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Outcomes in Coronary Artery Disease Patients with Sleepy Obstructive Sleep Apnoea on CPAP

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Methods

Sleep recordings - Cardiorespiratory polygraphy at home

Ambulatory, limited cardiorespiratory polygraphy (CRPG) sleep study was performed with the Embletta® PDS (Portable Digital System) device (Embla, Broomfield, CO, USA). This consisted of the following: 1) nasal pressure detector using nasal cannulae/pressure transducer system, recording the square root of pressure as an index of flow; 2) thoraco-abdominal movement detection from two XactTrace™ inductive belts with respiratory inductance plethysmography (RIP) technology; 3) finger pulse oximeter detecting heart rate and oxyhemoglobin saturation (SpO_2); and 4) body position and movement detection. The patient's sleep time was estimated based on self-reporting and patterns of body movement during the sleep study. Patients with an estimated sleep time of <4 hours were offered a new home-based sleep study. Apnoeas were defined as an almost complete (≥90%) cessation of airflow. Hypopnoeas were defined as a ≥50% reduction in thoracoabdominal movement and/or a ≥50% decrease in the nasal pressure amplitude for ≥10 seconds (E1, E2). In addition, the total number of significant oxyhemoglobin desaturations (decrease of ≥4% from the immediately preceding baseline) were scored, and the oxygen desaturation index (ODI) was calculated as the number of significant desaturations per hour of estimated sleep. Events with a ≥30% reduction in thoracoabdominal movement and/or a ≥50% decrease in the nasal pressure amplitude for ≥10 seconds were also scored as hypopnoeas if there was a significant desaturation (≥4%). Patients with an apnoea-hypopnoea index (AHI) ≥15 per hour of estimated sleep time, independent of symptom occurrence, were defined as having OSA. All baseline screening recordings were scored by the same observer (YP).

Overnight polysomnography in hospital

All patients with CAD and a diagnosis of OSA based on the first CRPG screening investigation underwent unattended overnight polysomnography (PSG) in hospital (Embla A10®, Embla,

Broomfield, CO, USA) for the comparison between sleepy versus non-sleepy OSA phenotypes as one of the secondary analyses (E3). The PSG system included sleep monitoring via three-channel electroencephalography, two-channel electrooculography, one-channel submental electromyography (EMG), bilateral tibial EMG and two-lead electrocardiogram in addition to the CRPG channels as described above. PSG recordings were scored based on 30-second epochs according to the Rechtschaffen and Kales criteria (E4) by an observer blinded to clinical data and baseline screening results from the previous CRPG recordings. Obstructive events on the PSGs were scored according to the same AASM criteria applied to the CRPG recordings (E1). CAD patients without OSA on PG did not undergo overnight PSG in hospital because AHI values of <5/h on the PG system used have been shown to reliably exclude OSA (E5).

Epworth Sleepiness Scale

The Epworth Sleepiness Scale (ESS) questionnaire was used to assess subjective excessive daytime sleepiness (E6). This questionnaire contains eight questions to evaluate the chance of dozing off under eight scenarios in the past month. Each item is scored from 0 to 3 for a total score ranging from 0 to 24. Excessive daytime sleepiness was defined as an ESS score of ≥10.

Baseline assessments

Venous blood samples were drawn between 07.00 and 08.00 hours in the morning following overnight PSG, after a fast of ≥10 hours, for determination of secondary endpoints as described previously (E3). Other assessments included quality of life questionnaires and echocardiographic investigations at baseline before the start of the randomized controlled trial (RCT) period (E3).

