Slow and fast changes in transmural pulmonary artery pressure in obstructive sleep apnoea

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ABSTRACT: Our purpose was to assess how pulmonary artery pressure changes in relation to hypoxia and oesophageal pressure during obstructive sleep apnoeas.

Transmural systolic pulmonary artery pressure (Ppa,STM), oxyhaemoglobin saturation (Sao_2) and oesophageal pressure were analysed in two samples of consecutive obstructive apnoeas in each of four patients.

In the first samples (samples A; probably recorded during non-rapid eye movement (NREM) sleep), Sao_2 swings were small and repetitive. In the second samples (samples B; probably recorded during rapid eye movement (REM) sleep), they were large and more variable. Oesophageal pressure oscillated similarly in the two groups of samples. In all cases, transmural systolic pulmonary artery pressure progressively increased throughout apnoeas, and subsequently decreased in the interapnoeic periods. However, both early and end-apnoeic transmural systolic pulmonary artery pressure, remained stable in samples A; whilst they progressively increased in samples B. Transmural systolic pulmonary artery pressure at the beginning of each apnoea was inversely correlated with Sao_2 at the end of the preceding apnoea. These results suggest that transmural systolic pulmonary artery pressure is influenced by Sao_2, but does not vary at the same speed as Sao_2. In all cases, beat-by-beat analysis showed, as expected, that the lower the oesophageal pressure, the higher the transmural systolic pulmonary artery pressure however, at each oesophageal pressure level, transmural systolic pulmonary artery pressure was more variable and higher, in samples B.

In conclusion, transmural systolic pulmonary artery pressure in obstructive apnoeas shows rapid changes, which reflect oesophageal pressure variations, and slower changes, which are likely to be caused by Sao_2.
Eur Respir J., 1994, 7, 2192–2198.

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Pulmonary circulation is profoundly affected by obstructive sleep apnoeas (OSA). Pulmonary artery pressure (Ppa) in OSA, as referenced to atmospheric pressure, shows wide variations during obstructed respiratory efforts and reaches the highest levels as ventilation is resumed [1–3]. Conversely, when Ppa is measured as referenced to intrathoracic pressure, *i.e.* as transmural pressure, its oscillations during occluded breaths are greatly blunted; a progressive increase in its values is observed throughout apnoea, followed by a decrease soon after ventilation is resumed, until the early portion of the following apnoea [4].

The pathogenesis of Ppa variations during OSA is not clear. The factors which have been proposed for the pathogenesis of Ppa changes in OSA are: changes in cardiac output [3, 5], the mechanical influences of intrathoracic pressure swings [6, 7], and hypoxia [1, 4, 5, 8].

Many studies have suggested that hypoxia developed during OSA may have an important influence on Ppa behaviour. In fact, Ppa during sleep increases more during room air breathing than during oxygen administration [5]; Ppa values during OSA are usually inversely correlated with arterial oxygen tension (Pao_2) or oxyhaemoglobin saturation (Sao_2) values [1, 4]; and Ppa at apnoea termination increases as Sao_2 decreases during repetitive airway occlusion trials in dogs [8]. However, when oxygen was administered to blunt Sao_2 oscillations during OSA occurring in non rapid eye movement sleep (NREM) sleep, no significant effect was found on transmural Ppa oscillations within apnoeas [9].

