

Transmural Pressure Measurements*

Importance in the Assessment of Pulmonary Hypertension in Obstructive Sleep Apneas

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Seven patients with OSAS were studied during nocturnal sleep in order to assess the trend of PAP throughout apneas and to identify factors possibly associated with such a trend. All patients underwent a polysomnography including the monitoring of PAP and esophageal pressure. While intravascular PAP decreased during apneas and increased at the resumption of breathing, transmural PAP values (*ie*, corrected for intrathoracic pressure swings) showed a trend toward a progressive increase throughout apneas and toward a decrease once ventilation had been resumed. The measurement of transmural values allowed a reliable

assessment of PAP changes occurring during apneas, and different degrees of such changes shown by different patients may be related to a host of factors relevant to wakefulness and sleep, including individual responsiveness to hypoxic stimulus. (Chest 1989; 95:338-42)

Ppl = pleural pressure; AI = apnea index; AT = apnea time; TST = total sleep time; Ps = systolic intravascular value; Pd = diastolic intravascular value; Pstm = transmural systolic pressure; Pdtm = transmural diastolic pressure

The hemodynamic characteristic of OSAS is the recurrence of cyclic oscillations in PAP during sleep.¹⁻⁷ However, no detailed analysis of the course of changes in PAP throughout the apneas has yet been reported; in addition, the hemodynamic data reported so far are relevant to measurements performed with reference to atmospheric pressure, *ie*, in terms of intravascular values. In such a way, they do not take into account the effect of oscillations in intrathoracic pressure of increasing magnitude which are noticed during occluded efforts of apneas, and to a lesser extent, in the early phase of the following unoccluded breathing. A similar phenomenon may be detected as an effect of lower airway obstruction;⁸ its analysis has led to the conclusion that in order to avoid an artifactual distortion of PAP tracing, all values are to be corrected for the intrathoracic pressure, *ie*, they are to be expressed in terms of transmural values.^{8,9}

The present investigation examined the following: (1) the detailed assessment of the changes in PAP during the course of apneas; (2) the evaluation of the effect of intrathoracic pressure in the various phases of these events; and (3) the identification of factors possibly associated with the hemodynamic changes.

PATIENTS AND METHODS

Seven patients, three men and four women, affected by OSAS, previously diagnosed by means of nocturnal polysomnography, were

studied; they showed normal or mildly altered blood gas tensions during wakefulness, normal spirometric values, and a variable degree of weight excess (Table 1). All patients gave informed consent to the following studies.

A Swan-Ganz catheter was introduced into the pulmonary artery through an antecubital or femoral vein and connected to a pressure transducer; mean PAP was measured during wakefulness (PAP W), before a sleep study was initiated (Table 1). Then, nocturnal polysomnography was performed, including, besides PAP, the following signals: electroencephalogram (unipolar leads C3 A2 and C4 A1), electrooculogram, and electromyogram, for conventional sleep staging; nasal airflow; electrocardiogram; oxyhemoglobin saturation (SaO₂) obtained by means of an ear oximeter; esophageal pressure, as an estimate of pleural pressure (Ppl), obtained with a balloon tipped catheter introduced in the lower third of the esophagus, connected to a pressure transducer and inflated with 1 ml of air. The state of filling of the esophageal balloon and the calibrations of Ppl and PAP were repeatedly checked during the night.

On each sleep study, the number of apneas per hour of sleep time (apnea index, AI), the mean apnea duration, and the percentage of sleep time spent in apnea (apnea time/total sleep time, AT/TST) were calculated. For each subject, we selected a sample including five to eight apneas whose duration approximated the one calculated over the whole sleep time. Within each apneic cycle, we analyzed the three unoccluded breaths preceding the onset of occlusion, all the occluded efforts, and finally, the subsequent three breaths after the resumption of ventilation. For each breath, we measured the corresponding PAP, Ppl, HR, and SaO₂ values as follows.

