced under continuous positive airway pressure

Nikolaus J. Buchner¹, Katrin R. Wissing¹, Johannes Stegbauer¹², Ivo Quack¹², Stefan M. Weiner¹, Bernhard K. Krämer¹ and Lars C. Rump¹²

¹Department of Internal Medicine I, Marienhospital Herne, Ruhr University Bochum, Bochum, Germany and ²Department of Nephrology, Heinrich Heine University, Düsseldorf, Germany

Correspondence and offprint requests to: Nikolaus J. Buchner; E-mail: nikolaus.buechner@rub.de

Abstract

Background. Impaired renal function has recently been reported in obstructive sleep apnoea (OSA). The underlying mechanisms, however, are not entirely understood. This study investigated the influence of mild-to-moderate OSA and its treatment on renal haemodynamics as assessed by the renal resistance index (RRI).

Methods. RRI has been measured by colour duplex ultrasound in 64 patients with newly diagnosed mild-to-moderate OSA and 61 controls without OSA at baseline and follow-up after 9.9 months. Treatment with continuous positive airway pressure was offered to all patients with OSA (apnoea/hypopnoea index ≥ 5/h).

Results. Increased values of RRI (≥ 1 SD [8.9%] above the age-adjusted normal value) were found in 41 out of 64 (64.0%) OSA patients when compared with 20 out of 61 (32.8%) controls (P < 0.001). The corresponding mean RRI was 70.50 ± 9.01 vs 66.51 ± 8.33 (P = 0.012). In multivariate analyses, the influence of OSA on RRI was independent from hypertension, diabetes mellitus, age and baseline renal function. At follow-up, RRI decreased only in patients with effective OSA treatment but remained unchanged in ineffectively treated OSA patients and controls.

Conclusions. For the first time, this prospective controlled observational study demonstrates an impairment of renal haemodynamics in OSA as measured by an increased RRI. These changes of renal blood flow may identify OSA patients at high risk of declining renal function. Both parenchymal and vascular renal diseases are proposed as pathomechanisms for this association. An effective treatment of OSA resulted in a decreased RRI, suggesting an improvement in renal perfusion. Further studies are needed to elucidate the role of impaired renal haemodynamics in OSA.

Keywords: continuous positive airway pressure; obstructive sleep apnoea; renal function; renal resistance index

Introduction

The renal resistance index (RRI) has been proven as a sensitive indicator and predictor of renal dysfunction as well as cardiovascular disorders [1-11]. On the other hand, obstructive sleep apnoea (OSA) and its management are known to influence cardiovascular diseases. Thus, increased cardiovascular morbidity and mortality has been found in patients with OSA. OSA in turn is highly prevalent in patients with established cardiovascular disease [12-14]. Whilst the mechanisms responsible for this association are not entirely understood, it still remains controversial whether OSA serves as an independent cardiovascular risk factor [13]. Treatment of OSA with continuous positive airway pressure (CPAP) resulted in a marked benefit as to cardiovascular outcome in severe [15] and even mild–moderate [16] OSA as well as in OSA patients without pre-existing cardiovascular disease [16].

There is growing evidence that OSA independently increases the occurrence and severity of classical cardiovascular risk factors. For example, it has been shown that OSA increases the risk to develop systemic hypertension independently from other known risk factors [14]. Although moderate impairment of renal function [17] and microalbuminuria [18] have also been demonstrated as independent predictors of cardiovascular risk, recent cardiovascular outcome studies in OSA patients did not account for the influence of renal function. Moreover, although OSA often coincides with known promoters of renal dysfunction (i.e. diabetes mellitus, hypertension, obesity, increased sympathetic nerve activity), few studies have addressed changes of renal function in OSA patients [19–21]. In a previous investigation, we were able to demonstrate increased serum creatinine in patients with OSA compared with those without OSA (1.11 ± 0.15 vs 0.91 ± 0.12 mg/dL, P < 0.001), recently confirmed by Agrawal et al. [20]. This association appeared independent from arterial hypertension and other covariates [19].
Accordingly, Fleischmann et al. found that the glomerular filtration rate in patients with sleep apnoea is reduced, particularly in patients with episodes of central sleep apnoea [21]. Kinebuchi et al. [22] found OSA patients generally being in a glomerular-hyperfiltrating condition as another correlate for the renal changes associated with OSA. Some studies observed microalbuminuria, an early marker of parenchymal renal disease, combined with OSA [23,24].