The studies published, so far, concerning the effect of hypoxia on Ppa in OSA have been limited to the highest nocturnal Ppa value [5], the highest value after occlusion [8], or the values recorded only in NREM sleep, when the range of Sao_2 oscillation is limited [9]. In our previous study [9], we hypothesized that although hypoxia may determine, if any, only a minor increase in Ppa within each apnoea, it could cause a sustained increase in Ppa in consecutive apnoeas, since the time course of the response of the pulmonary vessels
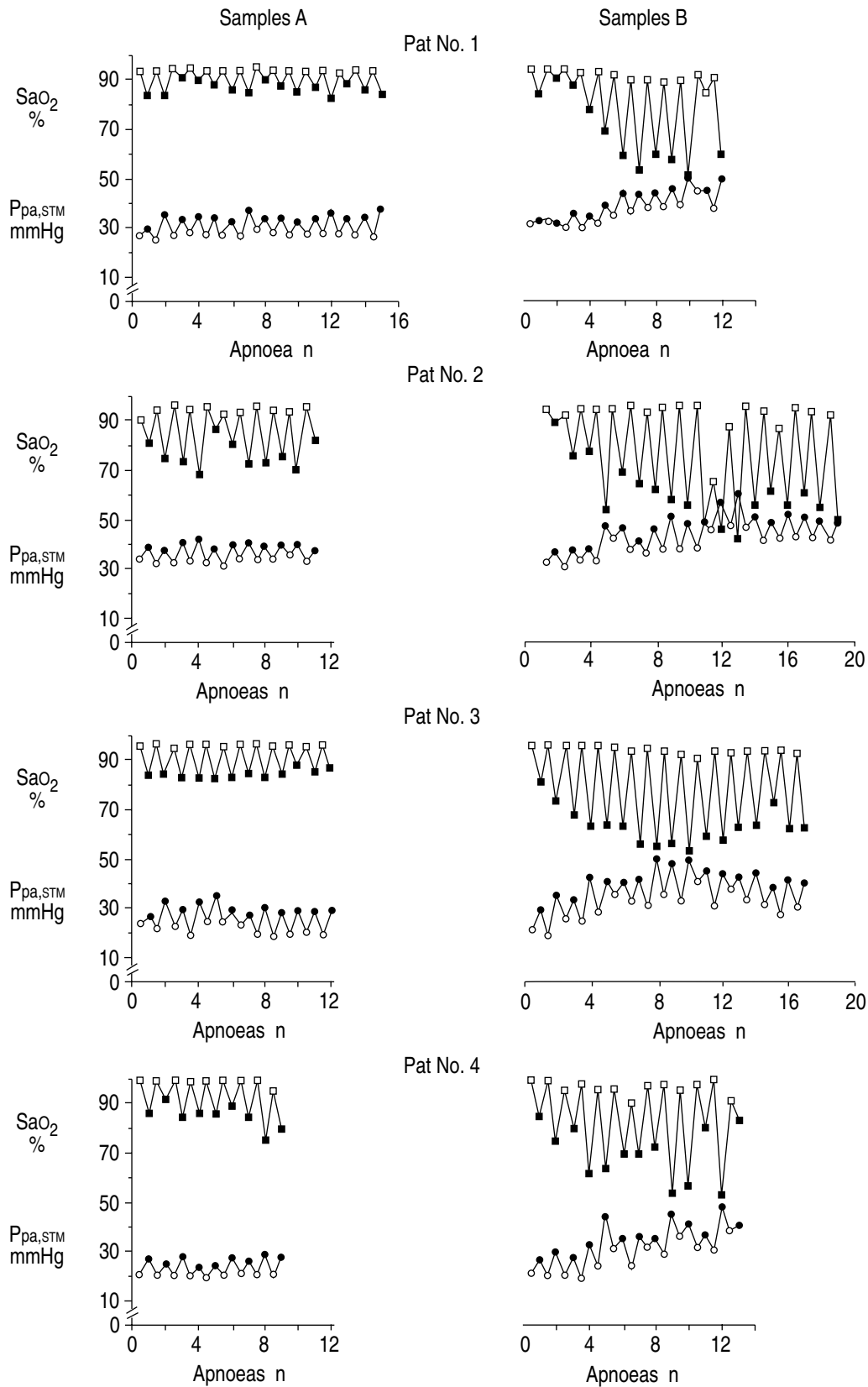
Fig. 1. – Consecutive values of Sao$_2$ (upper part of each panel), and simultaneous values of Ppa,STM (lower part of each panel), in the sequences of apnoeic cycles of the A (left panels), and B (right panels) samples in each patient. Open symbols indicate beginning of apnoea (□ Sao$_2$,b; ○ Ppa,STM,b), closed symbols indicate end of apnoea (● Sao$_2$,e, ● Ppa,STM,e).Pat: patient; Sao$_2$: arterial oxygen saturation . Ppa,STM: transmural systolic pulmonary artery pressure; Samples A: apnoeas with small Sao$_2$ falls; samples B: apnoeas with large Sao$_2$ falls.

to hypoxia may be slower than the Sao_2 swings occurring in each apnoea episode. However, we could not prove this hypothesis, probably because of the interference, in our analysis, of intrathoracic pressure.

