Acute Effects of Oxygen Administration on Transmural Pulmonary Artery Pressure in Obstructive Sleep Apnea*

Oreste Marrone, M.D.; Vincenzo Bellia, M.D., F.C.C.P.;
Daniele Pieri, M.D.; Adriana Salvaggio, M.D.; and
Giovanni Bonsignore, M.D., F.C.C.P.

In order to investigate the role of hypoxia on the cyclic oscillation of transmural pulmonary artery pressure (PAP) in obstructive sleep apnea, oxygen was administered during one half of the night to six patients affected by obstructive sleep apnea syndrome during a nocturnal polysomnographic study. In each patient, transmural PAP measurements were performed on 15 randomly selected apneas recorded while breathing room air, and on 15 during O_2 administration. During O_2 administration in all patients, apneas were associated with a higher oxyhemoglobin saturation (SaO_2), a smaller SaO_2 swing, and a higher transcutaneous Pco_2. The mean highest level of transmural PAP in the apneic episodes, commonly reached at their end, was significantly lower than while breathing room air in only two patients; however, due to a decrease in the mean lowest PAP level (at the beginning of apneas), the extent of the PAP increase within apneas did not differ between air and O_2 breathing; these patients showed the smallest increase in transcutaneous Pco_2 in our sample. End-apneic transmural PAP during O_2 administration was significantly higher in one subject (for systolic values) and was not significantly different in the remaining three subjects. The extent of the increase in transmural PAP within apneas was greater in one patient; it was smaller in another one, but only for the diastolic values; and it did not differ significantly with respect to the value observed while breathing room air in all of the other subjects. The results suggest that hypoxia in obstructive apneas, at least in some patients, may lead to a steady increase in PAP, detectable both at the beginning and at the end of the episodes; conversely, the increase in PAP within apneas does not seem to be influenced by the simultaneous decrease in SaO_2.
(Chest 1992; 101:1023-27)

AI = apnea index; DPdtm = Pdtme − Pdtmb; DPstm = Pstme − Pstmb; $DSaO_2$ = SaO_2e − SaO_2b; Pdtm = diastolic transmural PAP; Pdtmb = diastolic transmural PAP at beginning of apneas; Pdtme = diastolic transmural PAP at end of apneas; Ppl = pleural pressure; Pstm = systolic transmural PAP; Pstmb = systolic transmural PAP at beginning of apneas; Pstme = systolic transmural PAP at end of apneas; $tcPco_2$ = transcutaneous Pco_2; SaO_2b = SaO_2 at beginning of apneas; SaO_2e = SaO_2 at end of apneas

---

In obstructive sleep apnea syndrome (OSAS), upper airway narrowing and sleep-associated loss of tone in related muscles result in recurrent occlusive episodes, with consequent falls in oxyhemoglobin saturation (SaO_2).

In a previous report,[1] we demonstrated that transmural pressure in the pulmonary artery increases throughout each apnea and reaches its maximum value on the occasion of the last respiratory efforts against the occluded airway, as well as during the early phase of the unoccluded breathing; this value sometimes features a hypertensive level; afterwards, transmural pulmonary artery pressure (PAP) decreases again until approximately the second occluded effort of the following apnea. The significant linear correlation between transmural PAP and SaO_2 found in most patients of the cited study suggested a role of hypoxemia in the pathogenesis of these hemodynamic changes; however,

a correlation does not necessarily reflect a causal relationship.

Therefore the present study was aimed at evaluating the meaning of the relationship between PAP and SaO_2 by assessing the effect of oxygen administration on transmural PAP recorded during obstructive apneas, both in regard to its maximum end-apneic levels and its variations between the various phases of the apneic cycle.

MATERIALS AND METHODS

Six patients (three men and three women) affected by OSAS were studied. Their demographic and respiratory function characteristics are shown in Table 1. All patients gave informed consent to the study.

The patients underwent a nocturnal polysomnographic study that was divided into two parts, lasting 3 h each, one while breathing room air and one during O_2 administration via nasal prongs at a flow of 4 to 6 L/min. The sequence of the two parts was randomly established in each patient.

