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Obstructive sleep apnoea and signal averaged electrocardiogram

S. Andreas, B. von Breska, A. Schaumann, B.D. Gonska, H. Kreuzer

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ABSTRACT: Patients with obstructive sleep apnoea demonstrate an increased rate of ventricular arrhythmias. The present study was designed in order to investigate whether these arrhythmias may be related to myocardial injury, since myocardial injury of various aetiologies has been observed to change the signal averaged electrocardiogram (ECG).

Signal averaged ECG was registered in 23 patients with obstructive sleep apnoea diagnosed by polysomnography (apnoea index 43±20 events·h^{-1}, age 55±10 yrs). QRS duration, root mean square voltage of the last 40 ms of QRS, and low amplitude (<40 mV) signal duration were determined from the vector magnitude of the QRS, high-pass filtered at 40 Hz. Patients with coronary heart disease or bundle branch block were excluded.

No patient showed an abnormal signal averaged ECG. Mean duration of the filtered QRS complex was 96±9 ms, root mean square voltage 38±18 μV and low amplitude signal duration 26±8 ms. These results were not significantly different from 14 snoring subjects with an apnoea/hypopnoea index <10. Four patients showed no ventricular arrhythmias and six patients had Lown III or IVa in the Holter ECG. Echocardiography revealed increased left atrial (43.7±4.1 mm) and interventricular septal diameters (11.3±1.4 mm).

In conclusion, obstructive sleep apnoea does not generate a substrate for late potentials in the signal averaged ECG.

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Dept of Cardiology and Pneumology, University of Göttingen, Germany.

Correspondence: S. Andreas
Abteilung Kardiologie und Pneumologie
Universitätsklinikum
Robert-Koch-Str. 40
37075 Göttingen
Germany

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Obstructive sleep apnoea (OSA) is a common disease mainly affecting obese subjects. It is characterized by recurring upper airway collapse with ongoing respiratory effort during sleep, causing apnoea, negative intrathoracic pressure, and a fall in arterial oxygen saturation. Cardiac arrhythmias and conduction disturbances are common in OSA patients [1–8], and may be related to increased mortality in this disease [9, 10]. Tracheostomy is effective in preventing arrhythmias and conduction disturbances in severely affected patients [1]. However, it was recently found that in patients with only moderate OSA and a low incidence of cardiac or pulmonary disease the rate of ventricular arrhythmias was not increased [11]. In patients with myocardial injury due to various cardiac disorders, the occurrence of late potentials in the signal averaged electrocardiogram (ECG) was shown to be related to ventricular arrhythmias and sudden death [12–16]. The present study investigates whether late potentials are present in OSA patients without evidence of coronary heart disease, and whether they are related to ventricular arrhythmias.

Subjects and methods

Twenty eight consecutive male patients with OSA were examined in the sleep laboratory. Three of the patients had a complete right bundle branch block and two had a history of coronary heart disease, and were therefore excluded. Of the remaining patients, 12 were treated for known arterial hypertension (calcium antagonist in six, angiotensin converting enzyme inhibitor in four, diuretics and beta-blockade in two patients). Two other patients (Nos. 11 and 18) without antihypertensive treatment showed systemic arterial hypertension on three different occasions at rest (systolic blood pressure >160 mmHg or diastolic blood pressure >95 mmHg). None of the subjects investigated showed significant ST segment depressions during exercise, was on digitalis, or was hypokalaemic. Echocardiography had not revealed any significant valvular lesion. Two patients (Nos. 21 and 23) had mild obstructive lung disease. The OSA patients were compared with 14 subjects in whom OSA was suspected by a history of snoring with occasional apnoeas but was excluded by polysomnography (apnoea/hypopnoea index <10). Informed written consent was obtained from all subjects. The study was approved by the local Ethics Committee.

Polysomnography

The patients were monitored during a single night as described previously [17]. Electrodes for electroencephalogram (C3A2 and C4A1 of the international 10–20

system), electro-oculogram, electromyogram and electrocardiogram were positioned after skin cleansing. Airflow over the nose and mouth was recorded by thermistors, and thorax and abdominal wall motion was monitored (Respiration Monitor, Densa Ltd). Arterial oxygen saturation (Sa_{O_2}) was measured transcutaneously by pulse oximetry (Micro span 3040G). The polysomnogram was visually analysed in 30 s epochs, according to Rechtschaffen and Kales, on monitor (CNS sleep lab, 1000/AMPs). An apnoea was considered obstructive when nasal and oral flow were absent in the presence of abdominal or thoracic movements. Hypopnoea was scored if the amplitude of the respiratory movements decreased to 50% of the effort signals preceding the hypopnoea. All apnoeas and hypopnoeas were required to have a duration of at least 10 s. Mean Sa_{O_2} was calculated as the average nadir oxygen saturation during the obstructive apnoeas. OSA was diagnosed when the apnoea/hypopnoea index was ≥10. The apnoea/hypopnoea index is calculated as: obstructive apnoeas + hypopnoeas during total sleep time/total sleep time. Spirometry was performed. Vital capacity and forced expiratory capacity in one second was given as percentage predicted [18].