Therefore, it seems conceivable that OSA adversely affects the cardiovascular outcome partially by promoting impaired renal function. Whilst the underlying pathomechanisms of renal impairment in OSA are not completely known, both structural and functional renal changes have been considered.

The RRI is a marker of parenchymal renal damage and a predictor of the progression of renal dysfunction [1,2,10]. Thus, the RRI could contribute to the understanding of renal dysfunction in OSA.

We hypothesized that mild-to Moderate OSA promotes parenchymal and vascular renal diseases and, therefore, investigated changes in RRI in relation to mild–moderate OSA and its treatment.

Materials and methods

Patients

Consecutive patients admitted to our sleep clinic with suspected OSA or secondary hypertension were recruited between 2004 and 2005. Patients with known glomerulonephritis, analgesic nephropathy, renal artery stenosis, and end-stage renal disease as well as those with central sleep apnoea, Cheyne–Stokes respiration, hypoventilation syndromes, severe OSA or periodic limb movement in sleep as the predominant finding were excluded. Patients in whom a sleep-related breathing disorder could not be confirmed served as controls.

Polysomnography. All patients underwent overnight attended polysomnography as previously described [16]. Apnoea was defined as a complete cessation of airflow lasting ≥10 s and hypopnoea was defined as a ≥50% reduction in respiratory airflow lasting ≥10 s associated with an arousal or oxygen desaturation by ≥4%. The apnoea/hypopnoea index (AHI) was calculated as the average number of episodes of apnoea and hypopnoea per hour of sleep. OSA was diagnosed if AHI = 5.5/h (mild OSA: AHI, 5–15/h; moderate OSA: AHI, 15–30/h; severe OSA: AHI, ≥30/h).

Colour-coded duplex ultrasound. In all subjects, Doppler US examination with measurement of RRI was performed between 9.00 and 11.00 a.m. During the examination, patients were instructed to avoid forced inspiration. Colour Doppler examination was performed with a 4.0-MHz convex array transducer (ACUSON Sequoia 512) in supine position. Peak systolic velocity \(V_{\text{max}}\), in centimetres per second) and end diastolic velocity \(V_{\text{min}}\), in centimetres per second) were obtained for the calculation of the dimensionless resistance index values according to the following formula: resistance index \(= 1 - (\text{end diastolic velocity}/\text{peak systolic velocity})\). RRI was calculated as the average of four to six measurements both in representative interlobar and segmental arteries from the upper, middle and lower third of both kidneys. The mean of the right and left mean RRI was calculated as total RRI. Additionally, we calculated the difference to the age-adjusted normal value of RRI in percent (RRI%).

Renal function and cardiovascular risk assessment. Renal function was assessed in all subjects using serum creatinine and glomerular filtration rate estimated by the Modification of Diet in Renal Disease (MDRD) formula. The level of urinary albumin excretion rate was calculated from both 24-h urine collection and albumin/creatinine ratio in spot morning urine samples.

Standard baseline data included medical history, physical examination, fasting blood screening tests and electrocardiography. In addition, patients’ cardiovascular risk level at baseline was recorded in detail. In all patients, office blood pressure (BP) was measured in a sitting position after a rest of at least 5 min.

Twenty-four-hour ambulatory BP monitoring was carried out with a Custod Screen 200 device (custo med GmbH, Ottobrunn, Germany). Measurements were taken every 15 min between 6 a.m. and 10 p.m. and every 30 min between 10 p.m. and 6 a.m.

In patients without known diabetes mellitus, glucose metabolism was assessed by a 75-g glucose tolerance test according to the criteria of the American Diabetes Association.

The classification of risk factors was based on the following predefined criteria: arterial hypertension (defined as BP of ≥140/90 mmHg or use of antihypertensive drugs); diabetes mellitus (diagnosed when subjects were receiving insulin or oral antidiabetics, if fasting glucose was ≥7.0 mmol/L or if post-load blood glucose was ≥11.1 mmol/L); hypercholesterolaemia (defined as current use of cholesterol-lowering medications or plasma levels of ≥5.2 mmol/L and/or an LDL cholesterol value ≥3.4 mmol/L in a plasma sample drawn after an overnight fast).

