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Sleep patterns in patients with acute coronary syndromes

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ABSTRACT

Background: Little is known about sleep quality in patients with acute coronary syndromes (ACS) admitted to the coronary care unit (CCU). The aim of this study was to assess nocturnal sleep in these patients, away from the CCU environment, and to evaluate potential connections with the disease process.
Methods: Twenty-two patients with first ever ACS, who were not on sedation or inotropes, underwent a full-night polysomnography (PSG) in our sleep disorders unit within 3 days of the ACS and follow-up PSGs 1 and 6 months later.
Results: PSG parameters showed a progressive improvement over the study period. There was a statistically significant increase in total sleep time (TST), sleep efficiency, slow wave sleep (SWS), and rapid eye movement (REM) sleep, while arousal index, wake after sleep onset (WASO) and sleep latency decreased. Six months after the acute event, sleep architecture was within the normal range.
Conclusions: Patients with ACS have marked alterations in sleep macro- and micro-architecture, which have a negative influence on sleep quality. The changes tend to disappear over time, suggesting a relationship with the acute phase of the underlying disease.

1. Introduction

Sleep is a complex and dynamic physiologic state that is necessary for life; sleep architecture is the structural organization of sleep. To maintain sleep and wakefulness it is important that sleep-wake mechanisms work adequately. Several factors can influence these mechanisms negatively and reduce the quantity or quality of sleep. The physiological consequences of sleep deprivation include an increase in pain sensitivity, increases in sympathetic and decreases in parasympathetic cardiac activity, an impaired immune response, alterations in metabolic and endocrine systems, and a reduction in forced expiratory volume and forced vital capacity [1–7]. Furthermore, deprivation of REM sleep can be followed by a REM sleep rebound phenomenon, which may cause an increase in heart rate, hypoxemia, cardiac arrhythmias, and hemodynamic instability [8,9].

Sleep disruption in critical care units, such as the coronary care unit (CCU), is thought to be multifactorial and may leave patients with an acute coronary syndrome (ACS) in states of acute quantitative and qualitative sleep deprivation that can have a negative influence on the underlying disease. The factors involved include environmental ones, such as noise, patient-care interactions, disturbances of the light–dark cycle, mechanical ventilation [10–13], medications such as sedatives and inotropes [14] that might contribute to alterations in circadian rhythms [15], and the severity of illness [16]. Nevertheless, the contribution of each factor to sleep disruption in these patients is not clear.

The very few studies that evaluated sleep in patients in the CCU showed that sleep architecture is altered, with an increase in light sleep, less SWS and REM sleep, and a total sleep time that is not continuous, with frequent arousals [10–12,17–19]. Sleep has been noted to occur during 50–67% of the night and 54–57% of the day [10–12,17,18]. To the best of our knowledge, only one of these studies evaluated patients outside of the CCU environment in order to eliminate any potential environmental contribution to sleep disruption [20]. But the investigators did not objectively assess the possible influence of circadian rhythm disturbances, while the patients studied were heterogeneous with respect to concomitant sleep disorders. We therefore assessed nocturnal sleep quality in a homogeneous group of patients with ACS, who had no other medical or sleep disorder.

The aim of our study was to assess nocturnal sleep in ACS patients and to evaluate potential connections with the disease process. The study was carried out in our sleep disorders unit, away from the CCU environment, 3 days after the acute event, and 1

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and 6 months later. Our hypothesis was that ACS could be a cause of several alterations in sleep macro- and micro-architecture. These changes are probably not related to the CCU environment, but to the main disease (ACS), and represent a transient phenomenon which resolves over time.