Group assignment, randomization, interventions, and follow-up

Group assignment was based on the cardiorespiratory PG recordings. In-hospital PSG for OSA patients the day before start of the RCT was mainly planned for subsequent studies evaluating sleep architecture in different OSA phenotypes as well as for comparison with the baseline PG

recordings (E3). Scoring of the PSGs was done later during the follow-up period and group allocation was not changed on the basis of these results. Patients allocated to CPAP treatment were informed about the technical procedure in the morning after overnight PSG and provided with an automatic (self-titrating) CPAP device (S8®, or S9®; ResMed, San Diego, CA, USA) and a nasal or full-face mask and humidifier by trained staff at the study center. All participants assigned to CPAP were instructed to use the device at home every night for ≥4 hours, contacted by telephone after one week and given a check-up in the clinic after 1 month, 3 months, 6 months, 1 year, and then yearly to the end of the main study. All patients in the observational arm were evaluated at 3, 6, and 12 months, and annually thereafter, and were given standard cardiology treatment by their physicians. A new PG sleep recording was performed in all patients at 3 and 12 months, and annually thereafter (with CPAP in treated OSA patients).

Adherence to CPAP

Patients with OSA receiving CPAP treatment brought their device to the clinic at each scheduled follow-up visit; monitoring settings and hours of CPAP use were obtained from the internal clocks and recorded. In addition, pressure level, mask leak and residual AHI measures were noted. All necessary adjustments of the CPAP device and mask fittings were done according to clinical routines by the sleep medicine unit staff.

Cardiovascular endpoint criteria

An Independent Clinical Event Committee (ICEC) reviewed all data obtained from hospital records and death certificates by the end of May 2013, blinded to personal identity and group allocation. The ICEC review was based on a previously described definition of the endpoints (E7), which was applied in the HOT study (E8), and other trials. In summary, overall mortality was based on the death certificate. Cardiovascular mortality was defined as death from any of the following: myocardial infarction, stroke (cerebral hemorrhage or cerebral infarction), ruptured

aortic aneurysm (thoracic or abdominal), heart failure (as determined by the treating physician), sudden death with no cause other than presumed cardiac (malignant arrhythmias), death during or within 28 days of CABG or PCI, and pulmonary embolism. Myocardial infarction was defined as ≥2 of the following signs/symptoms: sudden chest pain and/or sudden shortness of breath and/or syncope; new left bundle branch block or new ST-elevation or transient ST- or T-wave changes; increase of troponin I levels to >0.10 μg/L in ≥2 samples or increases in myocardial necrosis biomarkers (other causes of troponin elevation should be excluded). Evidence of myocardial infarction at autopsy could also be used as a single criterion. Stroke was defined as sudden onset of focal neurological signs lasting >24 hours (other causes such as brain tumor, subdural or epidural hematoma, subarachnoid haemorrhage, psychosomatic, peripheral nerve lesions should be excluded). Stroke was defined as cerebral hemorrhage if computed tomography (CT) or magnetic resonance imaging (MRI) of the brain showed intracerebral blood, and as cerebral infarction if early CT brain was normal and subsequent follow-up was compatible with stroke, or if later CT brain or MRI showed signs of infarction; or, as a single criterion, evidence of cerebral haemorrhage or infarction at autopsy and determined by the pathologist as the cause of death. CABG was defined as an operation with grafts to coronary arteries, and PCI was defined as dilatation of the coronary arteries with or without stents. Pulmonary embolism was defined as sudden onset of chest pain and/or shortness of breath and/or syncope together with typical CT findings of the pulmonary arteries or pulmonary scintigraphy. Aortic aneurysm (either thoracic or abdominal) was defined as all 3 of: sudden onset of chest pain or abdominal pain; typical findings on chest or abdominal radiography or ultrasound; need for intervention (blood pressure treatment, or surgery, or percutaneous transluminal intervention with or without stent). Acute hospital admissions for cardiovascular reasons included myocardial infarction, stroke, pulmonary embolism, aortic aneurysm (as defined above) as well as acute hospital admissions for heart

failure, transient ischemic attacks, chest pain of presumed cardiac origin (e.g. angina pectoris), peripheral emboli, atrial fibrillation and other cardiac arrhythmias, and intermittent claudication.