OSA treatment and follow-up

In agreement with generally accepted national and international standards, CPAP treatment was recommended to all patients with OSA. Thus, there was no treatment assignment by randomization in this study. If patients did not tolerate the required CPAP pressure, the therapy was changed to bilevel positive airway pressure. Patients who refused mechanical treatment remained untreated. Follow-up with repeated Doppler US examination and polysomnography was intended after 6 months in all patients. Compliance was defined as use of CPAP for ≥4 h per night on average. We prospectively decided to compare effectively treated OSA patients with ineffectively treated OSA patients. OSA treatment was considered effective if the patient was compliant and AHI was reduced by ≥50% and below 10/h. OSA treatment was assigned as ineffective if the patient was not compliant or apnoeas/hypopnoeas have not been reduced sufficiently or the patient remained untreated.

Statistical analysis

Statistical analyses were performed with the computer software SPSS for Windows (SPSS, Chicago, IL, USA; version 11.5.1). Results are given as means ± standard deviation. All P-values reported are two-tailed. P-values below 0.05 were considered statistically significant. Intergroup differences were analysed for significance with chi-square test and Student’s t-test after confirmation of normal distribution.

The relationship between OSA and RRI was first explored by bivariate regression analysis. Subsequently, a multivariate linear regression model was established to determine an independent influence of OSA on RRI and RRI%. Parameters of OSA were separately introduced in the model to avoid their unintended statistical interaction. Further parameters included into this model were hypertension, diabetes mellitus, baseline serum creatinine, GFR (MDRD) and age (the latter only for RRI).

The study protocol is in agreement with the ethical principles of the Helsinki declaration. All patients gave informed consent with their participation in the study.

Results

General results

A total of 125 patients were enrolled. Clinical characteristics of patients with \((n = 64)\) and without \((n = 61)\) OSA at baseline are listed in Table 1. Briefly, there were no significant differences between patients with and without OSA.
with respect to cardiovascular co-morbidities and medication (including different antihypertensive drugs) and microalbuminuria as well. Table 2 summarizes polysomnographic data of patients with OSA and controls.

### Influence of OSA on RRI

Increased values of RRI (i.e. more than 1 SD [8.9%] above the age-adjusted normal value) were found in 41 out of 64 OSA patients (64.0%) compared with 20 out of 61 controls (32.8%, P < 0.001). In patients with OSA, RRI values were significantly higher than in controls (Table 3). Whilst RRI is known to significantly increase with age, RRI values of patients with OSA and controls were also pooled into decades and compared separately. As shown in Figure 1, RRI of patients with OSA were significantly increased compared with controls in each decade.

Additionally, when analysing only patients without established cardiovascular diseases (coronary artery disease, myocardial infarction, stroke, cerebrovascular or peripheral artery disease), the RRI (67.89 ± 7.48 vs 64.01 ± 6.87, P = 0.011) and RRI % (8.52 ± 11.21 vs 3.16 ± 9.54, P = 0.015) were significantly higher in patients with OSA compared with controls.

In univariate analyses, RRI was associated with the presence of OSA (r = 0.224, P = 0.012), AHI (r = 0.231, P = 0.009), age (r = 0.669, P < 0.001), mean oxygen saturation (r = -0.224, P = 0.020), serum creatinine (r = 0.374, P < 0.001), GFR according to the MDRD formula (r = -0.440, P < 0.001), present hypertension (r = 0.182, P = 0.043), office systolic BP (r = 0.189, P = 0.035), 24-h diastolic BP (r = -0.387, P = 0.001), use of antihypertensive drugs (r = 0.438, P < 0.001), present diabetes mellitus (r = 0.183, P = 0.041), coronary artery disease (r = 0.451, P < 0.001) and age (r = 0.681, P < 0.001). No correlation

