Changes in extracranial arteries in obstructive sleep apnoea

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ABSTRACT: Obstructive sleep apnoea (OSA) is linked with increased cardiovascular morbidity and mortality, possibly through an enhancement of atherosclerotic vascular changes. Up to now, however, only a few studies have tried to evaluate the occurrence of atherosclerosis in patients with OSA.

In the present study, ultrasonography of the large extracranial vessels was performed in a group of consecutively admitted OSA patients (n=35) and a control group of non-OSA patients (n=35). Common carotid artery-intima media thickness (CCA-IMT) was measured at the far wall of both proximal carotid arteries. Furthermore, the presence of plaques and stenoses of the extracranial vessels was determined. All measurements were carried out blinded to the status of the patients.

In the OSA group, CCA-IMT was significantly increased when compared with the non-OSA patients and was related to the degree of nocturnal hypoxia. Additionally, the formation of plaques was more pronounced and extracranial vessel stenosis was more common in the OSA patients.

In conclusion, these findings are in favour of an independent influence of obstructive sleep apnoea on atherosclerotic changes of the arterial wall, and represent further strong arguments for obstructive sleep apnoea being a risk factor on its own for the emergence of cardiovascular disease.

KEYWORDS: Atherosclerosis, cardiovascular disease, carotid arteries, obstructive sleep apnoea, ultrasonography

Obstructive sleep apnoea (OSA) is associated with increased cardiovascular morbidity and mortality. Epidemiological data strongly support a causal role of OSA in the development of arterial hypertension [1]. Moreover, there is accumulating evidence that OSA also carries an increased risk for occlusive vascular disease, i.e. coronary artery and cerebrovascular disease [2]. Through the stimuli of chronic intermittent hypoxia and shear stress, OSA probably enhances vasoconstrictive, proinflammatory and prothrombotic forces within the vascular milieu, and thereby leads to accelerated atherosclerosis [3].

During the early stages of atherosclerosis, lipid-laden macrophages are incorporated into the vascular wall. Furthermore, hypertrophy of vascular smooth muscle cells occurs. The later stages of atherosclerosis are characterised by the formation of plaques and stenoses. These anatomical changes can be visualised by ultrasonography of large vessels, such as the femoral and carotid arteries. In this context, common carotid artery-intima media thickness (CCA-IMT) is an established parameter to detect the early stages of atherosclerosis [4–6] and to predict the overall cardiovascular risk [7, 8].

Two studies have already reported an increase of CCA-IMT in OSA as compared with controls not suffering from sleep-disordered breathing [9, 10]. Moreover, a recently published paper has found that CCA-IMT was related to the degree of nocturnal hypoxia, thus suggesting a dose-response relationship between the severity of OSA and the cerebral atherosclerotic process [11]. However, these studies had some limitations. In the study by Silvestrini et al. [9], ambulatory monitoring was used instead of polysomnography to exclude or prove OSA. In the study by Kaynak et al. [10], the subjects investigated were not fully matched with regard to variables known to influence CCA-IMT. Finally, the study by Suzuki et al. [11] mainly investigated patients with only mild nocturnal desaturations, thus making it difficult to extrapolate the findings to the whole spectrum of OSA.

Against this background, the objective of the present study was to measure CCA-IMT in a patient cohort with polysomnographically proven
OSA and to compare it with a carefully matched control group of non-OSA patients. Furthermore, this study aimed to re-test the hypothesis that CCA-IMT in OSA is related to the degree of nocturnal hypoxia. Finally, the current authors intended to evaluate changes associated with the later stages of atherosclerosis, i.e. the occurrence of plaques and stenoses.

