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Chronic thromboembolic pulmonary hypertension: Reversal of pulmonary hypertension but not sleep disordered breathing following pulmonary endarterectomy☆

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ABSTRACT

Background: It has been hypothesized that pre-capillary pulmonary hypertension (PH) may trigger sleep disordered breathing (SDB). In patients with chronic thromboembolic PH (CTEPH), pulmonary endarterectomy (PEA) is potentially effective to improve PH. We assessed the pre- and post-operative prevalence of SDB in CTEPH patients submitted to PEA and the relationship between SDB and clinical, pulmonary and hemodynamic factors.

Methods: Unattended cardiorespiratory recording was performed the night before and one month after elective PEA in 50 patients.

Results: Before the intervention SDB prevalence (obstructive or central AHI ≥ 5/h) was 64%: 18 patients (66% female) had No-SDB, 22 (68% female) had dominant obstructive (dOSA), and 10 (20% female) had dominant central sleep apnea (dCSA). There were no differences in risk factors and the need for supplemental oxygen. Mean right atrial (mRAP) and pulmonary artery pressures (mPAP) showed a more compromised profile from No-SDB to dOSA and dCSA (mRAP: 5.5 ± 3.9 vs 7.0 ± 4.5 vs 9.7 ± 4.3 mm Hg ($p = 0.054$), mPAP: 39 ± 12 vs 48 ± 11 vs 51 ± 16 mm Hg ($p = 0.0.47$)). By contrast, cardiac index did not differ.

At post-intervention, the prevalence of SDB was 68%: 16 patients had No-SDB, while 30 had dOSA and 4 dCSA, with no relationship with the relief from PH. Interestingly, 5 patients with previous CSA moved to the OSA group and 2 normalized.

Conclusions: Prevalence of SDB is high in patients with CTEPH even after resolution of PH. Our data support the hypothesis that pre-capillary PH may trigger CSA but not OSA, and suggest that OSA may play a role in the development of CTEPH.

1. Introduction

Sleep related breathing disorders (SDB) have been reported as common in patients with pre-capillary pulmonary hypertension (PH) in a number of studies [1–5] mainly including patients with idiopathic pulmonary hypertension. Chronic thromboembolic pulmonary hypertension (CTEPH), one of the leading causes of severe pre-capillary pulmonary hypertension, was present in a limited number of patients. The prevalence estimate of obstructive sleep apnea (OSA) in CTEPH was about 30%, while central sleep apnea (CSA) was less frequent. In the only one study that examined an homogeneous sample of 49 CTEPH subjects referred for evaluation for pulmonary endarterectomy (PEA), SDB – defined as ongoing positive airway pressure use or apnea–hypopnea index (AHI) ≥ 5/h – was found in 57% of subjects [6].

The link between pre-capillary PH and SDB is still to be completely elucidated and is a subject of active discussion [7]. In the context of pulmonary arterial hypertension, it has been suggested that pre-capillary PH associated with right ventricular failure may promote instability of

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ventilatory control leading to sleep apnea through similar mechanisms as in left ventricular failure with Cheyne–Stokes respiration/CSA [8]. On the same line, in the CTEPH series studied by Orr et al. [6], it was found that subjects with SDB had a significantly lower cardiac index as compared to subjects without SDB.

Pulmonary endarterectomy is the treatment of choice in patients with CTEPH [9], providing immediate and effective relief from pulmonary hypertension. In a series of 37 patients at discharge from surgery, pulmonary vascular resistance was decreased by 70%, and mean pulmonary artery pressure was decreased by 50% compared with the preoperative values [10]. Cardiac index and cardiac output changed accordingly, whereas central venous pressure normalized. All of these hemodynamic variables remained stable over two years [10]. The technique is largely evolved during the last two decades, now allowing more distal disease to be cleared [11], with an excellent long-term prognosis of operated patients [12].

Thus, subjects undergoing PEA offer the unique opportunity to test the hypothesis that in CTEPH patients the occurrence of SDB is mainly related to the hemodynamic impairment caused by the thromboembolic pulmonary obstruction. If this were the case, the SDB prevalence should decrease following PEA in parallel with right ventricular remodeling.

On these bases, we undertook the present study to assess: 1) the pre- and post-operative prevalence of SDB in patients with CTEPH who had been submitted to PEA, and 2) the relationship between SDB and clinical, pulmonary and hemodynamic factors.

2. Methods

This is a prospective cohort study involving human subjects and performed according to the declaration of Helsinki. The study design was approved by our institutional Review Board and Ethical Committee (approval number: 886 CE 05/13). All the patients gave a written informed consent.

2.1. Patients

The study population was constituted by 50 adult (>18 years) patients undergoing elective PEA prospectively enrolled at the Cardio-Surgery Unit of the Fondazione Policlinico San Matteo Pavia, and who were subsequently admitted to our Institution for recovery and rehabilitation. Patients' recruitment was independent of the presence of sleep-related symptoms and the use of vasodilator drugs or nasal oxygen.

2.2. Clinical data collection and definitions

Preoperative characteristics, operative procedures, hospital outcomes, and follow-up data were prospectively entered into the Pavia Pulmonary Endarterectomy Registry. Use of this registry for research was approved by the hospital Review Board. For each patient anthropometric parameters as well as pre-operative and post-operative hemodynamic, echocardiographic, respiratory and functional parameters were collected in a dedicated database.