2. Methods

2.1. Patients

Consecutive patients admitted to the CCU with a first ever ACS and with preserved left ventricular systolic function (left ventricular ejection fraction, LVEF > 40%) were asked to participate voluntarily in this study. The selected patient group included subjects with first ever acute myocardial infarction (AMI) and acute EKG changes (i.e., ST segment elevation greater than 1 mm in two contiguous leads, new Q waves, ST segment depression or T wave inversion), along with positive cardiac enzymes and unstable angina. Exclusion criteria included confused patients, patients who had received sedatives or narcotics within the previous 48 h, inotropes on the day of the sleep study, post cardiac arrest patients, patients with chronic obstructive pulmonary disease, severe bronchial asthma, history of psychiatric disorders, stroke or sepsis, hemodynamic instability, or need for mechanical ventilation and cardiac assist, current smoking and concomitant sleep-breathing disorders (history of diagnosed obstructive sleep apnea [OSA]), restless legs syndrome (RLS) and periodic leg movement disorder (PLMD), based on the 2nd edition of the International Classification of Sleep Disorders (ICSD-2) criteria.

2.2. Study design

Patients underwent overnight PSG in our sleep disorders unit, away from the CCU environment but in the same hospital, on the third day after the acute event with follow-up PSGs 1 and 6 months later. No oral or intravenous sedation was given. The safety and feasibility of PSG for acutely ill patients in the sleep disorders center have been described previously [21]. A sleep history was taken from each patient and his/her relatives. The Epworth sleepiness scale (ESS) was used to evaluate daytime sleepiness. Left ventricular ejection fraction (LVEF) was estimated by echocardiography using the biplane Simpson method before every sleep study.

In order to avoid circadian rhythm disturbances due to the light–dark cycle (while being in the CCU environment), patients were kept in rooms with windows, and the light was dimmed every night at 10 p.m. They were encouraged to follow a normal sleep schedule and to avoid napping. Furthermore, they were continuously video-recorded in order to rule out any abnormalities in their sleep schedule that might influence the first PSG, performed 3 days after the acute event.

On the day of the sleep study the patients were instructed to avoid napping after 11 a.m. To minimize the "first-night effect" factor, the PSG procedure was explained to the patients and a short visit to our sleep disorders center was arranged on the day of the sleep study.

The study was approved by the hospital's Ethics Committee and each participant gave written informed consent.

2.3. Polysomnography

Overnight attended PSG (Alice 5, Respironics) was performed in our sleep disorders center, which is located in the same hospital as the CCU. Patients underwent 3 nights of full diagnostic PSG, one at each time point, according to our standard techniques, with monitoring of the electroencephalogram (EEG) using frontal, central and occipital leads, electro-oculogram (EOG), and electromyogram (EMG), flow (by oronasal thermistor and nasal air pressure transducer), thoracic and abdominal respiratory effort, oximetry, and body position. Snoring was recorded by a microphone placed on the anterior neck. A single modified EKG lead II was used for baseline cardiac monitoring (additional leads I, II, aVL, aVR and aVF were used as backup for further evaluation of features suggestive of cardiac ischemia observed in the main EKG lead). An infrared camera synchronized to the PSG was used, and the number and timing of interactions between nurse and patient were documented.

The same PSG protocol and criteria were used on each of the 3 nights. Polysomnographic recordings were manually interpreted over 30-s periods in accordance with the guidelines of Rechtschaffen and Kales and the new American Academy of Sleep Medicine (AASM) guidelines [22,23], and the scorer was blinded to the PSG findings of the first assessment. The determination of sleep stages and arousals was performed according to the AASM 2007 criteria and by using EEG montages including frontal, central and occipital leads [23].

2.4. Statistical analysis

Summary descriptive statistics are reported as mean ± SD (standard deviation) or frequency (%), as appropriate. The time course of the various parameters was assessed using repeated measures analysis of variance or, where appropriate, the non-parametric Friedman test. Post-hoc Bonferroni adjusted tests were performed to pinpoint differences and 95% confidence intervals were constructed to provide a better estimate of the magnitude of the changes. All tests were two-sided and were carried out at the 5% level of significance. The statistical package SPSS 16 (Chicago, IL, USA) was used for the entire analysis.