**PATIENTS AND METHODS**

**Recruitment of cases and controls**

The OSA patients enrolled in the present study were consecutively referred to the sleep laboratory (Dept of Pulmonary and Critical Care Medicine, Justus-Liebig-University, Giessen, Germany) for diagnostic polysomnography and the initiation of noninvasive ventilatory support, i.e. continuous positive airway pressure (CPAP) therapy. Prior to admission, all patients from this group had been investigated using an ambulatory device (SOMNOcheck; Weimann Inc., Hamburg, Germany) and interviewed for the presence of sleep-related symptoms, i.e. snoring, witnessed apnoeas, excessive daytime sleepiness. Simultaneously, controls were recruited from the pool of patients hospitalised at the Dept of Internal Medicine, Justus-Liebig-University, Giessen, Germany. They were selected by one of the current authors (R. Schulz) to match the OSA patients with regards to anthropometric parameters and the spectrum of comorbidity.

**Determination of patient characteristics**

The medical history of the patients was evaluated with special reference to the occurrence of vascular disease, i.e. arterial hypertension, coronary artery, peripheral occlusive vascular and cerebrovascular disease. Blood pressure at rest was measured at fixed time intervals (at 06:00 h, 12:00 h, 16:00 h and 20:00 h) with the patients in the supine position and after a resting period of 10 min. All blood pressure values obtained during the stay of the patients in the sleep laboratory were averaged to yield the mean daytime blood pressure in each patient.

Arterial hypertension was diagnosed if blood pressure values exceeded 140/80 mmHg during at least two different measurements or if there was known and medically treated hypertension. Coronary artery disease was defined by the presence of clinical symptoms (i.e. angina pectoris), a history of prior myocardial infarction, signs of ischaemia on electrocardiography and/or a finding of significant (i.e. $\geq 50\%$) narrowing of coronary vessels on angiography. The diagnosis of peripheral occlusive vascular disease was made on the basis of symptoms suggestive of leg ischaemia, i.e. exercise-induced claudicatio intermittens, and the results of Doppler studies and/or angiography of the lower extremities, if available. Cerebrovascular disease was assumed if the patients had suffered from stroke and/or transient ischaemic attacks, or if they presented with persistent neurological deficits, such as hemiparesis or aphasia. Furthermore, the findings of brain computed tomography/magnetic resonance imaging were taken into account if they had been performed.

To determine the presence of hypercholesterolaemia and diabetes mellitus, total cholesterol (normal: $<200$ mg·dL$^{-1}$), low-density lipoprotein and high-density lipoprotein cholesterol and glycated haemoglobin values (normal: $<6\%$) were measured in all patients. Peripheral venous blood samples were withdrawn at 07:00 h, before eating breakfast. All subjects were asked about their former and current smoking habits. Cigarette consumption was expressed as pack-yrs per patient. Finally, the use of antihypertensive, antidiabetic and lipid-lowering drugs was noted. Patients with known cerebrovascular disease were excluded from the study. Further exclusion criteria were the presence of mixed or central sleep apnoea, as well as the use of aspirin or other antithrombotic drugs. The study protocol had been approved by the local ethics committee and all patients had given their informed written consent.

**Sleep study**

All subjects were investigated by full-night attended polysomnography. The electroencephalogram (electrodes at positions C3-A2 and C4-A1 of the international 10–20 system), electrooculogram and electromyogram of the submental and praetibial muscles were simultaneously recorded. Ventilatory airflow at the nose and mouth was registered with oronasal prongs. Thoraco-abdominal breathing movements were monitored by inductive plethysmography. Oxygen saturation ($\text{Sa}_O_2$) was measured transcutaneously with pulse oximetry at the fingertip of the patient. Finally, an electrocardiogram was obtained. All data were stored on a computerised polysomnograph with capability for analogue registration (Sidus GS; IM GmbH, Wittenberg, Germany). Analysis of sleep stages was performed manually in 30-s intervals, according to the criteria of Rechtschaffen and Kales [12]. Arousal sequence were classified following the American Sleep Disorders Association (ASDA) criteria [13]. Breathing while asleep was scored as suggested by an ASDA task force [14]. The apnoea–hypopnoea index (AHI) was obtained by dividing the total number of apnoeas and hypopnoeas by the total sleep time (TST). An AHI $>10$·h$^{-1}$ in companion with sleep-related symptoms was considered as diagnostic of OSA.