Therefore, to test our previous hypothesis, and to assess the influence of intrathoracic pressure swings on P_{PA} measurements, we compared the variations in Ppa and Sao_2 in spontaneously occurring consecutive obstructive apnoeic cycles, from samples which markedly differed in Sao_2 falls, whilst monitoring oesophageal pressure ($Poes$).

Patients and methods

Four patients with a previously diagnosed OSA syndrome (mean apnoea index 75, range 52–91) underwent a nocturnal polysomnographic study with right heart catheterization. Patients were selected for this study if they showed a severe somnolence due to the OSA syndrome, so that they would be able to sleep with all the equipment necessary for the study. The study was approved by the scientific committee of our institution. Informed consent was given by all subjects. No complications were observed during the catheterizations.

The following signals were continuously recorded on an eight channel strip chart recorder (Hewlett-Packard 7758 B) and stored on magnetic tape (Hewlett-Packard 3968 A): Sao_2, by an Ohmeda Biox 3700 ear oximeter; oronasal flow; $Poes$, as an estimate of intrathoracic pressure, by a balloon-tipped catheter introduced in the lower third of the oesophagus, inflated with 1 ml of air, and connected to a Validyne pressure transducer (MP 45-30-871); Ppa, in two subjects by a Swan-Ganz floating catheter connected to a Statham P 23 ID pressure transducer, and in the remaining two patients by a Millar catheter with tip transducer (Millar Instruments, model TC510). Electroencephalogram (EEG), electro-oculogram (EOG) and submental electromyogram (EMG) for the identification of NREM and rapid eye movement (REM) sleep, were monitored, on paper, in two subjects.

Analysis

As an apnoeic cycle, we considered a period including all the occluded breathing efforts of an apnoea, as well as the unoccluded breaths of the ventilatory period, which preceded another apnoea. In each patient, two uninterrupted sequences of 9–18 obstructive apnoeic cycles were selected for analysis. The first sequence, called sample A, included apnoeic cycles associated with relatively small Sao_2 falls and little variability in Sao_2 swings. The second sequence, called sample B, included all the consecutive apnoeic cycles recorded during the night which were associated with marked Sao_2 falls, as well as the three apnoeic cycles with small Sao_2 swings preceding them; we included these three apnoeic cycles in samples B to analyse Ppa when the transition from relatively small into large Sao_2 swings occurs (see fig. 1). Airflow, Sao_2, $Poes$, and Ppa signals recorded in the selected apnoeic cycles were sampled at 5 ms intervals and, after

analogue-to-digital conversion, stored in the mass memory of a computer (VAX 8200, Digital Equipment) and then analysed. Transmural Ppa values were obtained by computerized subtraction of $Poes$ from intravascular Ppa.

Systolic transmural Ppa ($Ppa,_{STM}$) was measured during 2 min of quiet breathing at the beginning of the studies as the mean±SD $Ppa,_{STM}$ in all the cardiac cycles.

To assess slow changes in Ppa in the apnoea sequences, $Ppa,_{STM}$ was measured as the lowest value at apnoea beginning ($Ppa,_{STM},b$), and highest value at apnoea end or at the resumption of ventilation ($Ppa,_{STM},e$). Both values were taken during late expiratory time, as indicated by a stable $Poes$ level. These $Ppa,_{STM}$ values were studied in relation to Sao_2 levels, considered as highest Sao_2 at the beginning (Sao_2b) and lowest Sao_2 at the end of apnoeas (Sao_2e).