3. Results

We included 22 patients in our study (17 men, 5 women) who were admitted to the CCU for ACS. During the selection of the study population, 53 patients were excluded based on the above-mentioned exclusion criteria (19 patients had received sedatives or narcotics within the previous 48 h or were on inotropes the day of the sleep study, 8 patients had suffered post cardiac arrest with hemodynamic instability and/or need for mechanical ventilation, 5 patients had chronic obstructive pulmonary disease, one patient had severe bronchial asthma, one patient had a history of psychiatric disorder and one patient had suffered a stroke, 14 patients had a history of OSA, 3 patients fulfilled the clinical criteria of RLS and one patient had a diagnosis of PLMD based on the ICSD-2 diagnostic criteria).

The mean age was 58 ± 12 years, ex-smoking history (range time from quitting smoking) was 13 months to 3 years, and body mass index (BMI) was 27 ± 4 kg/m^2. Epworth sleepiness scale (ESS) score was 6.3 ± 1.2.

On admission, 15 patients presented with ST elevation myocardial infarction. Of these 15 patients, five were treated with primary angioplasty and 9 with thrombolysis. In one patient, whose arrival at the hospital was delayed, no lytic or percutaneous intervention was performed. Patients with non-ST elevation myocardial infarction (n = 5) and patients with unstable angina (n = 2) were put on the IIb/IIIa inhibitor eptafibatide. Most of the patients were given β-blockers (n = 17) and angiotensin converting enzyme inhibitors (n = 20) or angiotensin-1 inhibitors (n = 2), while all of them received aspirin and/or clopidogrel. All included subjects received the same scheme of potentially sleep-affecting medications (e.g., β-blockers), of which the administration remained unchanged during the study period. Thus, any possible alteration in the sleep

Table 1
Polysomnography (PSG) parameters (respiratory events and oxygenation) and left ventricular ejection fraction (LVEF) values within 3 days of acute coronary syndrome (0), 1 month and 6 months later. Values are given as mean ± SD and 95% confidence interval.

Variables	First PSG (3 days)	Second PSG (1 month)	Third PSG (6 months)	*p* value
AHI (apnea–hypopnea index)	4.9 ± 1.93 (4.06–5.76)	4.09 ± 1.54 (3.41–4.77)	2.59 ± 1.01 (2.14–3.04)	<0.05
Desaturation (⩾4%) index	6.36 ± 2.4 (5.29–7.43)	5.46 ± 2.28 (4.44–6.47)	6.14 ± 2.27 (5.13–7.15)	NS
Mean oxygen saturation during sleep	95.14 ± 0.75 (94.81–95.47)	95.38 ± 0.84 (94.99–95.76)	95.76 ± 0.68 (95.44–96.08)	NS
LV ejection fraction	47.96 ± 7.18 (44.77–51.14)	49.32 ± 4.95 (47.12–51.51)	50 ± 4.88 (47.84–52.16)	NS

NS, not statistically significant.

architecture during the follow-up period would have been recorded equally in each PSG, effectively eliminating any bias.

Coronary angiography was performed before discharge and in any case 3 days after the first PSG. Three-vessel disease was documented in 7 patients (31.8%), two-vessel disease in 10 (45.5%) and one-vessel disease in 4 (18.2%). One patient refused angiography. Apart from the medical treatment, 14 (63.6%) patients underwent coronary revascularisation. Coronary bypass grafting was performed in 4 (28.6%) of them, 2 months ($n = 3$) and 3 months ($n = 1$) after the acute event, while in 10 (71.4%) patients coronary angioplasty with stent implantation was performed during the first trimester.

The first PSG was performed 3 days after the acute event. Patients maintained a normal light–dark exposure, without napping during the day, as confirmed by video recordings. The mean number of documented nurse-patient interactions was 2.1 ± 1.4 times per night. No ischemic changes were documented on the EKG during the sleep study and none of the participants reported chest pain during PSG monitoring. The left ventricular ejection fraction (LVEF) was slightly but not significantly increased during the follow-up period. Table 1 shows the PSG parameters and LVEF values measured during the acute stage and 1 and 6 months later.