Signal averaged ECG

Signal averaged ECG measurements were obtained with the Corazonix predictor system (Oklahama, USA) using a bipolar X, Y and Z lead in the supine position the morning following polysomnography. Silver chloride electrodes were placed on the skin, according to the standards for analysis of ventricular late potentials [19]. Data were sampled with 2,000 Hz. Noise was measured in the average signal and was accepted only at <0.4 μV. A bidirectional filter was used (low pass filter at 250 Hz and high pass filter at 40 Hz). The trigger point was based on the earliest onset of QRS activity. The signal averaged ECG was considered to be pathological if: 1) the filtered (40 Hz) QRS duration was greater than 114 ms; and 2) root mean square voltage of the last 40 ms of QRS was less than 20 μV, and low amplitude (<40 mV) signal duration was >38 ms [19].

Holter ECG and echocardiography

Twenty four hour tracings were obtained with a two-channel recorder (Tracker, Reynolds). The tapes were analysed by a rapid scanner with visually superimposed ECG imaging (Reynolds Pathfinder 3 Mk II). This was carried out by a technician and one of the investigators. ECG print-outs were obtained for verification by visual inspection. Ventricular ectopic activity was graded according to the Lown classification [20]. Left atrial, interventricular septal, left ventricular posterior wall and left ventricular end-diastolic diameter were obtained by M-mode echocardiography from a left parasternal view [21]. A 2.5 MHz transducer (Hewlett Packard, Sonos 1000) was used.

Exercise ECG

Upright bicycle exercise ECG was performed, the workload being increased by 50 W every 3 min. Blood pressure was registered every minute throughout. At the end of exercise, heart rate had to be at least 85% of the calculated maximal heart rate. A ST segment depression of >0.1 mV in the precordial leads was considered positive. Exercise hypertension was recorded if maximal systolic blood pressure during exercise exceeded 210 mmHg.

Statistics

All variables were tested for normal distribution and are presented as mean±standard deviation. Dichotomous data, such as the absence or presence of arterial hypertension, were analysed by Chi-squared test. The two groups of patients were compared using the two tailed Student's t-test for unpaired data. An alpha-level of 0.05 and below was considered statistically significant.

The statistical power to detect a 5 mm difference between the OSA patients and the snorers in the diameter of the left atrium was 95%, as was the power to detect a 2 mm difference in the septal diameter. The power to detect a difference of 10% for sleep stages I or II was about 50%, as was the power to detect a difference of 30% in the incidence of Lown classification I or II.

Results

OSA patients were awake less often and showed less slow wave sleep as compared to the 14 snorers (table 1). No patient showed an abnormal signal averaged ECG

Table 1. – Anthropomorphic and polysomnographic data on OSA patients and snorers

	OSA	Snorers
n	23	14
Age yrs	55±10	53±11
BMI $kg \cdot m^{-2}$	34±6	27±6*
AI $events \cdot h^{-1}$	43±20	2±2*
AHI $events \cdot h^{-1}$	51±23	4±2*
Mean Sa_{O_2} %	83±6	90±2*
Min Sa_{O_2} %	66±13	81±5*
VC % pred	91±14	94±13
FEV_1 % pred	86±12	88±9
TIB min	500±29	493±43
TST min	442±51	385±101*
Sleep eff %	88±7	78±18*
Stage I %	40±28	31±18
Stage II %	43±26	47±16
Stage III %	3±0.5	5±5
Stage IV %	0.4±0.1	1.8±0.5*
Stage REM %	14±5	16±8

BMI: body mass index; AI: apnoea index; AHI: apnoea/hypopnoea index; Mean Sa_{O_2}: mean arterial oxygen saturation during apnoeas; Min Sa_{O_2}: minimal arterial oxygen saturation during apnoeas; VC: vital capacity; FEV_1: forced expiratory volume in one second; TIB: time in bed; TST: total sleep time; Sleep eff: sleep efficiency; Stage x: Stage x expressed as % of TST; OSA: obstructive sleep apnoea; REM: rapid eye movement; *: denotes significant differences.