For PAP, we directly measured the systolic (Ps) and diastolic (Pd) intravascular values (*ie*, relevant to atmosphere). From such values, we subtracted a pressure equal to Ppl measured in the same instant, in order to derive transmural systolic (Pstm) and diastolic (Pdtm) pressures. Then Ps, Pd, Pstm, and Pdtm were averaged for each selected breath and the mean for the subjects obtained.

The Ppl was measured as the maximum negative value per breath.

The HR was calculated on the cardiac cycles occurring within each breath.

For SaO₂, we measured the lowest value recorded over each

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Table 1—Characteristics of the Patients

Patient	Age, yrs	Sex	Weight, % Ideal	PaO ₂ , mm Hg	PaCO ₂ , mm Hg	FEV ₁ /VC %	TLC % Pred	Hb, g %	PAP W, mm Hg
1	39	F	198	64	49	79	112	14.1	28
2	40	M	176	78	46	83	102	17.3	22
3	56	F	156	69	42	74	131	15.2	18
4	63	F	186	72	44	73	130	14.8	12
5	35	F	222	62	42	80	92	13.0	15
6	34	M	153	89	40	82	92	14.2	10
7	38	M	276	76	42	82	90	15.0	22

breath and corrected it, taking into account the delay in the oximeter response. Since this delay is HR-dependent,¹⁰ we decided to discard the values recorded in the interapneic period and the first occluded breath of each apnea, when the more marked HR changes affect the SaO₂ measurement to a variable and hardly predictable extent. Conversely, values relevant to the later phase of apnea were retained and corrected assuming as a constant, the ten second delay which we measured between the end of apnea and the nadir of SaO₂. In addition, in each apnea, the lowest SaO₂ value and the fall in SaO₂ were measured.

For the sample as a whole, the trend of variation of all parameters was assessed by averaging the mean values obtained upon each corresponding breath in the individual patients: to account for the interindividual difference in apnea duration, we decided to restrict the calculation to the first eight and to the last two occluded efforts, independently of the actual number of efforts included in the apnea. Because of this criterion, data relevant to patient 7, whose apneas included less than eight breaths, were not considered for these calculations. Data concerning the preapneic and postapneic breaths were also averaged.

Finally, for each subject, the mean variation in Pstm (ΔPstm) and Pdtm (ΔPdtm) taking place during the apnea-postapnea cycles was calculated as an overall index of trend to pulmonary hypertension during obstructed breathing.

RESULTS

All patients were shown to be affected by severe OSAS, as demonstrated by a high frequency of apneas (AI = 89.9 ± 15.2 SD) of variable duration (26 ± 9.6 s), which accounted for a high AT/TST percentage (65.3 ± 15.6 percent). Only NREM sleep was recorded. The selected apneas were characterized by comparable duration (26.9 ± 8.3 s), resulting in marked falls in SaO₂ (lowest SaO₂, 77.3 ± 4.2 percent; SaO₂

fall, 12.1 ± 4.5 percent) (Table 2).

Periodic oscillations corresponding to the apnea-ventilation cycles were observed in both intravascular and transmural pressures; however, simultaneously with the progressive deepening of Ppl in the course of apneas, intravascular PAP was more and more displaced toward low values while transmural PAP progressively increased (Fig 1). As for intravascular PAP values, an irregular trend to Ps and Pd decrease throughout apneas, followed by a sharp increase at the resumption of ventilation, was observed in most subjects; exceptions were represented by patient 1, who increased her Ps in the last occluded breaths, and patient 6, who showed an increase in Ps and Pd in the intermediate portion of the apnea (Fig 2). Conversely, Pstm and Pdtm showed a more regular trend, represented by a decrease from the preapneic breaths to the first and second occluded breath, followed by a smooth increase until the last occluded breath or the first postapneic breath, and by a new decrease in the postapneic period; a different trend was observed in patient 6, who showed only minor variations in his Pstm and Pdtm in the course of his apneas.