The following signals were continuously recorded: electroencephalogram, electro-oculogram, and submental electromyogram for conventional sleep staging; SaO_2 by an ear oximeter (Ohmeda Biox 3700); oronasal flow; PAP by a Swan-Ganz floating catheter connected to a pressure transducer (Statham P23 ID); esophageal pressure, as an estimate of pleural pressure (Ppl), by a balloon-tipped catheter introduced into the lower third of the esophagus, inflated with 1 ml of air, and connected to a pressure transducer

Table 1—Characteristics of Patients

Patient, Sex, Age (yr)	BMI, kg/m²*	PaO₂, mm Hg	PaCO₂, mm Hg	FEV₁, percent of predicted	FEV₁/FVC, percent
1, M, 26	30.8	98	42	88	77
2, M, 45	28.6	71	44	75	71
3, F, 56	30.3	67	43	64	75
4, M, 49	45.7	71	42	72	76
5, F, 66	30.5	62	41	97	85
6, F, 60	37.2	77	42	82	81

*BMI, Body mass index.

(Sanborn 268B); and transcutaneous Pco_2 ($tcPco_2$) by a capnometer (Hewlett-Packard 47210A).

Since REM sleep, due to the cumbersome instrumentation, accounted for such short periods as to prevent any statistical evaluation, only NREM sleep was analyzed.

Concerning the pattern of breathing disorders over the whole night, we measured the apnea index (AI) and the highest $tcPco_2$ and calculated the average values of the duration of apnea and of the lowest SaO_2 recorded at the end of apneas; all measurements were performed separately for the portions spent, respectively, in air and in O_2.

Concerning the analysis of apneas, we selected two samples of 15 apneas each, relevant to the two portions of the night, at regular intervals; apneas occurring within the early 10 min of O_2 administration or of O_2 withdrawal were not selected. The following indices

Table 2—Respiratory Parameters Relevant to Whole Night

Period	AI*	Duration of Apnea, s	Mean Lowest SaO₂, percent	Maximum tcPco₂, mm Hg
Patient 1				
Air	89	32 ± 10	91 ± 4	55
O₂	65	41 ± 9	93 ± 3	58
Patient 2				
Air	49	24 ± 8	89 ± 3	54
O₂	44	36 ± 10	94 ± 4	56
Patient 3				
Air	105	18 ± 5	83 ± 4	49
O₂	106	20 ± 5	91 ± 2	59
Patient 4				
Air	97	26 ± 7	76 ± 6	
O₂	78	28 ± 11	94 ± 3	58
Patient 5				
Air	79	21 ± 9	78 ± 8	53
O₂	62	29 ± 12	96 ± 3	64
Patient 6				
Air	92	26 ± 7	86 ± 2	55
O₂	72	26 ± 10	91 ± 3	59

*Number of apneas per hour.