### Table 1. Clinical characteristics of OSA patients and controls at baseline

<table>
<thead>
<tr>
<th></th>
<th>OSA (n = 64)</th>
<th>Controls (n = 61)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>61.1 ± 11.0</td>
<td>58.6 ± 14.7</td>
<td>n.s.</td>
</tr>
<tr>
<td>Male gender, n (%)</td>
<td>37 (57.8)</td>
<td>33 (54.1)</td>
<td>n.s.</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>30.2 ± 5.3</td>
<td>28.8 ± 4.4</td>
<td>n.s.</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>52 (81.3)</td>
<td>52 (85.3)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>16 (25.0)</td>
<td>13 (21.31)</td>
<td>n.s.</td>
</tr>
<tr>
<td>IFG/IGT, n (%)</td>
<td>9 (14.1)</td>
<td>9 (14.7)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Fasting glucose</td>
<td>97.1 ± 21.4</td>
<td>94.5 ± 18.1</td>
<td>n.s.</td>
</tr>
<tr>
<td>Hyperlipidaemia, n (%)</td>
<td>45 (70.1)</td>
<td>40 (70.3)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Coronary artery disease, n (%)</td>
<td>13 (20.3)</td>
<td>11 (18.0)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Nicotine, n (%)</td>
<td>10 (15.7)</td>
<td>17 (27.9)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Antihypertensive treatment, n (%)</td>
<td>51 (79.7)</td>
<td>44 (72.1)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Chronic renal failure, n (%)</td>
<td>54 (84.3)</td>
<td>51 (83.6)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Stage 1</td>
<td>0 (0)</td>
<td>3 (4.9)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Stage 2</td>
<td>34 (53.1)</td>
<td>35 (57.4)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Stage 3</td>
<td>20 (31.3)</td>
<td>13 (21.3)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Microalbuminuria, n (%)</td>
<td>15 (23.4)</td>
<td>13 (21.3)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>1.02 ± 0.29</td>
<td>0.96 ± 0.24</td>
<td>n.s.</td>
</tr>
<tr>
<td>GFR (MDRD)</td>
<td>70.3 ± 17.6</td>
<td>77.1 ± 20.8</td>
<td>n.s. (P = 0.052)</td>
</tr>
<tr>
<td>Albumin/creatinine ratio</td>
<td>11.9 ± 14.7</td>
<td>14.7 ± 21.3</td>
<td>n.s.</td>
</tr>
<tr>
<td>Office BP sys (mmHg)</td>
<td>142.6 ± 26.9</td>
<td>148.9 ± 31.0</td>
<td>n.s.</td>
</tr>
<tr>
<td>Office BP dias (mmHg)</td>
<td>78.7 ± 14.3</td>
<td>83.8 ± 18.7</td>
<td>n.s.</td>
</tr>
<tr>
<td>Pulse pressure</td>
<td>63.90 ± 20.89</td>
<td>65.15 ± 20.80</td>
<td>n.s.</td>
</tr>
<tr>
<td>24-h BP sys (mmHg)</td>
<td>137.4 ± 16.7</td>
<td>139.7 ± 18.1</td>
<td>n.s.</td>
</tr>
<tr>
<td>24-h BP dias (mmHg)</td>
<td>75.1 ± 8.7</td>
<td>76.6 ± 11.2</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

OSA, obstructive sleep apnoea; BMI, body mass index; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; GFR (MDRD), glomerular filtration rate using the Modification of Diet in Renal Disease formula; BP, blood pressure; sys/dias, systolic/diastolic.

### Table 2. Polysomnographic data of OSA patients and controls at baseline

<table>
<thead>
<tr>
<th></th>
<th>OSA patients (n = 64)</th>
<th>Controls (n = 61)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AHI (per hour)</td>
<td>14.1 ± 6.2</td>
<td>2.22 ± 1.21</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Arousal index (per hour)</td>
<td>46.9 ± 21.1</td>
<td>33.1 ± 14.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SO2 mean (%)</td>
<td>92.5 ± 2.3</td>
<td>97.2 ± 2.5</td>
<td>n.s.</td>
</tr>
<tr>
<td>SO2 min (%)</td>
<td>82.8 ± 8.3</td>
<td>89.3 ± 3.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>t90 (%)</td>
<td>21.6 ± 32.2</td>
<td>5.9 ± 17.9</td>
<td>0.007</td>
</tr>
</tbody>
</table>

AHI, apnoea/hypopnoea index; SO2 min, minimal oxygen saturation; SO2 mean, mean oxygen saturation; t90, percentage of the night spent with oxygen saturation below 90%.