On the average, the variation between the highest and the lowest values of Pstm, and respectively, Pdtm were found to be statistically significant (p respectively <0.01 and <0.005) (Fig 3). In indices monitored together with Pstm and Pdtm, the following trends were observed: Ppl paralleled intravascular PAP; in fact, its depressions became less negative during the

Table 2—Characteristics of Respiration During Sleep

Patient No.	AI, No./h	AI/TST, (%)	Mean Apnea Duration s	Characteristics of the Selected Apneas				Mean Lowest Ppl (mm Hg)
				No	Mean Apnea Duration s	Mean Lowest SaO ₂ , %	Mean SaO ₂ fall, %	
1	76	83	39	5	35	76	18.2	-40
2	87	92	39	8	38	77	12.8	-42
3	82	58	23	6	23	80	8.3	-33
4	85	56	22	5	23	84	7.6	-13
5	103	59	19	6	22	79	10.8	-38
6	78	58	26	7	32	74	18.1	-18
7	118	51	14	6	15	71	8.7	-27
\bar{x}	89.9	65.3	26		26.9	77.3	12.1	-28.8
SD	15.2	9.6	15.6		8.3	4.2	4.5	11.7

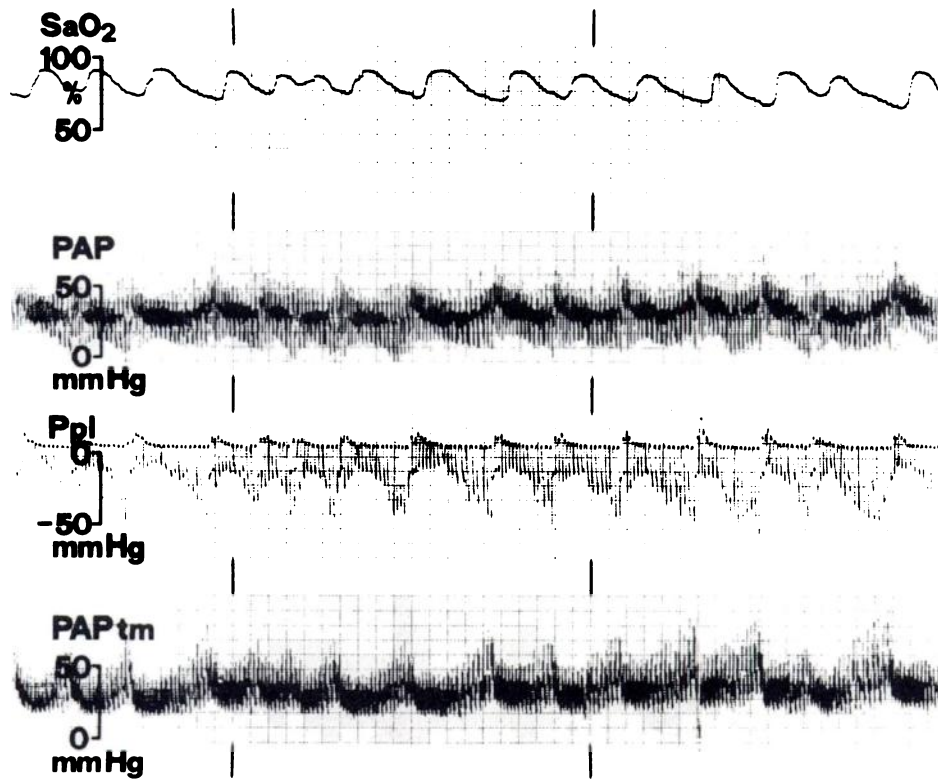


FIGURE 1. Mean values of Ps, Pd, Pstm and Pdtm in each patient as result from the analysis of a representative sample of apneas. On the abscissa: -3, -2, -1 = sequence of pre-apneic breaths; I-XIV is sequence of occluded breaths; SL, second last occluded breath; L, last occluded breath; 1, 2, 3, sequence of postapneic breaths. Circled numbers identify patients.

