Pulmonary haemodynamics in obstructive sleep apnoea: time course and associated factors


ABSTRACT: Changes in pulmonary artery pressure within an obstructive apnoea and elevations of transmural pulmonary artery pressure (P_{pa,tm}) towards the end of apnoea are well known. The purpose of our study was to examine which factors contribute to the increase of P_{pa,tm} in an apnoea. In addition, the time course of P_{pa,tm} and associated factors during a sleep study was investigated.

We analysed the association of changes in arterial oxygen saturation (S_a,O_2), oesophageal pressure (P_oes) to estimate intrathoracic pressure, systolic blood pressure (BP_syst) to estimate left ventricular afterload, apnoea duration and the change in P_{pa,tm} (ΔP_{pa,tm}) during the course of obstructive apnoeas. Consecutive apnoeas in nonrapid eye movement (NREM)-sleep at the beginning, the middle and the end of the sleep study were analysed in six patients with obstructive sleep apnoea.

The mean systolic P_{pa,tm} was 28.8±12.1 mmHg at the beginning of apnoea and 38.6±15.5 mmHg at the end (ΔP_{pa,tm} 10.5±7.4 mmHg; p<0.0001). ΔS_a,O_2 (p<0.0001; odds ratio (OR) 1.45; confidence interval (CI) 1.20–1.76) and ΔP_oes (p<0.0001; OR 1.22; CI 1.11–1.34) were independently associated with ΔP_{pa,tm} in a multiple regression analysis. Apnoea duration as well as ΔP_oes, ΔP_{pa,tm} and ΔS_a,O_2 were all significantly higher (p<0.05) in apnoeas at the middle of the sleep study than at the beginning or the end.

In conclusion, hypoxaemia and mechanical factors as an increase in negative thoracic pressure contribute to elevations of the transmural pulmonary artery pressure during an obstructive apnoea. The time course of pulmonary haemodynamics within a sleep study reveals that the highest transmural pulmonary artery pressure occurs in the middle of the night with no progressive increase towards the end of the sleep study.


Pulmonary hypertension is a potential complication of obstructive sleep apnoea. Most recent studies agree on a 15–20% prevalence [1]. The development of pulmonary hypertension is strongly linked to an obstructive ventilatory pattern, daytime hypoxaemia and hypercapnia, whereas the severity of obstructive sleep apnoea plays only a minor role [2]. However, some patients develop pulmonary hypertension despite normal waking arterial oxygen tension (P_a,O_2) levels [3]. In this group of patients, the nocturnal breathing disorder may be crucial for the development of pulmonary hypertension, since it has been hypothesized that episodic and recurrent hypoxemia, due to repeated apnoeas, could lead to permanent pulmonary hypertension [4].

Transient and repetitive elevations in pulmonary artery pressure, with reference to atmospheric pressure, have been described [5]. While intravascular pulmonary artery pressure decreases during apnoea and increases at the resumption of breathing, transmural pulmonary artery pressure (P_{pa,tm}) (i.e. corrected for intrathoracic pressure swings) shows a trend toward a progressive increase throughout an apnoea and toward a decrease once ventilation has been resumed [6]. Several factors and mechanisms, mainly mechanical events or hypoxic vasoconstriction, have been proposed as contributing to the changes in the pulmonary artery pressure (P_{pa,tm}) within an apnoea cycle. Mechanical events are caused preferably by intrathoracic pressure swings [7]. Limitation of left ventricular filling and emptying at low intrathoracic pressure could contribute to an increase in pulmonary vascular resistance by increasing the pulmonary venous pressure and blood volume [8]. On the other hand, several studies have indicated an association between changes in oxygen saturation and changes in pulmonary artery pressure during an obstructive apnoea [4, 9, 10]. Marra et al. [11] showed that hypoxia is a major determinant of the slow changes in the transmural pulmonary artery pressure over the whole course of an apnoea. In addition, they found rapid changes in the P_{pa,tm} that was synchronous with intrathoracic pressure changes breath-by-breath.

The purpose of our study was to examine which factors contribute to the increase of the P_{pa,tm} in an apnoea. Is this: 1), a response to increased right ventricular preload
and output due to increased venous return in the course of intrathoracic pressure swings; 2), due to pulmonary vasocostriction related to hypoxia; or 3), due to increased left ventricular afterload. Moreover, we analysed the time course of these factors within the sleep study.