Table 2. – Late potentials in patients with obstructive sleep apnoea

Pt No.	Age yrs	BMI $kg \cdot m^{-2}$	AI $events \cdot h^{-1}$	QRS ms	RMS µV	LAS ms
1	64	30	31	96	31	22
2	51	34	68	114	24	35
3	54	31	45	105	37	26
4	60	29	51	97	34	14
5	63	35	51	90	37	34
6	57	39	60	106	47	23
7	65	33	14	84	68	11
8	59	26	23	99	32	30
9	62	31	51	86	38	21
10	49	37	37	95	58	22
11	60	28	32	105	23	33
12	51	31	38	90	53	17
13	52	31	58	99	34	22
14	32	34	89	91	59	25
15	64	29	15	98	36	24
16	62	38	29	92	28	30
17	57	30	38	88	21	38
18	51	34	61	95	20	43
19	62	27	28	99	28	30
20	43	46	72	83	36	29
21	42	46	60	98	29	27
22	36	32	12	80	94	18
23	49	43	36	115	29	30

Pt: patients; BMI: body mass index; AI: apnoea index; LAS: low amplitude signal duration; QRS: QRS duration; RMS: root mean square.

Table 3. – Data of echocardiography and Holter ECG

	OSA	Snorers
Hypertension n	14 (61)	3 (21)
BP_{sys} mmHg	131±14	126±12
BP_{dias} mmHg	84±11	82±13
LA mm	43.7±4.1	40.2±4.2*
IVS mm	11.3±1.4	10.3±1.8
LVPW mm	11.1±1.4	10.2±1.9
LVED mm	54.4±3.5	52.2±4.1
VEB $>10 \cdot h^{-1}$	6 (26)	2 (14)
Lown 0 n	4 (17)	7* (50)
Lown I+II n	13 (57)	4 (28)
Lown III n	3 (13)	2 (14)
Lown IV n	3 (13)	1 (7)
QRS ms	96±9	96±10
RMS µV	38±18	51±30
LAS ms	26±8	29±11

Values in brackets are in %. ECG: electrocardiogram; Hypertension: patients with systemic arterial hypertension; BP_{sys}: systolic blood pressure; BP_{dias}: diastolic blood pressure; LA: left atrial dimension (normal ≤40 mm); IVS: interventricular septal dimension (normal ≤11 mm); LVPW: left ventricular posterior wall dimension (normal ≤11 mm); LVED: left ventricular end-diastolic dimension (normal ≤56 mm); VEB: ventricular ectopic beat; Lown x: patients with Lown x; LAS: low amplitude signal duration; QRS: QRS duration; RMS: root mean square; *: denotes significant differences.

(table 2). For OSA patients, mean duration of the filtered QRS complex, root mean square voltage and low amplitude signal duration were not significantly different as compared to the snorers (table 3). Cyclical variation of the heart rate was evident in all but four OSA patients, but not in the snorers. There was no sinus arrest >2 s in the Holter ECG. Three patients had Lown III (Nos. 5, 11 and 23) and another three Lown IVa (Nos. 4, 6, and 19). There was no sustained ventricular tachycardia. A significant difference between OSA patients and snorers was demonstrated only in the absence of any ectopic ventricular beats (table 3). In nine OSA patients there was an increase, in seven a decrease and in seven no change in the incidence of ectopic ventricular beats during the night. The hypertensive OSA patients showed larger interventricular septal and posterior wall diameters as compared to the nonhypertensive OSA patients (12.3±1.4 *versus* 10.4±0.5 mm and 11.9±1.4 *versus* 10.2±0.5 mm respectively; $p<0.01$). Other echocardiographic parameters showed no significant difference. Eight patients (Nos. 5, 7–9, 13, 18, 20 and 21) demonstrated exercise hypertension.

Discussion

In the present study, no increased incidence of late potentials was found. The signal averaged ECG allows the detection of late potentials, which have been associated with delayed and disorganized ventricular activation [19]. Diffuse or localized myocardial fibrosis is thought to be the cause of late potentials in coronary heart disease [12, 19], hypertensive heart disease [13, 14], idiopathic dilated cardiomyopathy [16], hypertrophic cardiomyopathy [15], progressive muscular dystrophy, and systemic sclerosis. The occurrence of late potentials in the signal averaged electrocardiogram was found to be related to ventricular arrhythmias and sudden death [12–16]. Since the signal averaged ECG is normal in patients with OSA, it cannot be used to predict or explain ventricular arrhythmias or sudden death in these patients. As various cardiac disorders with myocardial injury exhibit late potentials in the signal averaged ECG, it seems unlikely that significant myocardial injury is present in OSA.