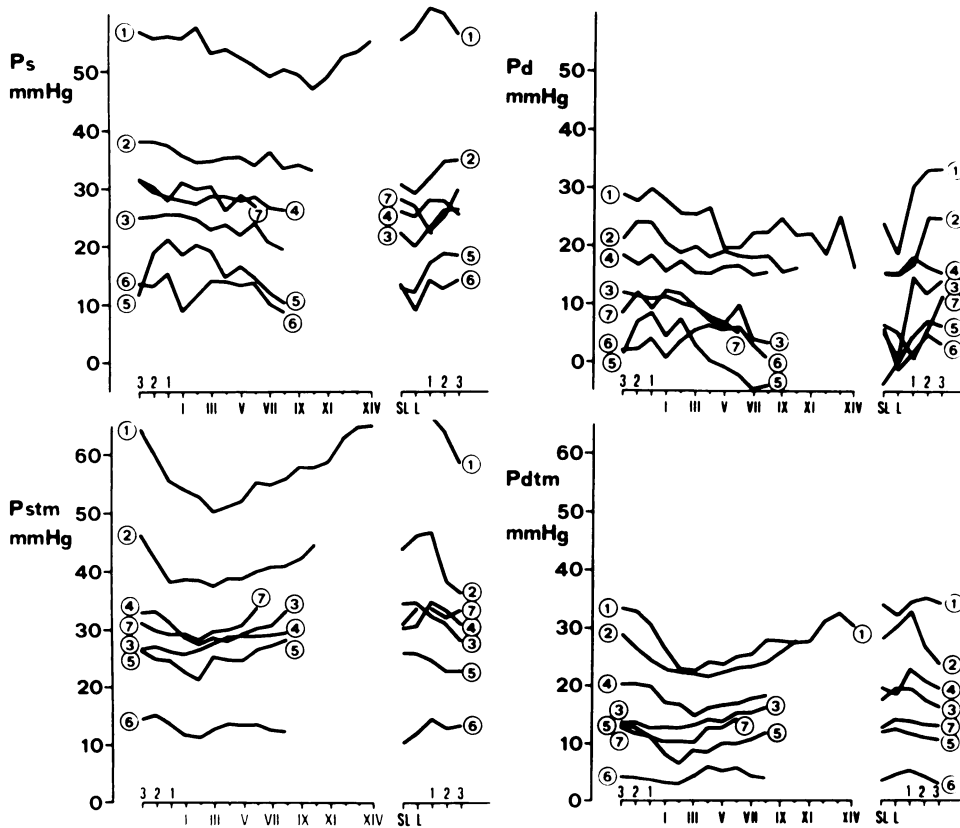


FIGURE 2. SaO₂, intravascular PAP, Ppl, and transmural PAP in several consecutive obstructive apneas in patient 2.

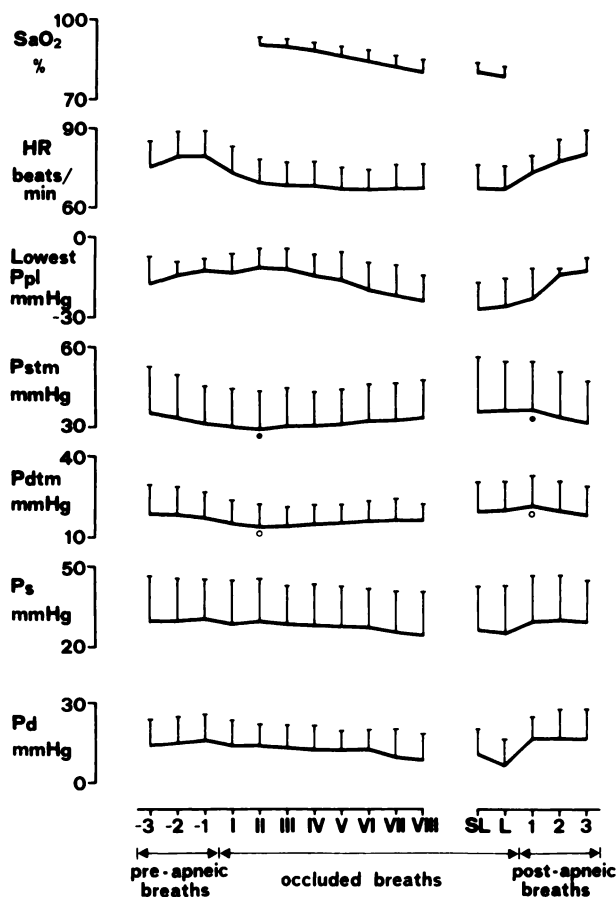


FIGURE 3. Means + SD of the various monitored signals in all patients. Abscissa like in Figure 1. Closed circles, $p < 0.01$; open circles, $p < 0.005$.