The initial PSG of the acute phase versus the first follow-up PSG (performed 1 month later), versus the second follow-up PSG 6 months after the acute event revealed difficulties in initiating and maintaining sleep, significantly shorter total sleep time (232.7 ± 39.8 min vs. 296.8 ± 40.4 min vs. 330.6 ± 25.2 min, $p < 0.05$), poorer sleep efficiency (59.8 ± 10.1% vs. 74.5 ± 6.1% vs. 82.6 ± 5.9%, $p < 0.05$) and latency (52.5 ± 13.4 min vs. 35.7 ± 10.8 min vs. 21.7 ± 7.9 min, $p < 0.05$), a significantly greater arousal index (26.6 ± 11.9 vs. 13.4 ± 6 vs. 3.9 ± 1.9, $p < 0.05$), a significantly greater WASO (99.2 ± 33.2 min vs. 49.5 ± 22.1 min vs. 29.3 ± 17.9 min, $p < 0.05$) and significantly less SWS (5.4 ± 2.1% of TST vs. 10.3 ± 2.6% of TST vs. 12.8 ± 2.5% of TST, $p < 0.05$) as well as REM sleep (3.1 ± 3.9% of TST vs. 10.9 ± 3.5% of TST vs. 13.1 ± 2.8% of TST, $p < 0.05$); values are given as mean ± SD (Figs. 1 and 2). Sleep architecture was less altered 1 month after the acute event, while 6 months later sleep duration and stages were within normal range. There were no significant differences in light-off/light-on or total time in bed (TIB).

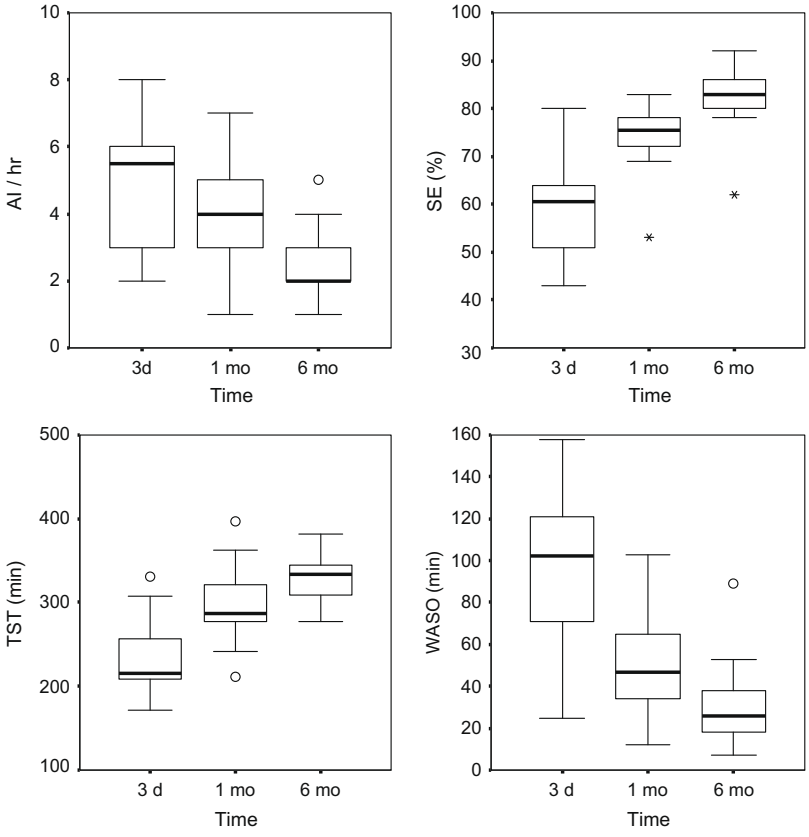

Fig. 1. Box plots of arousal index, sleep efficiency, total sleep time (TST) and wake after sleep onset (WASO) in ACS patients studied within 3 days of acute coronary syndrome (0), 1 month and 6 months later. Arousal index and WASO decreased steadily, while sleep efficiency and TST increased rapidly and continuously throughout the study period (o denotes mild outliers, ∗ denotes extreme outliers).