**Ultrasonography of extracranial vessels**

High-resolution B-mode ultrasonography of both carotid arteries was performed using the Sonoline Elegra, an 8-MHz transducer (Fa. Siemens, Erlangen, Germany), with the patient in the supine position.

CCA-IMT was measured from longitudinal images obtained at the far wall of the distal 1.0 cm of both CCAs, i.e. immediately proximal to the carotid bulb. All measurements were taken during end diastole and at plaque-free sites of the arterial wall. A total of 10 measurements of IMT were made in the right and left carotid arteries and were averaged to yield the mean IMT for each side and for both sides combined. Furthermore, the presence of plaques within the walls of both CCAs was determined. A plaque was defined as a localised thickening $>1.2$ mm, not involving the whole circumference of the artery. Plaque formation was graded as absent (0), mild ($1: <30\%$ of the vessel diameter), moderate (2: $30-50\%$ of the vessel diameter) or severe (3: $>50\%$ of the vessel diameter). By summarising the grades of the right and left carotid arteries, a plaque index was obtained for each patient [15]. The mean value from these individual measurements was taken as the plaque score of the whole group. Finally, all extracranial vessels (i.e. arteriae (Aa.) carotis communis, interna and externa; Aa. vertebralis) were screened for stenoses by colour-coded Doppler ultrasonography. A significant stenosis was defined as a reduction of the inner vascular diameter of $>50\%$ together with a peak systolic flow...
velocity of >1.5 m s⁻¹ [16]. All measurements were carried out with the investigator (M. Grebe) blinded to the status of the individual patient. Prior to the start of the study, variabilities in intraobserver measurements had been found to lie in a very narrow range (i.e. ±0.05 mm).

**Data analysis**

The data were analysed by employing an explorative statistical approach. Continuous variables were supposed to comply with a normal distribution and were given as mean ± SEM, including 95% confidence intervals.

First, the patient characteristics of both groups were investigated for the presence of a homogeneous distribution. This was done by using nonparametric tests for continuous variables and parametric tests for categorical variables. The same tests were also employed to evaluate intergroup differences of ultrasonographic read-out parameters, i.e. CCA-IMT, plaque score and stenoses. Next, the independent contribution of OSA to differences in CCA-IMT was evaluated by multi-way ANOVA. In this model, major factors known to influence carotid wall thickness, i.e. diabetes mellitus, arterial hypertension (systolic blood pressure) and smoking, were simultaneously entered. Finally, the relationship between CCA-IMT and parameters of OSA severity (AHI, indices of nocturnal oxygen desaturation) was tested by calculating Spearman’s correlation coefficients. A p-value <0.05 was regarded as statistically significant.

**RESULTS**

**Patient characteristics**

The anthropometric, clinical and laboratory data of the OSA group and the control group are summarised in table 1. The sleep recordings demonstrated moderate-to-severe sleep-disordered breathing in the OSA group, whereas nocturnal breathing and sleep architecture were normal in the control subjects.