preapneic period, more and more negative throughout the apnea, and again, progressively less negative in the postapneic period. The HR increased in the preapneic period, decreased in the first two occluded breaths; then, it remained substantially stable until the end of the apnea and increased again in the postapneic period. Finally, as expected, SaO_2 underwent a steady decrease throughout the apneas (Fig 3).

The SaO_2 values during apneas showed a significant negative correlation with the concomitant Pstm values in five of seven and with the concomitant Pdtm values in six of seven patients (Fig 4); in patient 3, Pstm, and in patient 6, both Pstm and Pdtm were not significantly correlated with SaO_2 .

The mean values of $\Delta Pstm$ and $\Delta Pdtm$ calculated

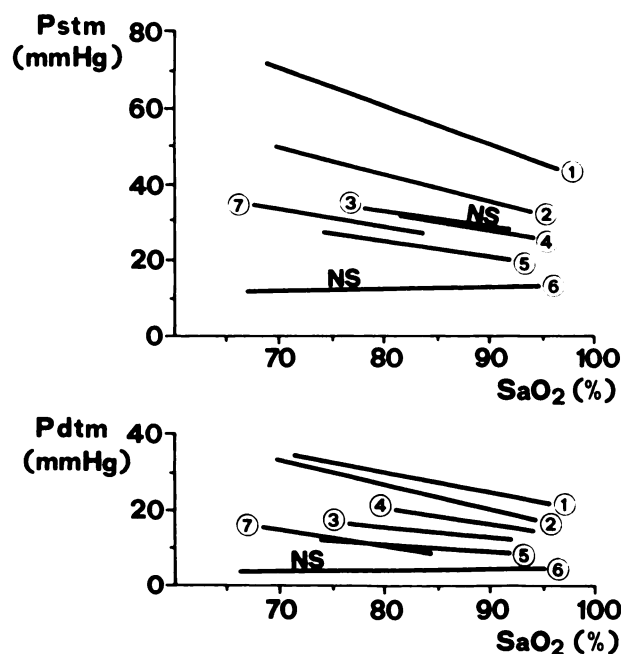


FIGURE 4. Slopes of the correlations between Pstm and SaO_2 (upper panel) and Pdtm and SaO_2 (lower panel) in each subject. Circled numbers identify patients.

for each subject were significantly correlated with the following variables: AT/TST, slope of the correlation of respectively Pstm or Pdtm with SaO_2 , $\bar{PAP} W$, and $PaCO_2$ during wakefulness (Table 3); no correlation was found between both values of transmural PAP variation, and respectively, PaO_2 and SaO_2 during wakefulness, AI, and mean fall in SaO_2 during apneas.

DISCUSSION

Evaluation of pulmonary hemodynamics during sleep-induced obstructive apneas clearly demonstrated that these events were associated with a progressive increase in PAP. Although this phenomenon had already been hypothesized,⁵ a reliable account of its actual relationship with mechanical and chemical variables throughout the apnea has never been reported, since all previous investigations have had major limitations. In fact, the only investigation¹ dealing with hemodynamic follow-up in the various phases of apneas ignored the concomitant changes in intrathoracic pressure; therefore, its results, comparable with ours concerning intravascular values, have misled toward

Table 3—Coefficients and Significance of Correlations of $\Delta Pstm$ and $\Delta Pdtm$ With Various Indexes

	AT/TST		Slope Transmural Pressure/ SaO_2		$\bar{PAP} W$		$PaCO_2 W$	
	r	p	r	p	r	p	r	p
$\Delta Pstm$	0.81	<0.025	-0.98	<0.005	0.81	<0.025	0.96	<0.005
$\Delta Pdtm$	0.87	<0.01	-0.87	<0.025	0.76	<0.05	0.97	<0.005

considering obstructive apneas as associated with a decrease in PAP. For the same reasons, in investigations pointing out only the hypertensive peak over the whole cycle of apnea,² maximum values are reported as occurring at the resumption of ventilation.