Methods

All patients underwent full diagnostic polysomnographic sleep studies to establish the diagnosis of obstructive sleep apnoea. Conventional spirometry and body plethysmography, echocardiography, bicycle exercise test and right heart catheterization were performed on the following day. The following sleep study included the haemodynamic measurements of pulmonary artery pressure and systemic artery pressure. The study was approved by the Ethics Committee of the University of Bonn, Germany. All patients gave written informed consent to all parts of the study.

Patients

Six male patients with moderate-to-severe obstructive sleep apnoea (apnoea/hypopnoea index (AHI) >20) were included in the study. No patient had a history or clinical signs of chronic airflow limitation. Patients with a history of coronary heart disease were excluded. Echocardiography revealed normal left ventricular diameters and normal ejection fraction in all patients. All antihypertensives and diuretics were discontinued 72 h before the study.

Pulmonary artery catheterization and blood pressure measurement

The pulmonary artery catheterization procedure was performed in the heart catheterization laboratory. Patients were at rest in a semirecumbent position, breathing room air. A Swan-Ganz catheter (Corodyn TD-E, B. Braun, Melsungen, Germany) was introduced into the pulmonary artery via a cubital vein and connected to a pressure transducer (Exadyn CMS Transducer, B. Braun). After calibrating the system, measurements of the pressures in the right atrium (Ppa) and the right ventricle (Ppv) were performed. The correct position of the catheter in the pulmonary artery was verified by chest radiography screening and by the typical wave-form of the pulmonary artery pressure. Recordings of the pulmonary artery pressure (Ppa) and the pulmonary capillary wedge pressure (PPcw) were performed at rest and at exercise. Invasive blood pressure measurement was performed by a cannula in the left-sided artery radialis. After connection to a pressure transducer the system was calibrated. At the end of the protocol in the heart catheterization laboratory the patients were transferred into the sleep laboratory and the sleep study was started within the next 6 h.

Sleep studies

Polysomnography included the following signals: two leads of electroencephalogram (C3,A2; C4,A1), two leads of electro-oculogram and a submental electromyogram were continuously registered by surface electrodes. Respiration was also continuously recorded: airflow was monitored by oronasal thermistors, abdominal and chest wall movements by inductive-plethysmography, and arterial oxygen saturation (Sao2) by pulse oximetry. Oesophageal pressure (Poes), as an estimate of intrathoracic pressure, was recorded by a piezo catheter (Gaeltec CTO, Novotronic GMBH Bonn, Germany) introduced in the lower third of the oesophagus and connected to a pressure transducer (Gaeltec S7b, Novotronic GMBH Bonn, Germany). The procedure of catheter placement was performed as described elsewhere in detail [12]. In addition, Ppa and systemic artery blood pressure (BP) were recorded continuously after connection to a pressure transducer and calibration was performed before starting the sleep study as follows: the whole system including the pressure transducer, the pressure monitor (Sirecust 404, Siemens München, Germany) and the computerized recording system (NewMedics Öhringen, Germany) was calibrated by two-point calibration using a mercury manometer for high level pressure and atmosphere for 0 level pressure. The transducer was placed 5 cm below the sternal angle manubriosternal joint. Systolic Ppa,tm was calculated by computerized subtraction of Poes from systolic Ppa.

All variables were recorded by a computerized system (NewMedics, Öhringen, Germany). Sleep was staged manually according to standard criteria [13]. Central, obstructive, and mixed apnoeas were defined according to the usual criteria [14]. We defined hypopnoea as a reduction of at least 50% in airflow from its value during quiet wakefulness for at least 10 s followed either by an oxygen desaturation of at least 4% or by an arousal. The total number of apnoea and hypopnoea were divided by total sleep time to make up the apnoea index (AI) and the hypopnoea index (HI). The sum of AI and HI then became the AHI.

Haemodynamic analysis

In each patient, 15 consecutive obstructive apnoeic cycles in nonrapid eye movement (NREM)-sleep in the first two hours (b), in the following two hours (m) and in the last two hours (e) of the sleep study were selected for analysis. An apnoeic cycle was divided into three phases as shown schematically in figure 1 and included the first three unoccluded breaths following the preceding occluded breaths. In every apnoeic cycle the following variables were calculated: duration of the apnoea, lowest systolic Ppa,tm at the beginning of the apnoea (Ppa,tm b, phase I), highest systolic Ppa,tm at the end of the apnoea or the first three unoccluded breaths following the apnoea (Ppa,tm e,

![Fig. 1. Schematic presentation of an obstructive apnoea in three phases.](image-url)
Fig. 2. – Representative traces of the haemodynamic changes during an obstructive apnoea. a) blood pressure (BP); b) pulmonary artery pressure (Ppa); c) oesophageal pressure (Poes); d) flow; and e) arterial oxygen saturation (SaO2). Arrows indicate values taken in phase I (start) and phase II or III (end) of the apnoea. (1 mmHg=0.133 kPa.)