**TABLE 1** Anthropometric, clinical and laboratory data of the obstructive sleep apnoea (OSA) patients and the controls

|                          | OSA group          | Control group        | p-value |
|--------------------------|--------------------|----------------------|---------|
| Patients n               | 35                 | 35                   |         |
| Age yrs                  | 55.7 ± 1.4 (52.0–58.4) | 56.1 ± 1.4 (53.2–59.2) | NS      |
| Males/females            | 34/1               | 34/1                 | NS      |
| BMI kg m⁻²               | 31.9 ± 0.6 (29.4–33.5) | 31.3 ± 0.5 (28.9–33.1) | NS      |
| Arterial hypertension    |                   |                      |         |
| % of patients            | 69                 | 60                   | NS      |
| Daytime blood pressure mmHg |             |                      |         |
| Systolic                 | 136 ± 4 (131–142)  | 132 ± 4 (127/138)    | NS      |
| Diastolic                | 81 ± 3 (78–84)     | 80 ± 2 (77/83)       | NS      |
| Antihypertensive drugs % | 54                 | 54                   | NS      |
| Coronary artery disease %| 19                 | 23                   | NS      |
| Peripheral occlusive vascular disease % | 3 | 3 | NS |
| Smoking                  |                   |                      |         |
| % of patients            | 37                 | 60                   | NS      |
| Pack-ys                  | 14.4 ± 3.9 (5.3–22.6) | 17.0 ± 3.3 (10.2–26.6) | NS      |
| Diabetes mellitus        |                   |                      |         |
| % of patients            | 20                 | 37                   | NS      |
| HbA1c %                  | 6.2 ± 0.2 (5.7–6.7) | 6.1 ± 0.2 (5.7–6.4)  | NS      |
| Antidiabetic drugs %     | 14                 | 26                   | NS      |
| Hypercholesterolaemia    |                   |                      |         |
| % of patients            | 59                 | 57                   | NS      |
| Total cholesterol mg·dL⁻¹ | 230 ± 7 (216–244)  | 219 ± 6 (193–224)    | NS      |
| LDL cholesterol mg·dL⁻¹  | 134 ± 5 (124–145)  | 141 ± 6 (129–153)    | NS      |
| HDL cholesterol mg·dL⁻¹  | 42 ± 1 (39–44)     | 39 ± 2 (33–42)       | NS      |
| Lipid-lowering drugs %   | 17                 | 20                   | NS      |

Data are presented as mean ±SEM (95% confidence interval), unless otherwise stated. BMI: body mass index; HbA1c: glycaated haemoglobin; LDL: low-density lipoprotein; HDL: high-density lipoprotein; NS: nonsignificant.
Extracranial vessel ultrasonography

Mean CCA-IMT was markedly increased in the OSA patients when compared with the control group (table 3). Within the OSA group, multi-way ANOVA showed an independent influence of OSA on CCA-IMT \( (p < 0.01) \). Furthermore, the degree of nocturnal oxygen desaturation was significantly related to CCA-IMT, i.e. those patients with more severe nocturnal hypoxia had greater carotid wall thickness and vice versa (Spearman’s correlation coefficients between CCA-IMT and \( \text{S}_a\text{O}_2 \); \text{mean} \( r = -0.51, p < 0.01 \); lowest \( \text{S}_a\text{O}_2 \); \text{mean} \( r = -0.41, p < 0.05; \text{S}_a\text{O}_2 < 90\% \) \% of TST); \text{mean} \( r = -0.49, p < 0.01 \); fig. 1). CCA-IMT also tended to be related to the AHI; however, this relationship did not reach statistical significance (\( r = 0.33 \)).

Although the degree of plaque formation was rather moderate in both groups, it was more pronounced in the OSA patients when compared with the controls. Five OSA patients were diagnosed to have extracranial vessel stenosis, whereas no patient showed significant narrowing of these arteries in the control group (table 3).

**DISCUSSION**

CCA-IMT was increased in the OSA patients when compared with the control subjects not suffering from sleep-disordered breathing. This observation is in line with the two preceding studies reporting an increase of CCA-IMT in OSA [9, 10]. There are, however, some relevant methodological differences between these studies and the current study. SILVESTRINI et al. [9] employed ambulatory monitoring for the diagnosis of OSA, whereas, in the current study, full-night polysomnography was used in all patients investigated. Moreover, in both earlier studies evaluating carotid vessel pathology in OSA, IMT was determined at both the far and near walls of the CCA. In contrast, the present authors measured IMT only at the far wall of the CCA. This site of measurement is generally recommended, since the thickness of the intima media complex may