Data collection and analysis

The primary outcome variables were documented prospectively and were not subject to observer bias. Baseline comorbidity data, results of sleep recordings, and CPAP compliance data were prospectively recorded in separate files at a specific server of the study hospital by research personnel blinded to study group allocation and/or unaware of the study outcomes.

Results

Comparison between home CRPG and in-hospital PSG

All OSA patients underwent unattended overnight PSG in hospital after baseline CRPG recordings (median 28 days, range 5-119 days). The mean total sleep time (TST) recorded during PSG was 394±92 minutes compared with 416±67 minutes estimated sleep time during CRPG ($P = 0.022$). Moreover, time spent in the supine position was 32.9±25.7% on home PG and 40.8±25.7% on PSG ($P < 0.001$). As expected, mean AHI values were higher on PSG (41.5±24.3/h) compared with those on PG (31.6±16.2/h; $P < 0.001$) because home PG usually underestimates the AHI due to recording time exceeding actual sleep time. As illustrated in eFigure 1, there was a linear correlation between AHI values based on PG versus those obtained using PSG (r=0.589; $P < 0.001$). Of patients who had an AHI ≥15/h on home-based PG, 19 had mild OSA (AHI ≥5/h to <15/h), and only 1 had no OSA (AHI <5/h) according to PSG. However, repeat PG recordings and data from the CPAP device in this treated patient was supportive of the initial group allocation (eTable 2).

Table E1. Coronary angiography findings (lesion types) and intervention characteristics at baseline (between-group differences were not statistically significant).

	Sleepy OSA on CPAP	**No-OSA**
Patients who underwent PCI	n=115	n=94
Number of vessels involved		
One-vessel disease	67	60
Two-vessel disease	37	29
Three-vessel disease	6	4
Missing data	5	1
Intervention type		
Acute/Subacute	82	71
Elective	33	23
Stent type		
Bare-metal stent	84	67
Drug-eluted stent	21	20
Missing data about stent type	7	5
Balloon dilation without stent	1	2
Missing data about stent or no-stent	2	0
Number of stents per patient		
One	87	66
Two	19	16
Three or more	6	10
Stent length per patient, mm	23.4 (14.4)	24.1 (15.3)

Patients who underwent CABG	n=40	n=18
Number of vessels involved		
One-vessel disease	2	2
Two-vessel disease	10	17
Three-vessel disease	26	8
Missing data	2	1
By-pass grafts		
Arterial only	3	2
Venous only	5	2
Both	21	7
Missing data	11	7

Values are % patients, apart from stent length, which is reported as mean (standard deviation).

Definition of abbreviations: CABG = coronary artery bypass grafting; CPAP = continuous positive airway pressure; OSA = obstructive sleep apnoea; PCI = percutaneous coronary intervention.

Table E2. Results of repeated sleep recordings and follow-up data for the OSA patient who demonstrated AHI <5/h on in-hospital PSG

	TST* (min)	**Time spent in supine position (%)**	**Overall AHI (/h)**	**Overall ODI (/h)**	**CPAP pressure (95th percentile; cmH_2O)**	**Adjusted CPAP usage (h/night) x (nights/period)†**
At baseline (PG)	364	19.7	25.9	13.9	-	-
At baseline (PSG)	274	2.0	3.1	3.3	-	-
At 3 months (on CPAP)	-	-	3.1†	-	11.0†	5.8
At 1 year (PG with CPAP)	489	15.4	2.2	2.0	10.9†	4.1

Definition of abbreviations: AHI = apnoea hypopnoea index; CPAP = continuous positive airway pressure; ODI = oxygen desaturation index; OSA = obstructive sleep apnoea; PG = polygraphy; PSG = polysomnography; TST = total sleep time.

*Estimated sleep time for PG recordings; - Not applicable; †Obtained from the CPAP device.