phase II or phase III). Both values were taken during end expiratory time; the difference between both was given as ΔPoes. The corresponding systolic BP at the beginning of the apnoea (BPsys) and at the end of the apnoea or the first three unoccluded breaths following the apnoea (BPsys) were calculated and the difference between the two made up the ΔBPsys. The highest Poes at the beginning of the apnoea (Poes) and the lowest Poes at the end of the apnoea or the first three unoccluded breaths following the apnoea (Poes) were calculated and the difference between the two made up the ΔPoes. The highest SaO2 at the beginning of the apnoea (SaO2) and the lowest SaO2 at the end of the apnoea (SaO2) were calculated and the difference between both made up the ΔSaO2. Figure 2 gives an illustration of a representative tracing.

Statistical analysis

Descriptive statistics for continuous variables were expressed as the mean ± standard deviation (SD), unless stated otherwise. We assessed differences in continuous variables using the Mann-Whitney U-test. Analysis of variance (ANOVA) with Bonferroni correction was used to determine differences between the beginning, middle and end of the sleep study with regard to apnoea duration, ΔPoes, ΔBPsys, ΔPpa, ΔPa, Δra, ΔSaO2. We performed a multiple linear regression analysis to assess factors independently associated with ΔPoes. In all cases, p-values of <0.05 were considered to be significant. Statistical analysis was performed with the Statistical Package for the Social Sciences (SPSS) for Windows™ (SPSS Inc., Chicago, IL, USA).

Results

The mean age of the six patients was 54.7±6.5 yrs, the mean body-mass index (BMI) was 31.1±4.1 kg·m⁻². The mean AHI was 52.1±13.5 (31–67). Detailed data on the patients’ characteristics in detail are given in table 1. Detailed results of the polysomnography are given in table 2.

We analysed a total of 270 obstructive apnoeas in NREM-sleep from six patients. The mean (range) duration of the 270 apnoeas was 22.7±12.7 s (10.0–94.0 s). Analysis of the pulmonary haemodynamics revealed a mean systolic Ppa of 28.0±12.1 mmHg at the beginning of apnoea and 38.6±15.5 mmHg at the end of apnoea (ΔPpa, 10.5±7.4 mmHg; p<0.0001). The corresponding

Table 1. – Data on patients’ lung function and haemodynamic measures at rest (awake) and on exercise

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age yrs</th>
<th>BMI kg·m⁻²</th>
<th>FEV1 % pred</th>
<th>VC % pred</th>
<th>PaO2 rest mmHg</th>
<th>PaO2 exercise mmHg</th>
<th>PaCO2 rest mmHg</th>
<th>PaCO2 exercise mmHg</th>
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<th>PaCO2 exercise mmHg</th>
<th>PaCO2 rest mmHg</th>
<th>PaCO2 exercise mmHg</th>
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<td>72</td>
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<td>Mean</td>
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<td>90.5</td>
<td>84.6</td>
<td>66.7</td>
<td>81.6</td>
<td>41.5</td>
<td>39.1</td>
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<tr>
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<td>±4.1</td>
<td>±23.7</td>
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<td>±6.1</td>
<td>±12.4</td>
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<td>±4.5</td>
<td>±1.8</td>
<td>±7.9</td>
<td>±13.8</td>
<td>±2.7</td>
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</table>

BMI: body mass index; FEV1: forced expiratory volume in one second; VC: vital capacity; PaO2: arterial oxygen tension; PaCO2: arterial CO2 tension; Ppa: right atrial pressure; Ppc: pulmonary artery pressure; Ppc: pulmonary capillary pressure. (1 mmHg=0.133 kPa.)
systolic BP were 162.4±32.6 mmHg at the beginning of apnoea and 177.0±35.6 mmHg at the end (ΔBPsys 14.7±20.0 mmHg; p<0.0001). The corresponding Poes were -4.1±5.1 mmHg at the beginning of apnoea and -19.9±10.0 mmHg at the end (ΔPoes 15.8±9.9 mmHg; p<0.0001). SaO2 was 96.2±2.1% at the beginning of apnoea and 88.5±5.1% at the end (ΔSaO2 7.7±4.9%; p<0.0001). Analysis of the pulmonary haemodynamics of patient number 4 in detail revealed significant differences in the other patients. The mean Pa,tm at the beginning of apnoea was 41.2±3.2 mmHg versus 25.4±1.5 mmHg (p<0.0001) and the mean Pa,tm at the end of apnoea was 54.0±7.2 mmHg versus 35.6±14.9 mmHg (p<0.0001). Moreover, the difference in Pa,tm from the beginning to the end of apnoea was significantly higher in this patient in comparison with the other patients (ΔPa,tm: 12.8±7.1 versus 10.1±7.4 mmHg; p<0.05).