To assess fast changes in Ppa within each apnoeic cycle, beat-by-beat $Ppa,_{STM}$ was taken into account. All the measured $Ppa,_{STM}$ values were plotted against the $Poes$ value in the immediately preceding end-diastolic time. Then, the $Poes$ range from +5 to -20 mmHg was divided into 5 mmHg intervals (+5 to 0, 0 to -5, -10 to -5, -15 to -10, and -20 to -15 mmHg). The variance of $Ppa,_{STM}$ for each $Poes$ interval was compared for each patient between samples A and B. Group mean values of $Ppa,_{STM}$ in each $Poes$ interval in samples A and B were also compared.

Statistical analysis

Data are given as mean±SD. Linear regression analysis was applied to study the relationship between Sao_2 and $Ppa,_{STM}$. Variance ratio test was performed to compare variances of $Ppa,_{STM}$ values between samples A and B for each $Poes$ interval. Means were compared by two-tailed t-test, unpaired or paired as appropriate. A $p<0.05$ was considered significant.

Results

Characteristics of the patients and their $Ppa,_{STM}$ whilst awake are shown in table 1.

In each patient, apnoeas were always separated by short ventilatory intervals. Apnoeas in samples B were longer, and were characterized by similar or less pronounced $Poes$ excursions than in samples A. Differences in Sao_2b between apnoeas in the two samples, although always significant, were small; whereas Sao_2e was always much lower in samples B (table 2).

In samples A, as Sao_2 showed monotonous and relatively small swings, both $Ppa,_{STM}b$ and $Ppa,_{STM},e$ values tended to remain constant in the consecutive apnoeic cycles. In samples B, as Sao_2 falls became greater, both $Ppa,_{STM},b$ and $Ppa,_{STM},e$ showed a trend to a progressive increase; after the transition from small to large Sao_2 swings, as large Sao_2 swings recurred, both $Ppa,_{STM},b$ and $Ppa,_{STM},e$ remained at higher levels than in the A samples (fig. 1).

In all patients, when we pooled sample A and B, $Ppa,_{STM},b$ was highly and significantly linearly correlated with Sao_2e in the preceding apnoea (fig. 2).

Table 1. – Characteristics of the patients

Pat No.		Age yrs	BMI kg·m⁻²	Awake SaO₂ %	Initial Ppa,STM,b mmHg
1	F	61	35.1	94	31.6±2.6
2	M	49	45.9	94	32.5±2.4
3	M	45	32.3	96	22.5±2.1
4	M	60	33.5	98	18.6±1.7

Pat: patient; F: female; M: male; BMI: body mass index; Sao_2: arterial oxygen saturation; Ppa,STM: systolic transmural pulmonary artery pressure.