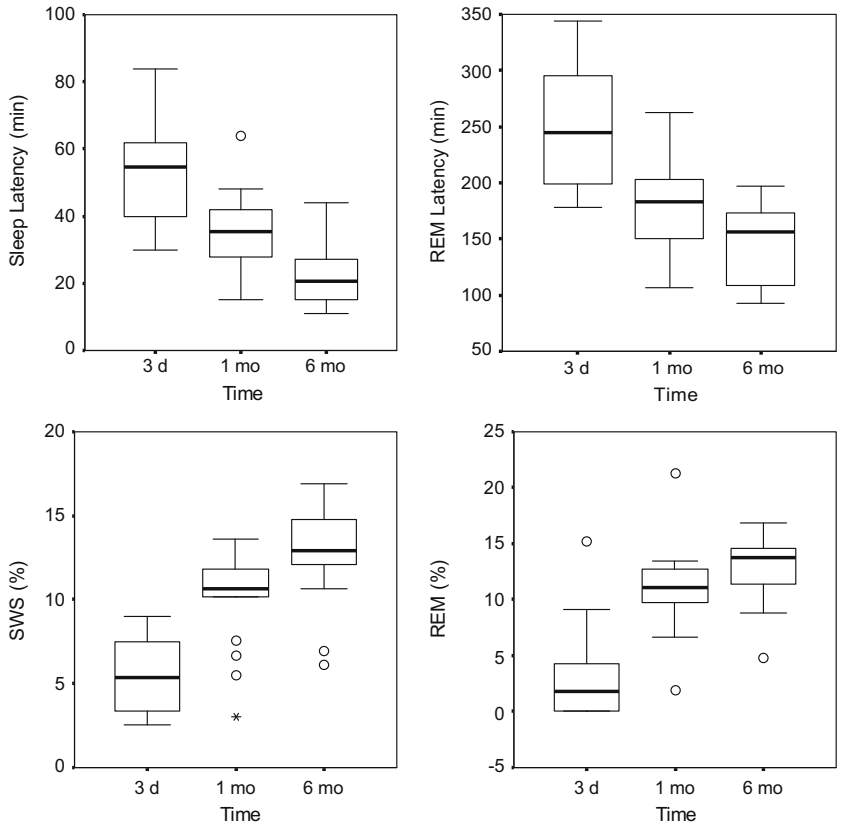

Fig. 2. Box plots of sleep latency, REM latency, slow wave sleep (SWS) and REM sleep in studied ACS patients within 3 days of acute coronary syndrome (0), 1 month and 6 months later. Sleep and REM latency decreased gradually, while SWS and REM had a very large increase at the 1 month time point (o denotes mild outliers, ∗ denotes extreme outliers).

4. Discussion

It is known that disturbances of sleep in CCU patients can be caused by patient care interaction, severity of illness, noise, mechanical ventilation, pain, medications, or alterations in circadian rhythm. The resulting sleep deprivation can lead to alterations in immune function, stress, fatigue, decrease in concentration, and delirium [10,11,13,14,16,24–29]. All of these factors might interact to adversely affect sleep architecture and the patient's outcome; however, there are very limited data concerning sleep in CCU patients after controlling for the majority of the above-mentioned factors.

Our study involved a homogeneous group of patients with ACS and preserved left ventricular function, who were not mechanically ventilated or on oral or intravenous sedation. We avoided the environmental factors by assessing sleep quality away from the CCU. We objectively controlled for circadian rhythm disturbances through maintenance of normal light–dark exposure and continuous video recordings inside the CCU. Furthermore, we carefully selected our patients in order to avoid concomitant diseases that could affect sleep architecture. In order to avoid possible alterations in sleep architecture attributable to the emotional stress accompanying the diagnosis of ACS, patients were thoroughly informed numerous times before the first PSG (related to the improvement in their health status and the expected favorable outcome with the advised treatment) and received ongoing encouragement, which was performed by the CCU psychologist once a day; in any other case the patients asked for psychological support.