Table E3. CPAP compliance data over time in 155 revascularized patients with coronary artery disease and sleepy obstructive sleep apnoea (patients who returned the devices are excluded)

	Number of patients on CPAP	**Number of CPAP devices checked**	**CPAP use (hours/night)**	**CPAP use (% nights/period)**	**CPAP pressure (95th percentile; cmH_2O)**	**Residual AHI (events/hour)**
At 1 month	146	135	4.9 (2.2)	80.9 (44.0)	10.2 (2.3)	7.0 (1.3)
At 3 months	135	128	5.2 (2.0)	78.5 (25.3)	10.0 (1.8)	6.5 (4.1)
At 6 months	125	118	5.5 (1.8)	74.8 (271)	10.3 (2.6)	5.6 (3.2)
At 1 year	119	116	5.7 (1.6)	76.4 (22-7)	10.3 (2.2)	5.5 (3.2)
At 2 years	115	109	5.9 (1.5)	74.3 (24.2)	10.4 (1..9)	5.1 (2.6)
At 3 years	85	86	6.1 (1.5)	76.2 (22.3)	10.5 (2.6)	5.1 (2.6)
At 4 years	60	57	6.0 (1.5)	74.2 (21.0)	10.0 (1.9)	6.0(3.8)
At 5 years	33	22	6.1 (1.3)	76.2 (17.1)	10.2 (1.6)	5.4 (2.8)
At 6 years	13	10	7.2 (0.6)	80.6 (21.2)	10.7 (1.3)	7.2 (6.0)

Values are number of patients or mean (standard deviation).

Definition of abbreviations: AHI = apnoea hypopnoea index; CPAP = continuous positive airway pressure.

Table E4. Number of individual primary and secondary endpoint events (between-group differences were not statistically significant).

	Sleepy OSA on CPAP	**No-OSA**
Overall	n=155	n=112
Repeat revascularization	25	13
Acute myocardial infarction	20	9
Stroke	4	3
Cardiovascular death	4	3
Noncardiovascular death	4	1
Acute hospital admissions for CVD	39	28
Patients who underwent PCI	n=115	n=94
Repeat revascularization	22	12
Acute myocardial infarction	17	8
Stroke	4	3
Cardiovascular death	3	2
Noncardiovascular death	2	1
Acute hospital admissions for CVD	36	25

Patients who underwent CABG	n=40	n=18
Repeat revascularization	3	1
Acute myocardial infarction	3	1
Stroke	0	0
Cardiovascular death	1	1
Noncardiovascular death	2	0
Acute hospital admissions for CVD	3	3

Definition of abbreviations: CABG = coronary artery bypass grafting; CVD = cardiovascular disease; CPAP = continuous positive airway pressure; OSAS = obstructive sleep apnea syndrome; PCI = percutaneous coronary intervention.