were measured: duration; lowest Ppl; SaO_2 at the beginning of apneas (SaO_2b); lowest SaO_2 at their end (SaO_2e); and the difference between the latter two ($DSaO_2$).
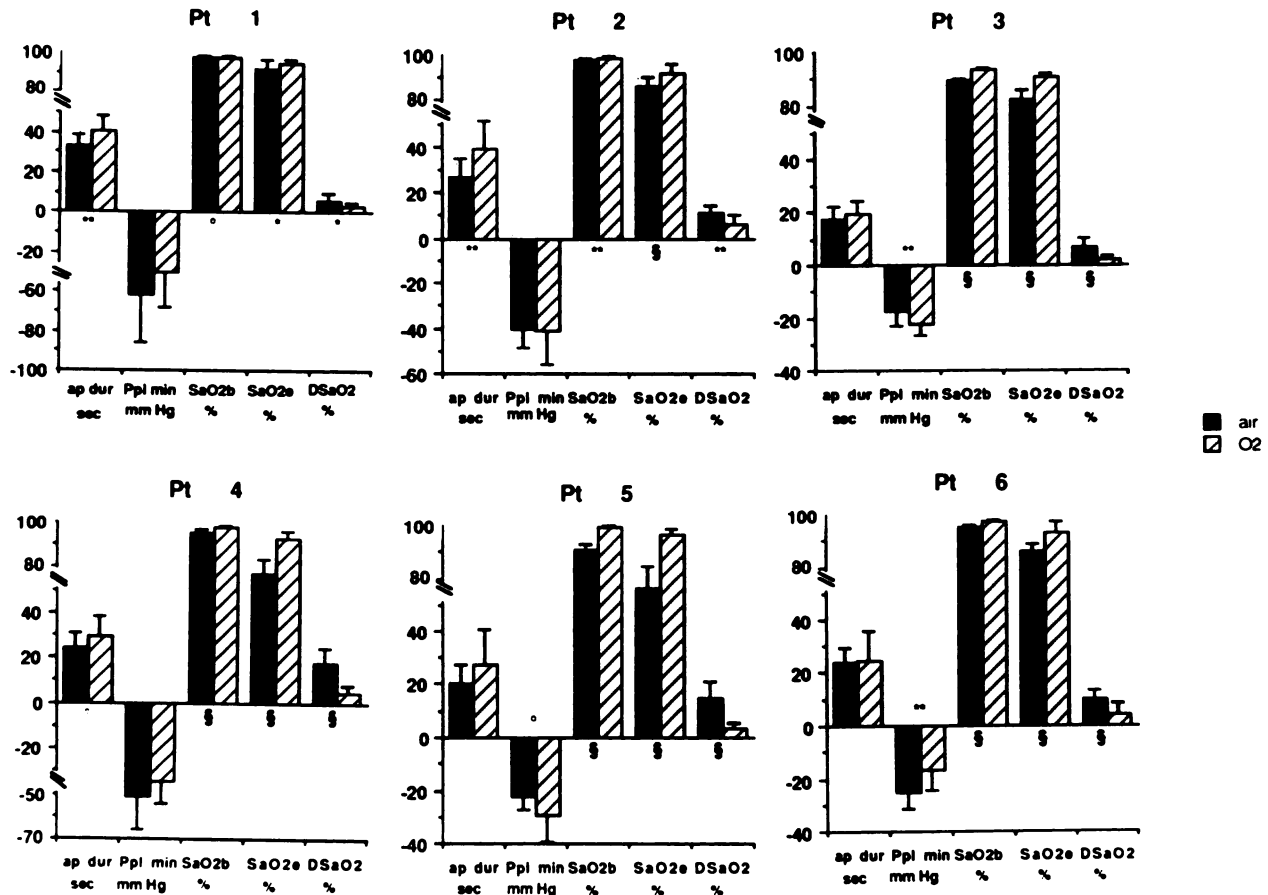

FIGURE 1. Mean (and SD) of some characteristics of selected apneas in each patient. Ap dur, Apnea duration; and Ppl min, lowest Ppl. Open circle indicates P<0.05; asterisk indicates p<0.01; double asterisks indicate p<0.005; and section mark indicates p<0.001.

In the same apneas, values for systolic and diastolic transmural PAP (respectively, Pstm and Pdtm) during each occluded breath, as well as during the first three unoccluded breaths following the apneas, were measured as the mean of the values relevant to all of the cardiac cycles occurring within the considered breath; the lowest Pstm and Pdtm values of each apnea were indicated as Pstmb and Pdtmb (since they occurred at the beginning of apneas); the highest values were indicated as Pstme and Pdtme (since they occurred at the end of the apneas or within the early three breaths following them). Finally, in order to evaluate the changes in PAP related to individual apneas, in the same sample the difference between Pstme and Pstmb (indicated as DPstm) and, respectively, between Pdtme and Pdtmb (indicated as DPdtm) were measured.

All of the parameters relevant to the selected apneas were separately averaged in each patient for the apneas recorded while breathing room air and during O_2 administration. The significance of the difference between values measured in air and in O_2 was evaluated by Student's t-test.