### Table 3. RRI at baseline in OSA patients and controls

<table>
<thead>
<tr>
<th></th>
<th>OSA (n = 64)</th>
<th>Controls (n = 61)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RRI</td>
<td>70.50 ± 9.01</td>
<td>66.51 ± 8.33</td>
<td>0.012</td>
</tr>
<tr>
<td>RRIseg</td>
<td>12.20 ± 13.45</td>
<td>6.48 ± 11.43</td>
<td>0.012</td>
</tr>
<tr>
<td>RRIint</td>
<td>71.01 ± 9.30</td>
<td>66.44 ± 8.44</td>
<td>0.006</td>
</tr>
<tr>
<td>RRI%</td>
<td>71.06 ± 9.12</td>
<td>66.74 ± 8.40</td>
<td>0.008</td>
</tr>
</tbody>
</table>

RRI, renal resistance index; RRIseg, renal resistance index of segmental arteries; RRIint, renal resistance index of interlobar arteries; RRI%, percentage of deviation from the age-adjusted normal value.
was found between RRI and BMI, office diastolic BP and 24-h systolic BP.

Subsequently performed multivariate analysis revealed that the presence of OSA increases both RRI ($\beta = 0.191$, $P = 0.013$) and RRI$_\%$ ($\beta = 0.193$, $P = 0.015$) independently from hypertension, diabetes mellitus, age and renal function.

Influence of OSA treatment on RRI

The mean follow-up was 9.9 ± 6.6 months. A trend towards a reduction of RRI was observed only in effectively treated patients with mild-to-moderate OSA (70.30 ± 9.6 vs 68.07 ± 8.81, $P = 0.07$). Considering only OSA patients with initially increased RRI, this reduction of RRI after effective OSA treatment was statistically significant (RRI, 73.48 ± 7.50 vs 71.02 ± 8.14, $P = 0.038$; Figure 2). In contrast, RRI remained unchanged in controls and in OSA patients in whom treatment turned out to be not effective (Figure 2). RRI changes at follow-up were not significantly different in patients with stable or decreased renal function (assessed by the course of serum creatinine) when compared with those with improved renal function ($-0.12 \pm 6.42$ vs $-0.64 \pm 4.87$, n.s.). Similarly, changes of serum creatinine at follow-up did not significantly differ between patients with increased and decreased values of RRI ($+0.08 \pm 0.31$ vs $-0.01 \pm 0.21$ mg/dL, n.s.). When evaluating the entire study group, however, changes of RRI were associated with changes of serum creatinine ($r = 0.357$, $P = 0.009$). No correlation was found between the degree of AHI improvement and the degree of RRI reduction. BP changes at follow-up were not significantly different between effectively and ineffectively treated OSA patients.

Discussion

The present prospective controlled study yielded two major new findings. First, the RRI is increased in patients with OSA and this association is independent from age, hypertension, diabetes mellitus and baseline renal function as known predictors of increased RRI. Second, RRI decreased after effective treatment of OSA, whereas it remained unchanged in patients in whom OSA treatment was ineffective.

Associations of increased RRI with renal and cardiovascular disorders have been reported from various studies. Thus, RRI has been considered as a marker of subclinical hypertensive end-organ damage [3–5], a surrogate of (early) atherosclerosis [6–8] and a predictor of future cardiovascular complications [5]. Furthermore, RRI was associated with traditional cardiovascular risk factors, in particular essential hypertension [9–11].

OSA often coincides with arterial hypertension, and the probability to develop systemic hypertension increases with increasing degree of OSA [14]. Thus, OSA might increase RRI by promoting systemic hypertension. However, in the present study, the prevalence of hypertension was not significantly different between OSA patients and controls. Moreover, in multivariate analyses, the influence of OSA on RRI proved to be independent from hypertension and other cardiovascular risk factors and co-morbidities as well.

In adults, increased RRI has also been strongly associated with age [26]. However, in our study, age was similar in OSA patients and controls. To further separate the influence of age, values of RRI have been adjusted for age by calculating the percentage deviation from age-related normal values [25].

