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Different Heart Rate Patterns in Obstructive Apneas During NREM Sleep

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Summary: Both bradycardia and a trend to tachycardia have been reported in obstructive sleep apneas (OSA). Because heart rate (HR) behavior may yield information on parasympathetic activity during OSA, we analyzed HR in samples of consecutive apneic cycles in non-rapid eye movement (NREM) sleep, recorded in normotensive patients breathing room air (n = 7) and supplemental O_2 (n = 4). In air, the patients showed different HR trends during apnea, as HR decreased (HR↓), remained constant (HR=), or increased (HR↑). By multiple regression analysis, development of HR trends correlated with the HR fall in the late interapneic period, HR at first effort, the decrease in esophageal pressure, and the lengthening of inspiration during apnea (R^2 = 0.42). O_2 abolished HR↓-OSA, whereas HR= and HR↑-OSA still occurred but at higher HR than in air. In both the air and O_2 series, the HR fall preceding apnea correlated significantly with the degree of hypoxia reached in the previous apneic cycle. These data indicate a complex modulation of HR during OSA, with the HR fall in the late interapneic period possibly reflecting the effectiveness of parasympathetic cardiac control in OSA patients during sleep. **Key Words:** Autonomic nervous system—Parasympathetic activity—Hypoxia—Arousal.

Alternating sequences of bradycardia and tachycardia have been considered characteristic of obstructive sleep apnea (OSA) since the earliest studies on OSA (1). However, the pathogenesis of such oscillations and their precise relationships to the respiratory changes in the apneic cycle are unclear. The first studies found bradycardia during the apneic phase (1,2), blunted by O_2 and inhibited by atropine (1), suggesting that hypoxia increased parasympathetic activity. Zwillich and coworkers (2) analyzed the difference in heart rate (HR) between immediate preapnea and end of apnea and found that the fall in HR correlated with the degree of hypoxia, similar to what had been described in dogs (3). Bradycardia was more severe in OSA during rapid eye movement (REM) sleep, but because OSAs were longer and more desaturating in REM than in non-REM (NREM) sleep, no independent effect of the sleep phase on HR was found (2). More recently, HR was found to increase from early to late apnea during NREM-OSA (4,5). However, a significant effect of hypoxia on HR was still reported, as HR decreased during apnea whenever oxygen saturation (SaO_2) fell by at least 15% (4). In summary, bradycardia during OSA was shown to be hypoxia dependent, but the factors possibly counteracting bradycardia during apnea are still uncertain.

Instead, there is general agreement on tachycardia at resumption of ventilation. The "pulmonary inflation reflex", by which hypoxia-induced bradycardia is overridden by activation of lung stretch receptors (3), may be involved in postapneic tachycardia. However, the role of vagal feedback from the lungs in HR modulation during hypoxia was recently challenged (6). The arousal at the end of apnea is another potential cause of postapneic tachycardia (7,8). Peak HR values in the interapneic phase were analyzed relative to the severity of OSA (9) and to the HR response to the Valsalva maneuver during wakefulness (4). Instead, the decrease in HR following peak HR values in the late interapneic phase was never analyzed. Because OSAs recur cyclically, one can hypothesize that the time courses of HR during apnea and interapneic phases may be related to each other.

In this study, we asked the following questions: 1) Are there different trends in HR during NREM-OSA and which factors modulate them? 2) Does the behavior of HR during the interapneic phase affect HR in the following apnea?

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TABLE 1. *Characteristics of patients*

Patient	Age (years)	BMI (kg/m²)	FEV1 (% pred)	FVC (l)	FVC (% pred)	Wake PaO_2/$PaCO_2$ (mmHg)	Wake HR (bpm)	AHI AIR	AHI $+O_2$	Mean lowest SaO_2 (%) AIR	Mean lowest SaO_2 (%) $+O_2$
1	45	28.6	75	3.5	87	71/44	85	49	44	82.2 ± 2.7	90.2 ± 5.0
2	26	30.8	88	4.5	97	98/42	72	89	65	93.3 ± 1.5	92.3 ± 1.0
3	49	45.7	72	3.9	81	71/42	70	97	78	72.3 ± 6.5	94.2 ± 2.4
4	21	48.7	113	5.3	110	81/41	84	95	98	76.9 ± 5.1	90.5 ± 3.9
5	48	45.0	83	3.4	89	83/39	73	98	—	83.4 ± 5.2	—
6	63	37.6	72	2.1	74	64/50	80	89	—	78.0 ± 8.5	—
7	45	32.3	60	3.5	89	61/46	78	52	—	82.5 ± 3.6	—
Mean	42.4	38.4	80.4	3.7	89.6	75.6/43.4	77.4	81.3	71.3	81.2	91.8
SD	±14.4	±8.1	±16.9	±1.0	±11.5	±12.8/3.6	±5.9	±21.3	±22.7	±6.6	±1.8

BMI, body mass index; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; HR, heart rate; AHI, apnea/hypopnea index; AIR, while breathing room air; $+O_2$, while breathing supplemental oxygen; SD, standard deviation.