RESULTS

Our patients spent in NREM sleep 100 ± 35 min (mean $\pm$ SD) while breathing room air and 90 ± 43 min during O_2 administration. Stages 1 and 2 accounted for 94.7 ± 6.9 percent of the NREM sleep time while breathing room air and for 90.9 ± 9.4 percent during O_2 administration; REM sleep was observed in only

three subjects while breathing room air (range of duration, 1.5 to 13 min) and in two subjects during O_2 administration (duration, 5 and 20 min).

The behavior of the respiratory parameters in each patient evaluated for the whole NREM sleep time in the night, separately for the periods of room air breathing and O_2 administration, is shown in Table 2. While breathing air the AI ranged from 49 to 105; O_2 administration resulted in a trend toward a decrease in this index (range, 44 to 106), although at a cost of a longer duration of events (at least in five out of six subjects). As expected, during O_2 administration, mean values of the lowest SaO_2 increased and were accompanied by some increase in $tcPCO_2$ peaks.

Concerning the characteristics of the sampled apneas (Fig 1), events recorded in O_2 lasted longer in all patients, but the difference was significant in only three of them (patients 1, 2, and 4); this difference did not result in consistent changes in intrathoracic pressure, since the minimum Ppl attained in O_2 was significantly more negative than in air in two subjects (subjects 3 and 5), was less negative in one (subject 6), and was not significantly affected in the remaining
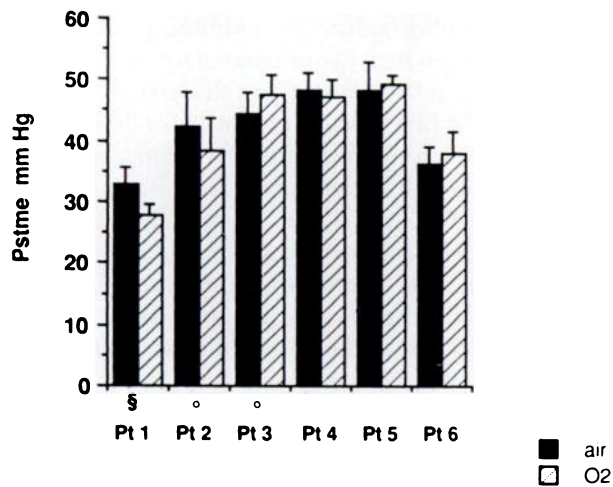

FIGURE 2. Mean (and SD) of Pstme and Pdtme in selected apneas while breathing air and during O_2 administration in each patient. *Open circle* indicates $p<0.05$; *asterisk* indicates $p<0.01$; and *section mark* indicates $p<0.001$.
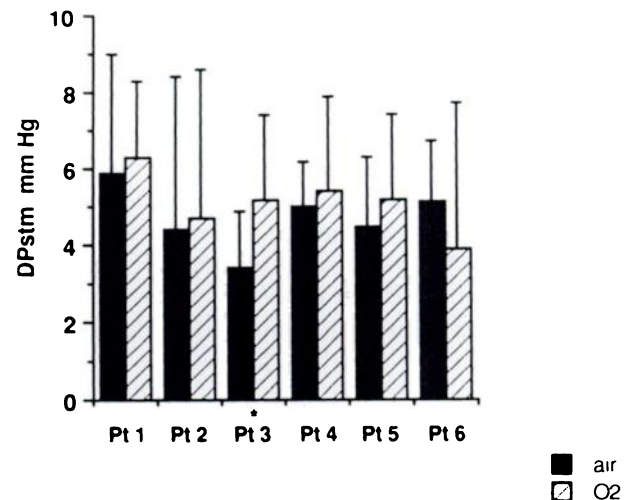
FIGURE 3. Mean (and SD) of DPstm and DPdtm in selected apneas while breathing air and during O_2 administration in each patient. *Asterisk* indicates $p<0.01$; and *open circle* indicates $p<0.05$.

three; the SaO_2b and SaO_2e increased while $DSaO_2$ decreased significantly in all subjects. In all cases, both the mean duration of apnea and the SaO_2e did not differ significantly from those calculated over the whole night.