Conversely, if, as in the present study, all values were corrected to account for the effect of large intrathoracic pressure swings, a different picture emerges: the apparent and irregular decline in intravascular values during apnea, followed by a sudden increase at the resumption of breathing, is replaced by a regular increase in transmural pressure up to a maximum value which is reached on the occasion of the last occluded efforts and sustained during the early phase of the reventilating period. Like the artifactual decrease, also the cited irregularity of intravascular variations is a consequence of intrathoracic pressure changes; in fact, because of the difference between HR and respiratory frequency, systoles and diastoles are randomly superimposed over the cycle of Ppl variations: as a consequence, the degree of the artifactual change in PAP, although dependent upon the magnitude of intrathoracic negative pressure, is variable and not proportional to the latter.

Unlike that relevant to intravascular PAP, the temporal relationship between transmural PAP and SaO₂ changes supports the hypothesis that the latter are the major determinants of pulmonary hypertension.

Within the context of this interpretation, the trend of PAP changes at the resumption of ventilation deserves an additional comment. The apparent steady increase noticed when dealing with intravascular values had been interpreted as possibly due to an increase in cardiac output, induced by the postapneic sympathetic discharge which is responsible for the characteristic tachycardia of that period.⁴ However, our results concerning the decline in transmural PAP after the first unoccluded breath, while HR is still increasing, do not lend support to this hypothesis and confirm once more the pivotal role of SaO₂ changes.

Other evidence supporting this role is represented by the significant linear correlation between transmural PAP and SaO₂ found in most patients. The lack of correlation found in the subject who underwent only minor transmural PAP change over the apneas, as well as the difference in the slope of correlation lines in the other six patients, may be interpreted as due to the well known interindividual variability in hemodynamic response to hypoxia.¹¹

Besides this individual character of responsivity, other factors have been found to correlate with transmural PAP variations, and therefore, may likely contribute in modulating the response to recurrent nocturnal hypoxia. The PAP during wakefulness is one of such factors; however, it remains to be established whether the clinical correlate of this index (*ie*, the

functional and anatomic state of pulmonary artery wall under baseline conditions) represents a causative factor, or merely the chronic consequence of the recurrent nocturnal stimulation.

Another factor found as highly correlated both to ΔP_{stm} and ΔP_{dtm} is represented by PaCO₂ during wakefulness: this index was selected as a rough estimate of the trend of PaCO₂ levels which may occur during obstructive apneas because of the well-known difficulties in performing such measurements during these episodes. The hypertensive role of hypercapnia is a minor one, if compared with that of hypoxia; this stimulus probably acts through the increase in hydrogen ion concentration promoting an enhanced response to hypoxia.¹²

In both these chemical stimuli, the longer the exposure, the more severe the hemodynamic consequence; this is demonstrated by the correlation between transmural PAP changes and the AT/TST.

Although on the basis of the cited evidence, the role of chemical stimuli cannot be overemphasized, from consideration of the similarity of obstructive apneic efforts and Müller maneuvers, a final question arises as to whether mechanical events *per se* may affect transmural pressure changes. In fact, previous authors had described the influence of Müller maneuvers upon the venous return to the right atrium^{13,14} and upon right ventricle filling pressure and stroke volume;¹⁵ moreover, the same maneuvers may increase left heart transmural pressure, resulting in an increase in the upstream pressure.¹³ Although in principle such a hypothesis cannot be rejected, it cannot be confirmed either, since the controlled experimental conditions of maintained inspiratory effort which allowed these experiences are hardly comparable with the natural event of recurrent, short-lived, and cyclically-changing inspiratory efforts of sleep apnea which recur within the context of independently acting, marked variations in SaO₂, HR, and cardiac output.

In conclusion, pulmonary hypertension in obstructive sleep apneas is the consequence of a complex interaction of manifold physiologic variables; transmural PAP measurements must always be performed for the evaluation of pulmonary hemodynamics in OSAS.

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