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**TABLE 2** Polysomnographic data of the obstructive sleep apnoea (OSA) patients and the controls

|                      | OSA group | Control group | p-value |
|----------------------|-----------|---------------|---------|
| Patients n           | 35        | 35            |         |
| AHI n h\(^{-1}\)     | 57 ± 3 (45–66) | 4 ± 1 (2–6)   | <0.01   |
| Mean \( \text{S}_a\text{O}_2 \) % | 91.1 ± 0.6 (89.9–92.9) | 94.5 ± 0.9 (92.1–96.6) | <0.05   |
| Lowest \( \text{S}_a\text{O}_2 \) % | 67.2 ± 2.0 (58.8–72.1) | 87.2 ± 1.0 (84.3–89.5) | <0.01   |
| \( \text{S}_a\text{O}_2 < 90\% \) (% of TST) | 25.9 ± 3.6 (18.8–31.4) | 1.9 ± 0.6 (0.7–2.5) | <0.01   |
| NREM 1–2 (% of TST)  | 73 ± 2 (63–79) | 62 ± 2 (56–68) |         |
| NREM 3–4 (% of TST)  | 15 ± 2 (10–18) | 25 ± 3 (18–31) | <0.05   |
| REM (% of TST)       | 12 ± 1 (8–14)  | 13 ± 2 (10–16) |         |
| Sleep efficiency (% of TIB) | 69 ± 2.1 (56–74) | 78 ± 1.9 (69–81) |         |
| Arousal index n h\(^{-1}\) | 45 ± 2 (37–64) | 14 ± 1 (8–16) | <0.01   |

Data are presented as mean ± SEM (95% confidence interval), unless otherwise stated. Statistics were performed using the Mann-Whitney U-Wilcoxon rank sum W-test for continuous variables and Chi-squared analysis for categorical variables. AHI: apnoea-hypopnoea index; \( \text{S}_a\text{O}_2 \): oxygen saturation; TST: total sleep time; NREM: non-rapid eye movement; 1+2: light sleep; 3+4: deep sleep; REM: rapid eye movement; TIB: time in bed; NS: nonsignificant.

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**TABLE 3** Common carotid artery-intima media thickness (CCA-IMT), plaque formation and stenoses of large extracranial vessels in the obstructive sleep apnoea (OSA) patients and the controls

|                      | OSA group | Control group | p-value |
|----------------------|-----------|---------------|---------|
| Patients n           | 35        | 35            |         |
| CCA-IMT left         | 1.04 ± 0.04 (0.93–1.13) | 0.80 ± 0.02 (0.74–0.85) | <0.01   |
| CCA-IMT right        | 1.03 ± 0.04 (0.92–1.10) | 0.79 ± 0.02 (0.74–0.85) | <0.01   |
| CCA-IMT combined     | 1.04 ± 0.04 (0.93–1.12) | 0.79 ± 0.02 (0.74–0.85) | <0.01   |
| Plaques              |           |               |         |
| Grade 0 %            | 14        | 36            | <0.05   |
| Grade 1 %            | 37        | 54            | NS      |
| Grade 2 %            | 40        | 7             | <0.01   |
| Grade 3 %            | 9         | 3             | NS      |
| Plaque score         | 1.43 ± 0.14 (1.10–1.62) | 0.96 ± 0.13 (0.83–1.17) | <0.05   |
| Stenoses %           | 14        | 0             | <0.05   |

Data are presented as mean ± SEM (95% confidence interval), unless otherwise stated. Statistics were performed using the Mann-Whitney U-Wilcoxon rank sum W-test for continuous variables and Chi-squared analysis for categorical variables. NS: nonsignificant.
be substantially underestimated when taken at the near wall [17]. The reason for this observation is that localised pressure of the ultrasonographic transducer head compresses the near arterial wall.

The current authors enrolled OSA patients with a wide spectrum of comorbidity and aimed to match these patients with the controls. This was important as numerous factors are known to influence CCA-IMT. Among these are anthropometric parameters (i.e. age, body weight and sex), individual smoking habits and pre-existing cardiovascular disease or metabolic disorders (i.e. diabetes mellitus, hypercholesterolaemia) [18, 19]. Statistical analysis revealed that all of these variables were homogeneously distributed between the OSA group and the control group, and that the presence of OSA had an independent influence on CCA-IMT. Nevertheless, it has to be kept in mind that the conditions/diseases impacting on CCA-IMT might display significant variations in their duration and severity. Thus, using the broad selection criteria of the present study, it was virtually impossible to fully match the OSA and non-OSA groups.