MATERIALS AND METHODS

Patient population and protocol

Seven normotensive men, with no previous history of diabetes or coronary artery disease (Table 1), and already diagnosed as OSA patients by conventional polysomnography in our sleep laboratory, gave their informed consent to the study. No patient received any medication. Data were collected during nocturnal polysomnography in all patients while breathing room air (AIR) and in four patients while breathing supplemental oxygen ($+O_2$) via nasal prongs at a flow of 4–6 l/minute. AIR and $+O_2$ data were collected in the same night, but their sequence was randomized. The following signals were recorded: electroencephalogram (EEG) (C4 A1), submental electromyogram (EMG), and electrooculogram (EOG) for conventional sleep staging; oronasal flow, oxyhemoglobin saturation (SaO_2), electrocardiogram (ECG) lead II, and esophageal pressure (Pes) for HR analysis. Airflow was monitored by nasal prongs connected to a pressure transducer (MP-45-18-871 Validyne, Northridge, CA), while SaO_2 was monitored by pulse oximetry (Ohmeda Biox 3700, Boulder, CO). Pes was recorded by a balloon-tipped catheter, inflated with 1 ml of air, positioned in the lower third of the esophagus, and connected to a calibrated differential pressure transducer (MP-45-30-871 Validyne, Northridge, CA). Signals were recorded on tape (Hewlett-Packard 3968A) for subsequent analysis.

Data analysis

Samples of consecutive apneas in stage 2 NREM sleep were randomly selected during AIR in all patients and during $+O_2$ in the patients studied under both AIR and $+O_2$ conditions (Table 2). Sampling intervals were 5 ms for ECG and 10 ms for Pes and airflow. The highest and lowest SaO_2 values, observed at the beginning and end of each OSA, respectively, were recorded, and ΔSaO_2 calculated. After analog-to-digital conversion, data were stored (VAX 8200, Digital Equipment) and analyzed as follows. After identification of respiratory efforts and nonobstructed breaths on the Pes and airflow tracings, each respiratory cycle was divided into inspiration and expiration and numbered according to its position in the apneic or interapneic phase. For each respiratory effort and interapneic breath, duration of inspiration (Ti), and expiration (Te), their sum (Ttot), and Pes nadir were recorded. Mean HR was calculated for each effort or breath.

Figure 1 and Table 3 report how the time course of HR during the apneic cycle was described and the ΔHRs calculated. Mean HR was recorded for each OSA (Table 3) 1) at the beginning of apnea ($HR_{first\ effort}$); 2) at its lowest value (HR_{min}) during apnea, together with the corresponding effort number (effort HR_{min}); 3) at the end of apnea ($HR_{last\ effort}$); and 4) at its highest value (HR_{max}) observed during the interapneic phase, together with the number of the breath in which it occurred (breath HR_{max}). In addition, we calculated: 1) the difference between $HR_{last\ effort}$ and $HR_{third\ effort}$ (ΔHR_{apnea}, see Results section for further details); 2) the increase in HR during postapnea ($\Delta HR_{early\ postapnea}$) as the difference between HRmax and the preceding $HR_{last\ effort}$; and 3) the decrease in HR during late postapnea ($\Delta HR_{late\ postapnea}$) as the difference between HRmax and the following $HR_{last\ breath}$.

Data were transferred to a Macintosh personal computer and analyzed using a statistical package (Statview, Brainpower Inc, Calabasas, CA). Significance of HR changes during the apneic cycle was assessed in each patient by repeated measures analysis of variance (ANOVA), followed by Scheffé test, and by comparisons between data collected in obstructed efforts and the interapneic period during AIR and $+O_2$. Relationships between variables were studied by simple and backward multiple linear regression analysis. Significance was set at $p < 0.05$.