Beat-by-beat analysis showed, in all cases, that Ppa,STM was higher when preceded by a more negative Poes (fig. 3); therefore, the highest Ppa,STM values were recorded during the inspiratory efforts preceding the interapnoeic breaths, where the most negative Poes values are found. However, in samples B, at each Poes level Ppa,STM values were more variable than in samples A (fig. 3); in fact the variance of Ppa,STM was significantly greater in samples B (p always <0.001) at every Poes interval. In addition, the group mean of Ppa,STM for every Poes interval was always significantly higher in samples B (fig. 4).
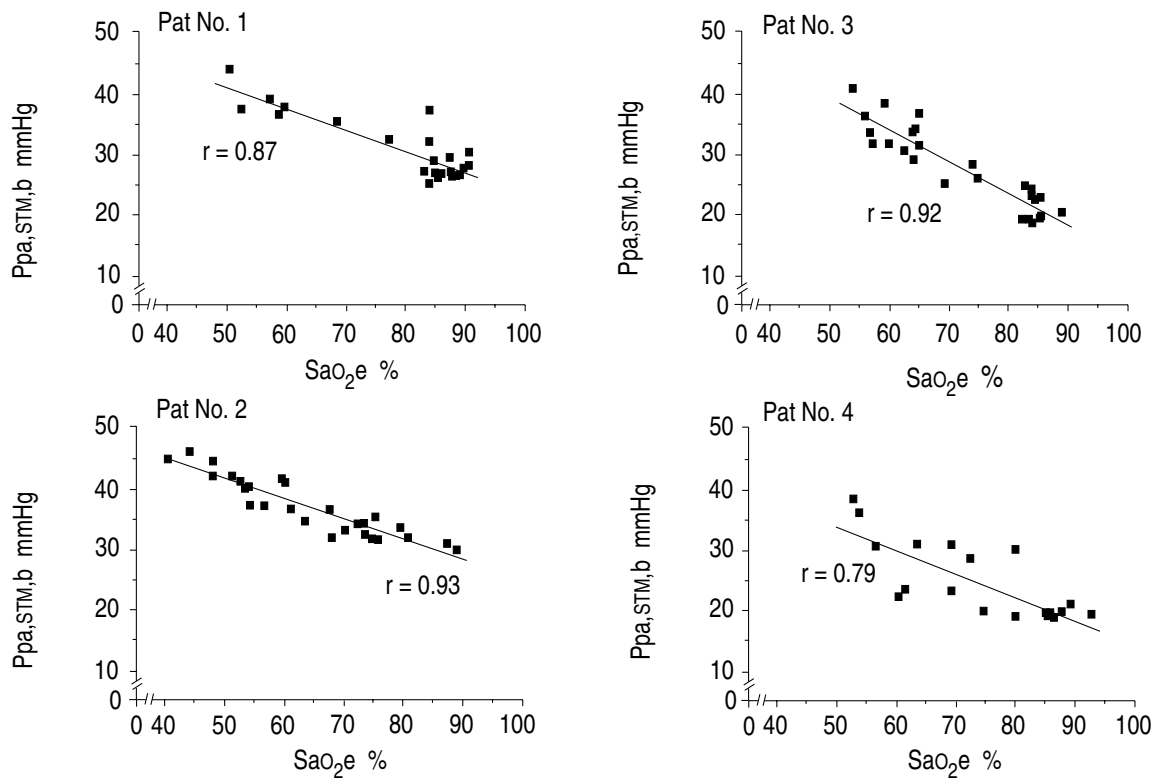

Fig. 2. – For each patient, correlations of Ppa,STM,b with Sao_2e of the preceding apnoeic cycle. Apnoeic cycles of both samples A and B have not been separated for this analysis. For abbreviations see legend to figure 1.

Table 2. – Characteristics of the selected apnoeas

Pat No.	Sample	Apnoeas n	Apnoea duration s	Interapnoeic duration s	Lowest Poes mmHg	Sao_2b %	Sao_2e %
1	A	15	20.3±4.3	14.3±4.8	-20.3±4.7	93.8±0.7	87.0±3.4
	B	12	32.5±14.2*	12.4±4.3	-17.8±3.7	91.5±1.8†	69.2±14.7***
2	A	11	23.5±5.6	14.1±4.0	-39.6±8.4	94.1±8.4	76.1±5.7
	B	18	35.9±15.4**	11.9±5.2	-32.1±7.1**	90.7±7.2	58.6±12.1†
3	A	12	31.3±2.8	18.6±2.6	-33.4±4.8	96.4±0.3	85.6±3.1
	B	17	47.3±9.2†	12.3±2.1†	-32.9±6.2	94.8±1.5***	62.4±6.0†
4	A	9	42.5±8.8	13.6±2.5	-36.5±9.1	98.9±1.4	85.0±5.1
	B	13	44.9±15.5	13.7±2.9	-34.7±7.2	96.1±2.8**	67.5±10.3†