As far as the hemodynamic changes are concerned, during O_2 administration the Pstme and Pdtme (Fig 2) showed a significant decrease in patients 1 and 2; conversely, Pstme increased significantly in patient 3; in the remaining three subjects, O_2 administration did not result in significant changes in either Pstme or Pdtme. In terms of transmural PAP changes (Fig 3), in no patient was O_2 administration associated with an attenuation of the hypertensive trend consequent to apneas, at least as concerns Pstm, while in just one patient (patient 1), the decrease in Pdtme resulted in a significantly lower DPdtm; conversely, in patient 3, O_2 administration was associated with an increase in both DPstm and DPdtm.

DISCUSSION

The results of the present study point out that in spite of the marked attenuation in the falls and oscillations in SaO_2 seen in all patients, O_2 administration in the majority of cases affects neither the levels of transmural PAP nor the amplitude of its variations induced by obstructive sleep apneas.

The results of the only study on pulmonary hemodynamics previously performed in patients with OSAS to whom O_2 was administered during sleep[2] suggested that hypoxemia plays a major role in causing some increase in PAP within apneas, with the possible occurrence of hypertensive values; however, that study suffered some major limitations. Besides the small size of the sample (three patients), no data were reported regarding PAP swings; in addition, only intravascular PAP measurements were taken, while it has been later demonstrated that, given the disturbing effect of Ppl oscillations during apneas, transmural values are more meaningful in the assessment of PAP in obstructive apneas.[1]

The present study does not lend support to the hypothesis of apnea-induced desaturation as the leading cause of PAP behavior in obstructive apneas; however, it must be pointed out that apneas recorded during air and O_2 breathing did not differ only with respect to SaO_2, but, in some patients, also in regard to the duration of apneas, the $tcPco_2$ recorded during their occurrence, and the lowest Ppl at their end. Therefore, any interpretation of these results must be regarded in the light of the possible interference of these parameters.

Concerning the duration of apnea, its effect on PAP cannot result from time *per se*, but from other parameters that may change when the duration changes, like Pco_2 or the extent of Ppl swings.

As far as Pco_2 is concerned, conflicting results on the effect of CO_2 on pulmonary vascular tone have been reported;[3] however, it is generally believed that CO_2 potentiates the hopoxic vasoconstrictive effect, either modifying hydrogen ion concentration[4,5] or not.[6] In our sample, this mechanism does not hold, since hypoxia was prevented by administration of O_2; however, the interference could have been exerted through the minor direct effect of CO_2 on the pulmonary vasculature. Although it cannot be demonstrated, an interesting clue for this hypothesis is the fact that cases 1 and 2, apparently showing some hemodynamic response to O_2 administration, were also characterized by the smallest variation in $tcPco_2$ during this treatment.

Concerning the alternative mechanism of interference (ie, changes in Ppl), in situations characterized by increased negative intrathoracic pressures, left ventricle stroke volume decreases, mainly as an effect of an increase in its afterload[7,8] and, in turn, may cause an increase in left atrial transmural pressure.[9] Actually, a decrease in left ventricular stroke volume, related to the negativity in Ppl during the preceding diastole, has been observed in obstructive apneas by impedance cardiography;[10] in addition, in the same circumstances, an increase in pulmonary wedge pressure, possibly related to this mechanism, has been reported.[11] On this basis, it cannot be excluded that any tendency toward decreased PAP consequent to the prevention of hypoxemia may have been masked by the opposite trend due to a more negative Ppl; however, patient 3 was the only one who showed a significant increase in Pstme, DPstm, and DPdtm, along with wider Ppl swings in agreement with the previous hypothesis, whereas in the other patients, there was no clear relationship between the change in Ppl and the expected change in PAP behavior.