The pre-operative hemodynamic study was performed in close relationship with the sleep study and the surgical procedure. In detail, as the majority of patients underwent elective surgery (and had been admitted to hospital the day before the planned intervention) the hemodynamic study was performed on the same day of admission. For those patients, who for several reasons, had a delay in the planned intervention, the hemodynamic assessment was performed within a maximum of 6 days from the sleep study.

2.3. Polygraphy

On the night preceding the surgical procedure each patient underwent an unattended in-hospital nocturnal cardiorespiratory recording between 11:00 p.m. and 6:00 a.m. using the portable sleep apnea monitor (Embletta — Natus Middleton WI USA), which included: nasal airflow by a pressure transducer, thoracoabdominal movements through respiratory inductance plethysmography, O_2 saturation by pulse oximetry with a finger probe, body position, and movement. An identical recording was carried out one month later. Manual scoring of all Embletta tracings was carried out by the same expert scorer using the Remlogic PSG software accordingly to AASM rules [13].

Each recording was scored by an expert scorer according to the American Academy of Sleep Medicine (AASM) guidelines [13], using the Somnologica sleep diagnostic software version 5.1.0 (Embla, Thornton, CO, USA).

Central apneas were scored when there was a drop in the peak-to-peak thermistor signal by ≥90% of pre-event baseline, lasting ≥10 s and associated with absent respiratory effort. Obstructive apneas were scored when there was a drop in the peak-to-peak thermistor signal by ≥90% of baseline, lasting ≥10 s and associated with continued or increased respiratory effort. Hypopneas were scored when there was a drop in the peak-to-peak nasal pressure by ≥30% of pre-event baseline, lasting ≥10 s, associated with a ≥3% drop in oxygen saturation or an arousal. Hypopneas were classified as central or obstructive if, respectively, i) thoraco-abdominal movements were in-phase and there was no evidence of airflow limitation on nasal pressure or snoring, and ii) thoraco-abdominal movements were out-of-phase and/or there was evidence of airflow limitation on nasal pressure or snoring.

In the presence of an AHI ≥ 5, a patient was classified as dominant central sleep apnea (dCSA) if >50% of the events were central in nature and the central AHI was ≥5/h, or as dominant obstructive sleep apnea (dOSA) if ≥50% of the events were obstructive in nature and the obstructive AHI was ≥5/h. If none of these criteria were met, the patient was classified as having no sleep-disordered breathing (No-SDB).

2.4. Statistical analysis

Descriptive statistics are reported as mean ± SD for continuous variables and N (%) for categorical variables. Between-group comparisons for continuous variables were performed by one-way ANOVA with the least-significant-difference post-hoc test. Comparisons for categorical variables were performed by the Chi-square test. A p-value <0.05 was considered statistically significant and all tests were two-sided.

3. Results

At the pre-intervention study, the overall prevalence of a dominant SDB was 64%: 18 patients (36%) had No-SDB, 22 (44%) had dOSA, and 10 (20%) dCSA. Table 1 reports the clinical and functional parameters according to the sleep disturbance characterization. Although all patients had been admitted for elective PEA, at the time of surgery 80% of them were in advanced NYHA class and 44% were receiving oxygen therapy. No significant differences were observed in demographic and clinical characteristics among the three groups except for a higher prevalence of female gender among dOSA patients. Moreover, there were no differences with respect to the history of deep venous thrombosis, atrial fibrillation, systemic hypertension, diabetes, COPD and the need for supplemental oxygen therapy. Interesting observations can be drawn from the analysis of the hemodynamic data. While cardiac index did not differ at all, mean right atrial pressure (mRAP) and mean pulmonary artery pressure (mPAP) showed an increase from No-SDB to dOSA and dCSA (levels of significance for the various comparisons are reported in Table 1). Similarly, there was an increasing trend in right ventricular diameter (RVD) (albeit not statistically significant) and a decrease in TAPSE at echocardiography (significant only between No-SDB and dOSA, Table 1).

Mean AHI in SDB patients was 22.7 ± 18.7 events/h, and was markedly higher in dCSA patients as compared to dOSA patients (37.1 ± 25.2 vs 16.2 ± 10.0 events/h, $p < 0.0001$). Similarly, the ODI was significantly larger in patients with dCSA as compared to patients with dOSA (40.6 ± 20.3 vs 20.9 ± 13.3 events/h, $p < 0.0001$).

There were no significant differences among pulmonary function data and PaO_2 and $PaCO_2$ were similar among the 3 groups.

Table 2 shows the significant benefit of PEA on pulmonary hypertension. Mean PAP and pulmonary vascular resistance were decreased by >50% and cardiac index was increased by >20%. Right ventricular cavitary dimensions were significantly decreased whereas left ventricular diastolic diameter increased. By contrast, at the post-intervention sleep study, the severity of SDB as assessed by the AHI and ODI (Table 2), as well as the overall prevalence of SDB (68%) did not show any significant change. However, there was a marked change in the relative distribution of dOSA and dCSA patterns ($p < 0.0001$); indeed, 16 (32%) patients had No-SDB, 30 (60%) had dOSA and 4 (8%) had dCSA. Fig. 1 illustrates individual changes among SDB patterns: 12 out of the 18 patients who had No-SDB at the entry study remained negative and 6 developed dOSA; 19 out of the 22 patients who had dOSA at the entry study maintained an OSA dominance while, of the remaining three, 2 became negative and 1 developed dCSA. Interestingly, major changes occurred in the subset of patients who initially had shown a dCSA pattern: only 3 of them maintained the same dominance while, of the remaining seven, 5 moved to an OSA dominance and 2 normalized to No-SDB.