Therefore, we assume that our results are not confounded by age or hypertension as two major inducers of RRI increase.
Renoparenchymal disease

Assessment of renal vascular resistance is a useful tool to determine the degree of renal organ damage. Even in patients with normal renal function, increases in RRI indicated both intrarenal atherosclerosis and interstitial renal damage [2,3,27–31]. Moreover, RRI was associated with worsening renal function [1,2,10] and future decline in renal function [10]. Thus, increased values of RRI in patients with OSA may be considered as an indicator of renoparenchymal disease.

In a previous study, we showed first evidence that OSA is associated with impaired renal function. These results were independent from hypertension and other confounders [19] and could be confirmed recently by Agrawal et al. [20]. In another recent study, glomerular filtration rate was found to be reduced in patients with sleep apnoea, particularly in those with episodes of central sleep apnoea [21].

Therefore, OSA may increase RRI by promoting interstitial renal disease. In principle, OSA patients have a higher risk for parenchymal renal damage due to the high prevalence of hypertension. However, other studies failed to link OSA with microalbuminuria, which is an early marker of hypertensive renal disease [19,20]. Thus, additional pathophysiologic pathways need to be discussed in this field.

Episodic hypoxia is a hallmark of OSA and has been shown to increase nocturnal and daytime [32] as well as renal [33] sympathetic nerve activity. In addition to activating the renin–angiotensin–aldosterone system, long-term sympathetic overactivity has also been shown to induce proliferative structural renal damage [34], which goes along with increased RRI.

Furthermore, glomerular hyperfiltration is thought to induce parenchymal renal disease. In OSA, forced inspirations against closed upper airways (Mueller manoeuvre) accompany the apnoeas and induce negative intrathoracic pressures reaching −65 mmHg that in turn cause central hypervolaemia. Moreover, OSA is strongly related to obesity which is known to induce glomerular hyperfiltration [35]. Accordingly, glomerular hyperfiltration has been found in OSA by Kinebuchi et al. [22] and, therefore, could explain progressive renal disease and hence increased RRI.

Taken together so far, OSA might increase RRI by inducing glomerular and tubulointerstitial renal disease as a result of hypertension, increased sympathetic nerve activity, volume expansion and obesity.

Nevertheless, whilst some studies linked OSA to microalbuminuria as a surrogate of parenchymal renal damage [23,24], the present study as well as other studies [19,20] could not find any evidence for an increased incidence of microalbuminuria in patients with OSA. Our results, therefore, suggest that either structural renal damage may not be an important mechanism for the observed impairment of renal haemodynamics in OSA or the observed period was too short to detect parenchymal damage in these patients. In addition, in the present study, renal size, admittedly an imprecise surrogate of interstitial renal disease, was not different in the two study groups and also not significantly associated with RRI (data not shown).

Renovascular disease

Therefore, primary vascular changes have also to be taken into consideration as a possible pathophysiologic explanation for the observed increases of RRI.

Due to its nature, RRI can be influenced by changes of the vascular tone and structure. As a result, RRI has been associated with endothelial function, arterial stiffness and signs of atherosclerosis. These changes have recently been described in OSA [36] and are likely to influence RRI. Furthermore, episodic hypoxia, a typical feature of OSA, has been shown to increase renal sympathetic nerve activity, which in turn causes renal vasoconstriction by increased angiotensin II [33]. These vascular changes are considered partially reversible and, therefore, an interesting therapeutic target in terms of cardiovascular prevention.

Due to its definition, the RRI can also be increased by systemic haemodynamic changes, in particular those with increased pulse pressure. Whilst OSA has been linked to both hypertension and chronic heart failure, peripheral pulse pressure in the present study was not different between patients with and without OSA. Therefore, we assume that RRI was not significantly influenced by systemic haemodynamic alterations.

Influence of OSA treatment

Taken together, several confounding factors and proposed pathomechanisms are probably part of a complex network that influences RRI in OSA. The true extent of influence of each single component is difficult to estimate even if multivariate statistical analyses are performed. Therefore, although OSA proved to be associated with RRI independently from different confounders in the present study, interventional studies may be better suited to investigate a presumed causal relationship in this field.