In the OSA group, less patients showed Lown 0 as compared to the snorers, but there was no difference in the presence of simple or complex ventricular arrhythmias (table 3). In normal subjects at our institution, the incidence of Lown I+II was 41%, Lown III 17%, and Lown IV 7% [22], and was thus below the incidence found in the OSA patients (table 3). Ten percent of the normal subjects had more than 10 ventricular ectopic $beats \cdot h^{-1}$ [22]. These findings in normal subjects were consistent with 21 other studies, also there were wide variations in these studies [22]. The modest increase in ventricular arrhythmias in our OSA patients lies between the increase found in studies of patients with severe OSA [1, 2, 4, 7, 8] and patients with less severe OSA [11]. Ventricular arrhythmias were reported to be frequent in OSA patients, especially if Sa_{O_2} was lower than 60%, but no control group was reported [1, 2, 4, 6, 8].

In contrast to some former studies, in which cardiac and pulmonary diseases were not excluded [1, 2, 6, 8], we did not notice ventricular tachycardias. However, cardiac and pulmonary disease is important in the pathogenesis of arrhythmias. KOEHLER *et al.* [4] observed ventricular tachycardias only in OSA patients with coronary

heart disease. Recently, FLEMONS *et al.* [11] found that the prevalence of cardiac arrhythmias was not increased in mild OSA with a low incidence of cardiac comorbidity. The apnoea/hypopnoea index however, was 33 in their study and, hence, lower than our data and those of former studies [1–8]. There was no difference in the incidence of ventricular arrhythmias during day and night in our patients. This corresponds to some [4, 6] but not all [1, 8] previous studies. That the cyclical variation of the heart rate, accompanied by conduction abnormalities in some patients, is strongly associated with the apnoeas and, therefore, with sleep has been demonstrated in all studies [1–8].

The mechanism causing ventricular arrhythmias in OSA is complex. Systemic hypertension, which is common in OSA, causes ventricular arrhythmias [23–25]. Reversible impairment of left ventricular contractility and changes in the autonomic nervous system were demonstrated in OSA, and can also cause ventricular arrhythmias [3, 23, 26]. Arousal stimuli during sleep are frequently associated with bursts of sympathetic nerve activity in normal subjects [27]. It is conceivable that the sympathetic activation accompanying the arousals during obstructive apnoeas may also be a cause of ventricular arrhythmias [26]. Myocardial ischaemia causes arrhythmias, but was demonstrated only in OSA patients with coronary heart disease [4].

Our patients showed concentric left ventricular hypertrophy and increased left atrial diameter (table 3). This is not surprising, since systemic hypertension causes concentric hypertrophy and left atrial dilatation [28]. Furthermore, obesity augments cardiac output, stroke volume and left ventricular filling pressure, thereby leading to eccentric myocardial hypertrophy and left atrial dilatation [29]. Our findings are in agreement with other studies showing left ventricular hypertrophy [30], and left atrial enlargement [5, 30] in OSA patients. However, HANLY *et al*. [31] reported no left ventricular hypertrophy. This may be explained by their somewhat less obese and hypertensive patients. The small differences in echocardiographic parameters between the OSA patients and snorers in our study and that of HANLY *et al.* [31] might be due to the high incidence of obesity and hypertension in the snorers. A high incidence of exercise-induced hypertension was demonstrated in our study. The prognostic implications of this finding are still unclear [32].

OSA patients showed less slow wave sleep as compared to the snorers (table 1). This is in agreement with the current opinion that repetitive apnoeas disturb sleep. That the difference between the two groups were only small corresponds to other studies [31]. That the OSA patients were less awake as compared to the snorers (table 1) can be explained by their increased sleepiness, enabling them to fall asleep faster during the first night in an unfamiliar environment.

Limitations of the study

In this as in other studies [11, 30, 31], the OSA patients were compared to subjects in whom OSA was suspected but was excluded by polysomnography, and who were, therefore, likely to be overweight and hypertensive. This may well have influenced the occurrence of ventricular arrhythmias, sleep disturbances and certainly left ventricular hypertrophy [25, 28]. However, we were primarily interested in the relationship between OSA and the signal averaged ECG and, hence, needed a control group similar to the OSA patients. The number of patients enrolled was quite small, especially when analysing parameters with large variations, such as arrhythmias. This resulted in a high type II error, as indicated by the low power of the t-test. Therefore, we might have underestimated pathological findings in our OSA patients.

In conclusion, OSA does not generate a substrate for late potentials in the signal averaged ECG. Thus, it seems unlikely that ventricular arrhythmias in these patients are caused by a change in myocardial structure.

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