Data are presented as mean±SD. Sample A: apnoes with small Sao_2 falls; sample B: apnoes with large Sao_2 falls. Pat: patient; Poes: oesophageal pressure; Sao_2b: arterial oxygen saturation at beginning of apnoea; Sao_2e: arterial oxygen saturation at end of apnoea; *, **, ***, †: p<0.05, 0.02, 0.002, 0.001 respectively, A vs B.
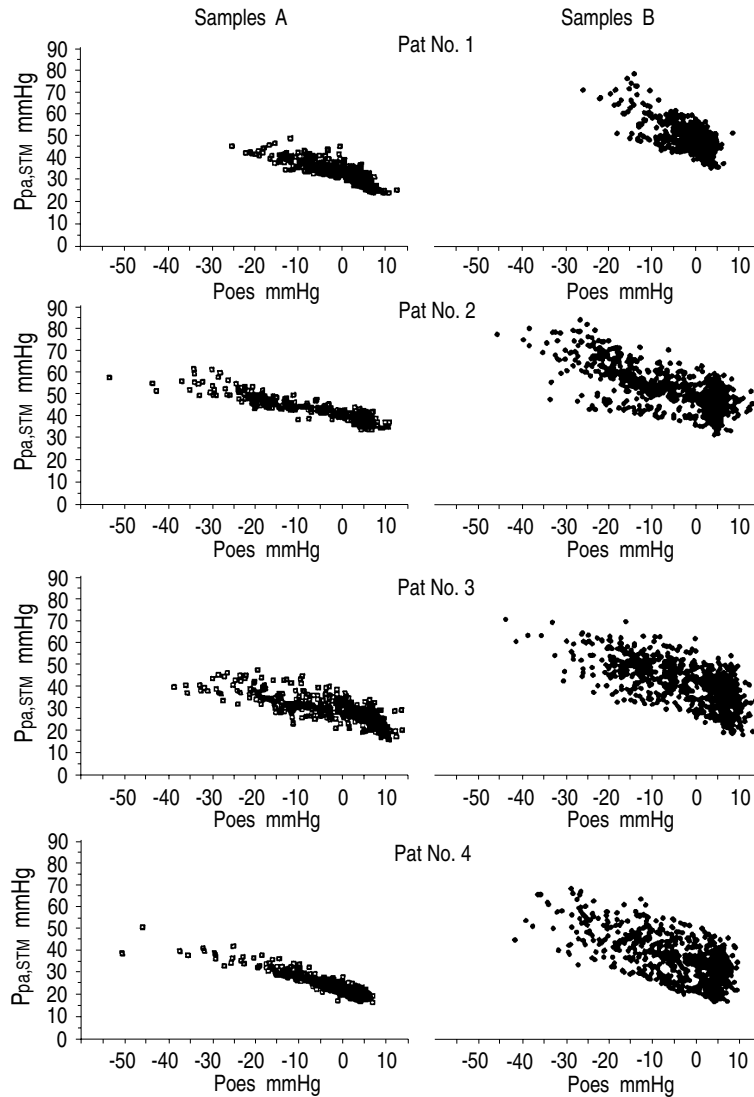
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Fig. 3. – Beat-by-beat transmural systolic pulmonary artery pressure (Ppa,STM) measurements in the whole apnoeic cycles plotted against the immediately preceding end-diastole Poes in each subject. Poes: oesophageal pressure; Pat: patient.
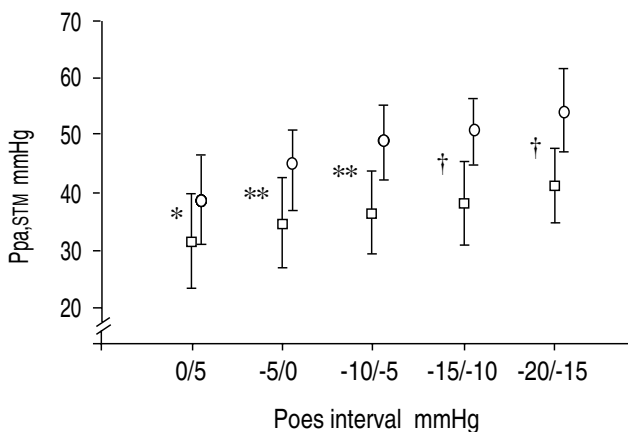

Fig. 4. – Group mean±SD for all patients of Ppa,STM recorded at different Poes intervals in samples A (□) and B (○). Levels of significance of differences between the two samples are shown as: *: p<0.01; **: p<0.005; †: p<0.002. For abbreviations see legend to figure 3.