We, therefore, compared the course of RRI in patients with effective vs ineffective treatment of OSA. During our follow-up, RRI decreased in effectively treated OSA patients with previously increased values of RRI, whereas it remained unchanged when OSA was not or not effectively treated.

OSA treatment has been shown to improve the cardiovascular outcome [15,16] as well as early signs of atherosclerosis, namely, endothelial dysfunction [37], carotid intima–media thickness [38], arterial stiffness as assessed by pulse wave velocity [38] and central augmentation index [39]. These beneficial changes in vascular function and structure are likely to be reflected in a reduction of previously increased RRI. However, RRI did not reach levels of the control group, suggesting that the underlying structural changes are not completely reversible at least after a follow-up of 9.9 months.

Limitations

Because of the proven benefit of CPAP on cardiovascular outcome, we neither randomized our patients nor used a placebo group for ethical reasons. Instead, as in other previous studies, patients who have not been treated effectively served as controls. We, therefore, cannot exclude that our...
control patients might differ from the effectively treated OSA patients in terms of lifestyle and compliance with cardiovascular medications.

Also, statistically significant RRI differences between patients with and without OSA and particularly between effectively and ineffectively treated OSA patients have to be taken with caution because of the high standard deviation in the mean values.

A high prevalence of cardiovascular co-morbidities, in particular hypertension, might interfere with an association between OSA and RRI. We knowingly did not exclude these covariates because we intended to study a representative cohort of OSA patients with all their associated co-morbidities. As clinical characteristics and cardiovascular co-morbidities do not differ between patients with OSA and controls, we expect that these co-morbidities would affect the RRI in both groups in the same manner. Moreover, multivariate analyses demonstrated that OSA increases the RRI independently from hypertension, diabetes mellitus, age and renal function.

Conclusion

For the first time, this prospective controlled observational study demonstrated that mild-to-moderate OSA is associated with increased RRI independently from various covariates. In addition, RRI improved only in effectively treated OSA patients. These findings extend our understanding of the recently shown mild renal impairment in OSA and could possibly be important to easily identify OSA patients at high risk for declining renal function.

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Conflict of interest statement. None declared.

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Inflammation, kidney function and albuminuria in the Framingham Offspring cohort

Ashish Upadhyay1, Martin G. Larson2,4, Chao-Yu Guo2, Ramachandran S. Vasan2,3, Izabella Lipinska5, Christopher J. O’Donnell2,6, Sekar Kathiresan6, James B. Meigs7, John F. Keaney Jr.8, Jian Rong2,9, Emelia J. Benjamin2,3,9 and Caroline S. Fox2,10

1Division of Nephrology, Tufts Medical Center and Tufts University School of Medicine, Boston, MA, USA, 2Boston University and National Heart, Lung and Blood Institute’s Framingham Heart Study, Framingham, MA, USA, 3Preventive Medicine and Cardiology Sections, and Whitaker Cardiovascular Institute, Boston University School of Medicine, Boston, MA, USA, 4Department of Mathematics and Statistics, Boston University, Boston, MA, USA, 5Cardiovascular Division, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA, USA, 6Division of Cardiology, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA, 7Division of General Internal Medicine, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA, 8Division of Cardiovascular Medicine, UMass Memorial Health Care and University of Massachusetts Medical School, Worcester, MA, USA, 9Department of Epidemiology, School of Public Health, Boston University, Boston, MA USA and 10Department of Endocrinology, Brigham and Women’s Hospital and Harvard Medical School, Boston, MA, USA

Correspondence and offprint requests to: Ashish Upadhyay; E-mail: aupadhyay@tuftsmedicalcenter.org
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Abstract

Background. Inflammation and chronic kidney disease (CKD) are both associated with cardiovascular disease (CVD). Whether inflammatory biomarkers are associated with kidney function and albuminuria after accounting for traditional CVD risk factors is not completely understood.

Methods. The sample comprised Framingham Offspring cohort participants (n = 3294, mean age 61, 53% women) who attended the seventh examination cycle (1998–2001). Inflammatory biomarkers [C-reactive protein (CRP), tumour necrosis factor (TNF)-alpha, interleukin-6, TNF receptor 2 (TNFR2), intercellular adhesion molecule-1 (ICAM-1), monocyte chemoattractant protein-1 (MCP-1),...