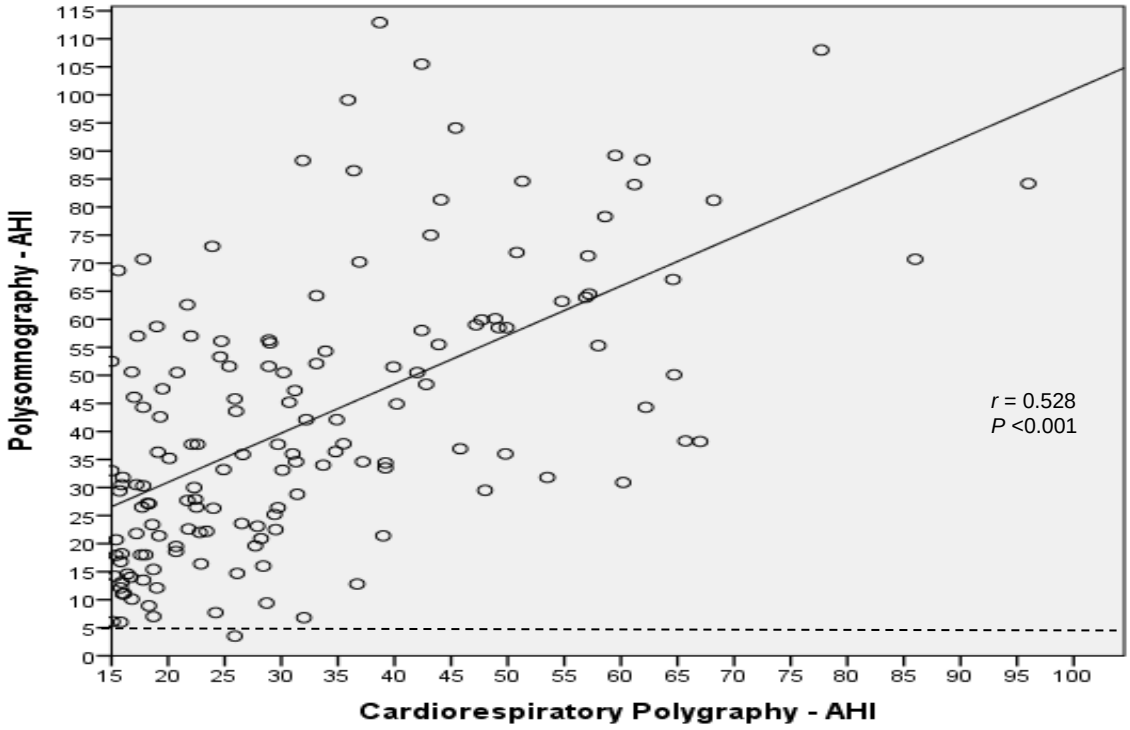
Table E5. Cox regression analysis of baseline covariables associated with risk for adverse cardiovascular outcomes in revascularized patients with coronary artery disease and sleepy obstructive sleep apnoea adherent with continuous positive airway pressure at 2-years' follow-up versus no obstructive sleep apnoea (n=227; 46 patients reached the composite endpoint).

	Univariate			Multivariate		
	Hazard Ratio	**95% CI**	***P* Value**	**Hazard Ratio**	**95% CI**	***P* Value**
Sleepy OSA on CPAP vs. no-OSA	1.60	0.89-2.90	0.119	1.21	0.45-3.22	0.704
Age	1.05	1.01-1.09	0.007	1.05	1.00-1.09	0.040
Females vs. males	0.55	0.22-1.39	0.204	0.46	0.17-1.21	0.115
Apnoea-hypopnoea index	1.01	0.99-1.02	0.230	1.00	0.98-1.03	0.903
Body mass index	1.03	0.97-1.09	0.287	1.03	0.95-1.11	0.546
CABG vs. PCI	0.42	0.17-1.06	0.067	0.34	0.12-0.98	0.045
Current smoking	0.47	0.19-1.19	0.111	0.63	0.24-1.68	0.356
Hypertension	1.62	0.89-2.94	0.116	1.39	0.74-2.61	0.305

Diabetes mellitus	1.75	0.92-3.33	0.088	1.36	0.66-2.77	0.403
Acute myocardial infarction	0.98	0.55-1.75	0.937	0.86	0.43-1.72	0.665
Previous PCI or CABG	2.23	1.19-4.18	0.012	1.66	0.83-3.31	0.154
Pulmonary disease	1.31	0.55-3.09	0.540	1.11	0.45-1.75	0.823
LVEF	0.99	0.95-1.02	0.415	1.00	0.96-1.04	0.957

Definition of abbreviations: CABG = coronary artery bypass grafting; CI = confidence interval; CPAP = continuous positive airway pressure; LVEF = left ventricular ejection fraction; PCI = percutaneous coronary intervention.

Figure E1. Apnoea-hypopnoea index (AHI) in patients with obstructive sleep apnoea based on polygraphy versus polysomnography



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