Discussion

In this study, we analysed the lowest and highest Ppa,STM and Sao$_2$ values in each of several consecutive apnoeic cycles, so as to investigate whether the time course of Ppa variations differed from the time course of Sao$_2$ swings (fig. 1). We also measured Ppa,STM beat-by-beat to assess the rapid Ppa changes occurring in each apnoeic cycle.

Our main findings were twofold: a) obstructive apnoeas are associated with Ppa changes which are related to hypoxia but are not as rapid as Sao$_2$ changes; in fact, Sao$_2$ after each interapnoeic period (Sao$_2$b tended to return to a substantially constant value, whatever the extent of its drop in each apnoea, whilst Ppa,STM was not reverted to a constant level after the largest increases (fig. 1); and b) transmural Ppa undergoes rapid changes, which reflect the changes in Poes (fig. 3): within each breath, either occluded or unoccluded, Ppa,STM was higher during the inspiratory time, when Poes falls, and was lower during the expiratory time, when Poes increases.

When examining the slow changes in $Ppa,_{STM}$, *i.e.* those between the two extremities of apnoeic cycles, we took into account only expiratory $Ppa,_{STM}$ values, in order to minimize possible effects of intrathoracic pressure on our measurements. By using this approach, we observed that, as long as Sao_2 swings were relatively small and monotonous, $Ppa,_{STM}$,b and $Ppa,_{STM}$,e remained substantially constant; conversely, as Sao_2 swings became more pronounced, due to greater Sao_2 drops at the end of apnoeas, $Ppa,_{STM}$ progressively increased, both in the levels recorded at the beginning and at the end of apnoeic cycles. In addition, we found that $Ppa,_{STM}$ in the early portion of each apnoea was closely correlated with Sao_2 at the end of the preceding one.

In the two subjects in whom EEG, EOG and EMG were monitored, we verified that the apnoeic cycles in samples A were recorded during NREM, and those in samples B during REM sleep; this probably also occurred in the remaining two subjects. A contribution of influences linked to NREM or REM sleep state to the Ppa behaviour in obstructive apnoeic cycles cannot be ruled out, but we are not aware of any study concerning a difference in the hypoxic pulmonary vessels response between NREM and REM sleep. However, our findings may be explained on the basis of the well-known time course of the pulmonary vessels response to hypoxia, which is slower than Sao_2 changes during apnoeic cycles. In fact, hypoxic pulmonary vessel response starts within a few seconds of exposure to hypoxia but peaks only after some minutes [10–14]. Sao_2 falls during sleep apnoeas are generally produced in less than a minute, and are reverted in only a few seconds. Therefore, the increase in Ppa from the beginning to the end of obstructive apnoeic cycles may not represent a full response to the level of hypoxia reached during apnoeas, but only part of the response that would occur if the same level of hypoxia were maintained for a longer time. Moreover, when hypoxia is relieved during the interapnoeic ventilatory interval, Ppa may not return to its baseline level, particularly when Sao_2 falls markedly during apnoeas, because the relief of hypoxia is of too short a duration.

In addition, as suggested by PODSZUS and co-workers [6, 7], hypoxia, in association with hypercapnia, could lead to a prolonged Ppa increase as a result of an insufficient interapnoeic ventilation.

Eventually, the effect of hypoxia could also derive from the repeated hypoxic challenges in the closely recurring OSA episodes. In fact, some authors have found an increase in the hypoxic pulmonary vasoconstriction with repeated intermittent hypoxia [15, 16]. However, this finding has not been universal, and could be secondary to the experimental procedure [17].