In order to test the possibility that repeated apnoeas could lead to a greater drop in SaO2 with a progressive increase in Pa,tm, we compared the first five apnoeas with the last five apnoeas of each 15 consecutive apnoeas of all patients and found no difference with regard to Pa,tm, BP, SaO2 or Poes.

With regard to the influence of apnoea duration, intrathoracic pressure swings and oxygen saturation on transmural pulmonary pressure we found the factors ΔSaO2 (odds ratio (OR) 1.45; 95% confidence interval (CI) 1.20–1.76; p<0.0001) and ΔPoes (OR 1.22; 95% CI 1.11–1.34; p<0.0001) were independently associated with ΔPa,tm in a multiple regression analysis. Apnoea duration and ΔBPsys were not associated.

Analysis of the NREM apnoeas during the night revealed that the apnoea duration was significantly longer (p<0.05) at the middle of the sleep study (30.1±16.8 s) than at the beginning (17.9±6.4 s) or the end (20.2±9.0 s). In addition, ΔSaO2, ΔPoes, and ΔPa,tm were all significantly higher (p<0.05) in the apnoeas in the middle of the sleep study than at the beginning or the end (fig. 3a-d). ΔBPsys was highest in the middle of the sleep study as well, but this difference was not statistically significant (fig. 3e). The absolute values toward the end of the apnoeas had the highest systolic Pa,tm at the middle of the sleep study (40.6±15.9 mmHg) in comparison to the beginning (38.5±14.8 mmHg) and the end (36.7±15.7 mmHg), but this difference was not statistically significant. Systolic BP at apnoea end was slightly, but not significantly higher at the middle of the sleep study (179.7±35.7 mmHg) than at the beginning (177.9±36.2 mmHg) or the end (173.4±34.7 mmHg). The corresponding Poes values toward the end of the apnoeas were significantly lower (p<0.05) in the middle of the sleep study (173.4±10.2 mmHg) than at the beginning (180.0±9.1 mmHg) or the end (18.3±9.9 mmHg).

The values of SaO2 at the end of the apnoeas were also significantly lower (p<0.05) in the middle of the sleep study (85.7±5.6%) than at the beginning (90.1±4.2%) or the end (89.7±4.1%).

Discussion

We found that the difference in the Poes as an estimate of intrathoracic pressure swings within an apnoea and the difference in SaO2 during an apnoea were independently associated with an increase in Pa,tm from the beginning to the end of an apnoea. Analysis of these differences in Pa,tm, BP, Poes and SaO2 with regard to the time course of a whole sleep study revealed that the greatest differences and the highest absolute values were found in the middle of the sleep study. In addition, apnoea had the longest duration in the middle of the sleep study.

In order to investigate the pulmonary haemodynamic characteristics throughout an obstructive apnoea cycle, the best way is to analyse Pa,tm, i.e. intravascular Ppa minus intrathoracic pressure, as first described systematically by MeGillivray et al. [6]. They found that the apparent and irregular decline in intravascular values during apnoea, followed by a sudden rise at resumption of breathing, was replaced by a regular increase in transmural pressure up to a maximum value during the final occluded efforts and sustained during the early phase of hyperventilation. Our results were similar to these findings with a progressive increase in systolic Pa,tm of 10 mmHg as a mean towards the end of apnoea. Among the underlying mechanisms it was suggested that alveolar hypoxia played an important role, because a significant negative correlation between Pa,tm and SaO2 was found in most patients [6]. This hypothesis was further tested by evaluating the effect of oxygen administration on Pa,tm during obstructive ap-noeas [10]. However, in most patients, oxygen administration affected neither mean Pa,tm, nor the amplitude of Pa,tm swings [10]. On the other hand, oxygen administration prevented the occurrence of pulmonary hypertensive peaks in a dog model of obstructive sleep apnoea [9]. Re-cently, Laks et al. [21] examined the awake Pa response to a ramp of acute hypoxia similar to that found in sleep apnoea and the interaction between hypoxia and hypercapnia. They found a Pa increase in both normal subjects and patients with obstructive sleep apnoea exposed to a ramp of acute
isocapnic hypoxia, but there were clear interindividual differences in $P_{pa}$ response. Hypercapnia did not produce clinically significant changes in $P_{pa}$ in either group.