In order to determine if OSA alone increases CCA-IMT, a study of OSA patients without any disease and not on medication compared with well-matched healthy controls would be optimal. Further possible limitations of this study were the relatively low numbers of patients in both groups and the fact that the findings might only be applicable to the male sex.

The most prominent finding of the current study was that CCA-IMT in the OSA group was significantly related to the degree of nocturnal oxygen desaturation. This is in line with the data of Suzuki et al. [11]; however, it should be noted that these authors mainly included patients with only mild nocturnal hypoxia. Accordingly, the mean CCA-IMT in this study was markedly lower than in the current study, and in a range that is usually not considered to be associated with an increased cardiovascular risk (0.84 mm).

In the present authors’ opinion, the close relationship between indices of oxygen desaturation and CCA-IMT lends support to the well-known hypothesis that chronic intermittent hypoxia is the major stimulus for the development of atherosclerosis in OSA [3]. In this context, it has long been postulated that systemic hypoxia may be an important cause of atherosclerosis [20, 21]. First, animal models have shown that chronic hypoxia might lead to the evolution of atherosclerotic lesions [22, 23]. Secondly, cell culture experiments performed under hypoxic and normoxic conditions have suggested numerous mechanisms by which hypoxia might provoke vascular remodelling [24]. Finally, concerning the condition of OSA, a growing number of vascular disease biomarkers has been reported to be specifically altered in these patients. For example, patients with OSA have higher levels of circulating catecholamines, reduced endothelial nitric oxide generation and increased oxidative stress [25–27]. Furthermore, inflammatory markers of atherosclerosis, such as C-reactive protein, cytokines and vascular adhesion molecules, are upregulated [28–30]. Platelet activation and an increase in fibrinogen levels might also play important roles [31, 32].

These biochemical and cellular changes within the vascular micromilieu probably lead to endothelial dysfunction and thereby to atherosclerosis. Of note, it has recently been demonstrated that otherwise healthy OSA patients exhibit impaired brachial artery flow-mediated vasodilation, and that this phenomenon is equally related to parameters of OSA severity, such as the AHI and the degree of nocturnal hypoxia [33]. As the majority of the aforementioned changes are reversible after CPAP ventilation, the intriguing question that arises is if CCA-IMT decreases in long-term users of this form of therapy.

Another striking observation was that the OSA patients had more severe plaque formation than the controls. Furthermore, five of the 35 OSA patients had significant extracranial vessel stenosis, whereas all control patients were free from such lesions. These data seem to be in favour of a significant effect of OSA also on the later stages of atherosclerosis. However, it is thought that this needs to be corroborated in larger numbers of patients. Furthermore, it has to be considered that the evaluation of plaque formation employed in the current study was rather qualitative. Measurements of plaque cross-sectional area or even volume are more accurate and meaningful [34]. These issues have to be addressed by future studies.

In summary, common carotid artery-intima media thickness is increased in untreated obstructive sleep apnoea patients and is related to the degree of nocturnal hypoxia. Moreover, obstructive sleep apnoea is possibly linked to an increased risk of plaque formation and extracranial vessel stenosis. These findings are in favour of an independent influence of obstructive sleep apnoea on early and late atherosclerotic changes of the arterial wall, and represent further strong arguments for obstructive sleep apnoea being a risk factor on its own for the emergence of vascular disease.

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**FIGURE 1.** Correlation between common carotid artery-intima media thickness (CCA-IMT) and the degree of nocturnal oxygen desaturation (time spent with oxygen saturation ($\text{S}_\text{ao}_2$)<90% as a percentage of total sleep time (TST)) in the patients with obstructive sleep apnoea ($r=0.49$; $p<0.01$).
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