Another aspect of our results deserving a comment is represented by the amplitude of the changes in transmural PAP occurring between the onset and the termination of apnea. As mentioned previously, only one patient (patient 1) showed a significant decrease in DPdtm, and no one showed a decrease in DPstm; this phenomenon occurred despite the fact that two patients (patients 1 and 2) showed a significant decrease in both Pstme and Pdtme. These results demonstrate that in most cases the possible reduction in end-apneic PAP levels following the prevention of SaO_2 decreases does not result from a blunting in PAP variations, but from a sustained decrease in its levels from the beginning to the end of the apnea. In fact, the response of pulmonary vessels to O_2 tension variations is relatively slow, since it takes some minutes in order to be completed,[12,13] while the variations in SaO_2 during apneas occur within few seconds. Therefore, the hypothesis may be put forward that in some

subjects the recurrence of rapid desaturations determines a sustained increase in pulmonary vascular resistance and PAP; in these subjects, further cyclic increases in PAP, determined by mechanisms different from hypoxia, would be superimposed; O_2 administration would prevent the sustained increase in PAP, leaving its apnea-related fluctuations unmodified. The interindividual differences that we observed may be accounted for by the individual reactivity to hypoxia and Pco_2, by the already cited variable increase in $tcPco_2$ with O_2 administration, or by the age of the patients. In fact, it is noteworthy that the patients who showed a decrease in PAP levels were the youngest in our sample; therefore, it cannot be excluded that they had been affected by the sleep apnea syndrome for a lesser amount of time, so that their vascular bed was more compliant and could respond more clearly to the removal of hypoxia.

In conclusion, in our sample the acute correction of hypoxia following obstructive apneas does not appear to influence end-apneic PAP levels in the majority of patients with OSAS, while in some patients, it could determine a sustained decrease in PAP levels throughout apneas; PAP fluctuations occurring within apnea cycles do not appear to be related to the simultaneous SaO_2 oscillations.

REFERENCES

1 Marrone O, Bellia V, Milone F, Ferrara G, Romano L, Salvaggio A, et al. Transmural pressure measurements: importance in the assessment of pulmonary artery pressure in obstructive sleep apneas. Chest 1989; 95:338-43

2 Schroeder JS, Motta J, Guilleminault C. Hemodynamic studies in sleep apneas. In: Guilleminault C, Dement WC, eds. Sleep apnea syndromes. New York: AR Liss Inc, 1978:177-86

3 Emery CJ, Sloan PJM, Mohammed FH, Barer GR. The action of hypercapnia during hypoxia on pulmonary vessels. Bull Eur Physiopathol Respir 1977; 13:763-76

4 Enson Y, Giuntini C, Lewis ML, Morris TQ, Ferrer MI, Harvey RM. The influence of hydrogen ion concentration and hypoxia on the pulmonary circulation. J Clin Invest 1964; 43:1146-62

5 Barer GR, McCurrie JR, Shaw JW. Pulmonary vasodilator and vasoconstrictor actions of carbon dioxide. J Physiol (Lond) 1971; 213:633-45

6 Malik AB, Kidd BSL. Independent effects of changes in H^+ and CO_2 concentrations on hypoxic pulmonary vasoconstriction. J Appl Physiol 1973; 34:318-23

7 Robotham JL, Lixfeld W, Holland L, McGregor D, Bryan AC, Rabson J. Effects of respiration on cardiac performance. J Appl Physiol 1978; 44:703-09

8 Buda AJ, Pinsky MR, Ingels NB, Daughters GT, Stinson EB, Alderman EL. Effect of intrathoracic pressure on left ventricular performance. N Engl J Med 1979; 301:453-59

9 Sharf SM, Brown R, Tow DE, Parisi AF. Cardiac effects of increased lung volume and decreased pleural pressure in man. J Appl Physiol 1979; 47:257-62

10 Tolle FA, Judy WV, Yu PL, Markand ON. Reduced stroke volume related to pleural pressure in obstructive sleep apnea. J Appl Physiol 1983; 55:1718-24

11 Buda AJ, Schroeder JS, Guilleminault C. Abnormalities of pulmonary artery wedge pressures in sleep-induced apneas. Int J Cardiol 1981; 1:67-74

12 Ohe M, Minata T, Haneda T, Takishima T. Time course of repeated vasoconstriction with repeated hypoxia and glucose depletion. Respir Physiol 1986; 63:177-86

13 Thompson BT, Massoun PM, Kradin RL, Hales CA. Acute and chronic hypoxic pulmonary hypertension in guinea pigs. J Appl Physiol 1989; 66:920-28