In addition to the effects of hypoxaemia on the pulmonary haemodynamics, mechanical factors, especially intrathoracic pressure swings, have to be considered, as first suggested by Peters et al. [15]. Unfortunately, they did not record intrathoracic pressures in order to calculate $P_{pa,tm}$. Our data strongly support the fact that both oxygen desaturation and intrathoracic pressure swings account for the changes in $P_{pa,tm}$ within an apnoea. This is consistent with the data from Mannone et al. [11], who observed rapid changes which reflect intrathoracic pressure variations and slower changes likely to be caused by $S_{a,O2}$ changes.

In contrast to our study, they investigated firstly $P_{pa,tm}$ beat-by-beat, in reference to the immediately preceding end-diastole $P_{oes}$ and, secondly, $P_{pa,tm}$ changes in reference to $S_{a,O2}$ changes within an apnoea. We analysed the changes in $S_{a,O2}$ and $P_{oes}$ as compared to $P_{pa,tm}$ from the beginning to the end of the apnoea in one model, because $P_{oes}$ as well as $S_{a,O2}$ decrease progressively towards the end of an obstructive apnoea. Consequently, both factors should be investigated together in one model. In addition, we analysed arterial BP as a rough estimate of left ventricular afterload. We did not include the absolute values at the end of the apnoea in this model but the changes from the beginning to the end may better reflect the dynamic process of intrathoracic pressure swings.

The patient (number 4) with markedly elevated $P_{pa}$ at rest and during exercise had more pronounced changes in $P_{pa,tm}$ during apnoeas than the other patients. The repetitive elevations in $P_{pa,tm}$ during apnoeas may be crucial for the development of elevated $P_{pa}$ awake in this patient.

Prolonged oxygen desaturation may lead to hypoxic vasoconstriction and therefore result in an increase in $P_{pa,tm}$, but intrathoracic pressure swings may also affect the pulmonary circulation since it has been demonstrated that $P_{pa,tm}$ rises during snoring, independent of changes in $S_{a,O2}$ [16]. An increase in $P_{pa,tm}$ could be a direct consequence of right ventricular afterload and output due to an increase in blood volume from prolonged negative intrathoracic pressure. The effects of low intrathoracic pressure on the left heart could be another mechanism. Reduced intrathoracic pressure can increase left ventricular afterload as shown by elevated left ventricular volumes due to Mueller manoeuvres [17, 18], and this may explain the development of pulmonary oedema in obstructive sleep apnoea [19]. The effects on left ventricular afterload are still under debate. We found no association of systolic BP changes as a rough estimate of left ventricular afterload with the changes in $P_{pa,tm}$ in our study. However, it is difficult to investigate the contribution of the mechanical factors in detail in such a clinical study. This could be aimed with an experimental setting of an animal study. Moreover, other factors such as the role of the sympathetic response or reflex mechanisms have to be considered [20]. In fact, we analysed all apnoeas in NREM-sleep. The effect in rapid eye movement (REM)-sleep is not known, since in REM-sleep apnoeas may be longer and the extent of $S_{a,O2}$ reduction pronounced. In addition, the influence of reflex mechanisms and the sympathetic tone may be different in REM-sleep.

We examined a possible progressive increase in $P_{pa}$ during the night, as had been pointed out in early studies [22], by dividing the sleep study in three phases of two hours, beginning, middle and end. We found no progressive increase throughout the night, but found the highest values and marked changes from apnoea beginning to apnoea end in the middle of the sleep study. The fact that apnoea duration was the longest and $S_{a,O2}$ and $P_{oes}$ were the lowest in this period suggests that these factors played a major role. Recently, Sirbza et al. [23] found a nocturnal trend of a small progressive increase of $P_{pa}$ in patients with obstructive sleep apnoea, but not in snorers, by analysing...
selected apnoeas every hour of the sleep study. They concluded that this increase in $P_{pa}$ reflects the cumulative effects of apnoeas and nocturnal hypoaxaemia. However, apnoea duration increased throughout the night in their study as well and the effect of intrathoracic pressure is not known, since $P_{oes}$ was not recorded.

In conclusion, transmural pulmonary artery pressure increases from the beginning towards the end of apnoea. A drop in arterial oxygen saturation and mechanical factors as an increase in negative thoracic pressure are independently associated with this rise in transmural pulmonary artery pressure. There is no progressive increase of transmural pulmonary artery pressure throughout the night.

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References