Previous studies have shown a high prevalence of sleep-disordered breathing in patients with ACS [30,31]—a known cause of sleep disruption—so we excluded patients with sleep-breathing disorders revealed by the initial PSG and/or previous medical history. We further excluded patients with other causes of sleep disruption such as RLS, PLMD and current smoking [32,33]. Additionally, we tried to maintain stable medication and anthropometric parameters during the study period.

To our knowledge, no previous study has objectively assessed the above-mentioned factors. Despite controlling for all of these factors, we found that sleep architecture was clearly worse in the acute post-ACS phase than at follow-up. During the acute event TST, sleep efficiency, SWS and REM sleep were significantly reduced and a significant negative impairment in sleep micro-architecture was noted due to an increased arousal index. Sleep architecture was improved 1 month later, while 6 months after the acute event sleep duration as well as sleep stages were within the normal ranges. Taken together, these findings indicate that the severity of illness and the physiological and inflammatory changes (e.g., cytokines) associated with it may make a major contribution to alterations in sleep architecture. On the other hand, minor positive alterations to sleep architecture may also be related to the fact that patients were more accustomed to the sleep laboratory environment during subsequent visits. Four of the included subjects underwent open heart surgery during the follow-up period 2–3 months after the acute event. The improvement in their sleep architecture during the second follow-up PSGs (6 months after the acute event) was similar to that noted in the remaining subjects.

One study that assessed sleep in the ICU with repeated EEGs throughout the night showed that normal sleep patterns did not return to patients with ACS until 9 days after discharge from the ICU [34]. In a previous study, Bahammam evaluated the sleep qual-

ity of 20 patients with acute myocardial infarction within 3 days of the acute event and 6 months later in the sleep disorder center outside the CCU environment [20]. Arousal index, spontaneous arousals, stage shifts, REM latency, and wake time were significantly greater, while TST, sleep efficiency, and REM sleep were significantly less during the acute event compared with 6 months later; this is in accordance with our results. The Bahammam study, however, did not objectively control for circadian rhythm disturbances and for concomitant known causes of sleep disruption, such as sleep-breathing disorders, RLS, PLMD and smoking. The data of the present study challenge the traditional assumption that many factors may cause sleep disruption in CCU patients. The acute phase of the illness and its consequences in circulating cytokines and other inflammatory mediators may play a major role in sleep disruption and deserve further research. The expression of many cytokines is upregulated in patients with ACS [35], with inflammatory cytokines having both somnogenic and sleep-inhibitory effects depending on the type, dose and circadian time of application, and it has been reported to influence sleep and sleep depth [36].

One possible limitation of our study is the absence of a control group. Nevertheless, the progressive improvement of sleep architecture, with almost complete normalization 6 months after the initial PSG, in the same patient population suggests that the acuity of illness may have been the main factor responsible for sleep disruption. Another limitation is the absence of a baseline sleep study inside the CCU. PSGs in the CCU environment present many technical difficulties; however, this will be the aim of a future study. Despite our attempt to avoid or at least significantly reduce sleep architecture alterations due to emotional stress after the ACS event (e.g., ongoing encouragement by our CCU psychologist), this issue demands further specifically designed studies.

In conclusion, our data show that patients with ACS have alterations in sleep architecture, with difficulties initiating and maintaining sleep, increased arousals, and decreased TST, SWS and REM sleep, despite objectively controlling for the majority of known sleep-disrupting factors; this suggests that the acuity of illness may make the major contribution. Further studies, however, should explore the physiological and inflammatory changes associated with the underlying cardiac disease and their contribution to the alterations in sleep architecture. Additionally, further studies are necessary in order to assess alterations in sleep architecture parameters in ACS patients with and without cardiac complications after the acute event and during the follow-up period. This might provide useful data related to the association between cardiac pathophysiology and sleep alterations in such patients. Sleep quantity and quality have a direct influence on quality of life and are probably related to the short and long term outcome in ACS patients. The need for further research along the lines of the current study, in view of the emerging evidence that altered sleep duration/architecture may adversely influence cardiovascular physiology and related biology and vice versa, remains a crucial future goal.

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