In both A and B apnoea samples, the analysis of beat-by-beat $Ppa,_{STM}$ showed that transmural Ppa closely follows Poes, so that the more negative the immediately preceding Poes, the higher $Ppa,_{STM}$ along the entire range of Poes. However, at every Poes level, $Ppa,_{STM}$ was higher and more variable in B than in A samples. These findings suggest that, as a result of the previously described influence of Sao_2 on $Ppa,_{STM}$, at each Poes level $Ppa,_{STM}$ progressively increased in consecutive ap-

noeic cycles of the B samples, whilst the effect of Poes on $Ppa,_{STM}$ measurements remained unmodified; this explains the higher $Ppa,_{STM}$ variance in the B samples. In addition, the relationship between Poes and $Ppa,_{STM}$ measurements helps explain why transmural Ppa measurements, at variance from the intravascular ones, may sometimes be higher at apnoea end, when Poes excursions are marked, than immediately after apnoea [4].

The possibility for Ppa to increase progressively during the night had been pointed out in early studies [2, 3, 5]. However, in those papers, Ppa trend had not been studied in detail or correlated with the changes in Sao_2. Our data suggest that a trend to a progressive increase in Ppa during repetitive apnoeas occurs and becomes evident only when the pattern of Sao_2 behaviour changes from small to large swings.

The design of this study does not allow for a clear recognition of the role of intrathoracic pressure on transmural Ppa. In fact, we could not compute a regression beween Poes and $Ppa,_{STM}$, since Poes during systole, which is very close to end-diastole Poes, is included in the calculation of $Ppa,_{STM}$, and we would have obtained a spurious correlation.

However, other studies have demonstrated that negative intrathoracic pressure increases transmural Ppa [18–20]. Such an increase could be consequent to an increase in right ventricular preload [21] and output [21, 22], or to an increase in left ventricular afterload [18–20, 23]. However, PODSZUS and co-workers [6] considered negative intrathoracic pressure as a possible cause for a decrease, and not for an increase, in Ppa, due to possible extrathoracic vein collapse and venous return limitation; in fact, venous return was found to be limited by extrathoracic vein collapse when threshold negative intrathoracic pressure levels were exceeded [24]. As concerns left ventricular afterload, its increase was regarded as the possible cause for an increase in pulmonary wedge pressure recorded in OSA, which, in turn, could determine an increase in Ppa [25]. Conversely, in a canine experimental model, no difference was found between the left ventricular systolic pressure recorded in the inspiratory and in the expiratory time during periodic upper airway obstruction [26]; which is not consistent with an increase in afterload during the inspiratory effort. In fact, the afterloading effect of negative intrathoracic pressure on the left ventricle is controversial, and could be evident only when intrathoracic pressure reaches very negative levels [27]. In OSA patients, echocardiographic evaluation of right and left ventricular volume, performed while monitoring Poes, demonstrated that both ventricular volumes change during each obstructed breath of OSA; as documented by Poes, the right ventricle reaches the largest size, and the left ventricle the lowest size, during the inspiratory effort, whilst the opposite occurs at the release of the inspiratory effort [28].

Our data may thus suggest that there is an effect of intrathoracic pressure on Ppa, but other data in the literature more strongly support that effect. Whatever the mechanism by which negative intrathoracic pressure may act, the results of most studies on this subject support our view that the decrease in intrathoracic pressure may cause an increase in transmural Ppa.

A possible role for an increase in cardiac output at the release of obstruction as a cause of the postapnoeic increase of Ppa, as previously suggested [3, 5], can no longer be upheld, in the light of the recent studies which have shown a decrease in cardiac output in the immediate post-apnoeic period [29, 30].

In conclusion, in this study we have found that transmural Ppa in obstructive apnoeic cycles shows two types of oscillation: a) rapid changes, which are synchronous with Poes changes and can be detected in each breath, either occluded or unoccluded; and b) slower changes, consisting of an increase from the beginning to the end of the apnoeic cycle, and a decrease from the end of the apnoeic cycle to the beginning of the following one. We believe that hypoxia is a major determinant of the slower transmural Ppa changes in OSA. However, pulmonary vessels are not able to fully respond to the ra-pid SaO_2 changes occurring during apnoeas. Thus, the variation in Ppa in the apnoeic cycle may include only an incomplete response to the level of SaO_2 that is reached either at its beginning or at its end, whilst some effects of hypoxia may still be present beyond the time of the apnoea where it is produced, in the following apnoeic cycle.

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