TABLE 2. *Characteristics of apneas analyzed*

Patient	Analyzed recording (minutes)		Analyzed apneas (n)		Apnea duration (seconds)		Efforts in the apneic phase (n)		Interapneic phase duration (seconds)		Breaths in the interapneic period (n)		Pes nadir (cm H_2O)	
	AIR	$+O_2$	AIR	$+O_2$	AIR	$+O_2$	AIR	$+O_2$	AIR	$+O_2$	AIR	$+O_2$	AIR	$+O_2$
1	8	8	10	8	32 ± 4	36 ± 15	8 ± 2	9 ± 4	13 ± 5	19 ± 6	4 ± 2	5 ± 2	−69 ± 9	−75 ± 15
2	8	10	9	10	31 ± 8	45 ± 4	11 ± 3	17 ± 2	10 ± 4	11 ± 4	3 ± 1	4 ± 1	−82 ± 31	−89 ± 17
3	14	8	18	10	24 ± 7	30 ± 10	7 ± 2	9 ± 3	14 ± 6	17 ± 10	5 ± 2	6 ± 4	−37 ± 10	−35 ± 17
4	20	29	19	29	48 ± 5	37 ± 10	14 ± 2	12 ± 3	15 ± 3	17 ± 9	4 ± 1	4 ± 2	−47 ± 18	−62 ± 21
5	18	—	21	—	22 ± 9	—	8 ± 3	—	17 ± 7	—	6 ± 2	—	−11 ± 4	—
6	15	—	19	—	27 ± 12	—	7 ± 3	—	12 ± 6	—	4 ± 2	—	−98 ± 20	—
7	7	—	10	—	30 ± 7	—	11 ± 3	—	14 ± 4	—	4 ± 1	—	−54 ± 15	—
Mean	12.8	13.8	15.1	14.3	30.6	37.0	9.4	11.8	13.6	16.0	4.3	4.8	−56.9	−65.3
SD	±5.2	±10.2	±5.2	±9.9	±8.5	±6.2	±2.6	±3.8	±2.2	±3.5	±1.0	±1.0	±29.1	±23.0

AIR, while breathing room air; $+O_2$, while breathing supplemental oxygen; Pes, esophageal pressure; SD, standard deviation.

RESULTS

HR in OSA-AIR

One hundred and six apneic cycles with a mean lowest SaO_2 of 81.2 ± 6.6% (mean ± SD) were analyzed (Tables 1 and 2). Mean apnea duration was 30.6 ± 8.5 seconds, corresponding on average to 9.4 ± 2.6 obstructed efforts. Figure 2 illustrates mean HR at selected time points in the apneic cycle in each of the seven subjects studied. Interindividual variability was large for both HR changes during apnea and mean HR over the entire apneic cycle. In the first obstructed efforts (see efforts 1 and 3 in Fig. 2), HR was stable or decreased. In the following efforts, HR decreased in patients 1 and 2, changed little in patients 3 and 5, and increased in patients 4, 6, and 7 (all changes tested by ANOVA). In the early interapneic period, HR increased at resumption of ventilation in all patients. However, its decrease after the peak varied, as it was absent in patients 1 and 2, large in patient 4, and intermediate in the others. Mean HR over the apneic cycle was highest in patient 2, lowest in patients 3 and 5, and intermediate in the remaining patients.

Because changes in respiratory rate may account for at least part of HR variability (10), we asked whether mean HR and Ttot of obstructed efforts were correlated, but insignificant relationships were found in four patients, and variable weak correlations in the other three (data not shown).

Relationships between characteristics of OSA and HR behavior during apnea in AIR

To analyze the HR changes during apnea in the whole sample of OSA, we took the value of mean HR at the third obstructed effort ($HR_{effort3}$), corresponding to the point of lowest HR (HR_{min}) in most of our patients (Fig. 2), and calculated the difference between $HR_{last\ effort}$ and $HR_{effort3}$ (ΔHR_{apnea}) in each apnea. This allowed us to analyze HR trends during apnea by using a continuous variable. Figure 1 illustrates examples of obstructive apneas with decreasing (left panel) and increasing (right panel) HR from two patients.

To identify the variables related to the difference in HR behavior during apnea, the relationships between ΔHR_{apnea} and the following variables were analyzed: 1) HR at the beginning of apnea ($HR_{first\ effort}$); 2) the time course of HR in the preceding late interapneic phase, exemplified by the HR fall from HR_{max} to $HR_{last\ breath}$ ($\Delta HR_{late\ postapnea}$); 3) the duration of the preceding interapneic phase; 4) the ΔSaO_2 during apnea; 5) the mechanical effects of OSA, i.e. the amplitude of Pes swings at last effort; and 6) apnea duration. In addition, we hypothesized that increased duration of inspiration (Ti),

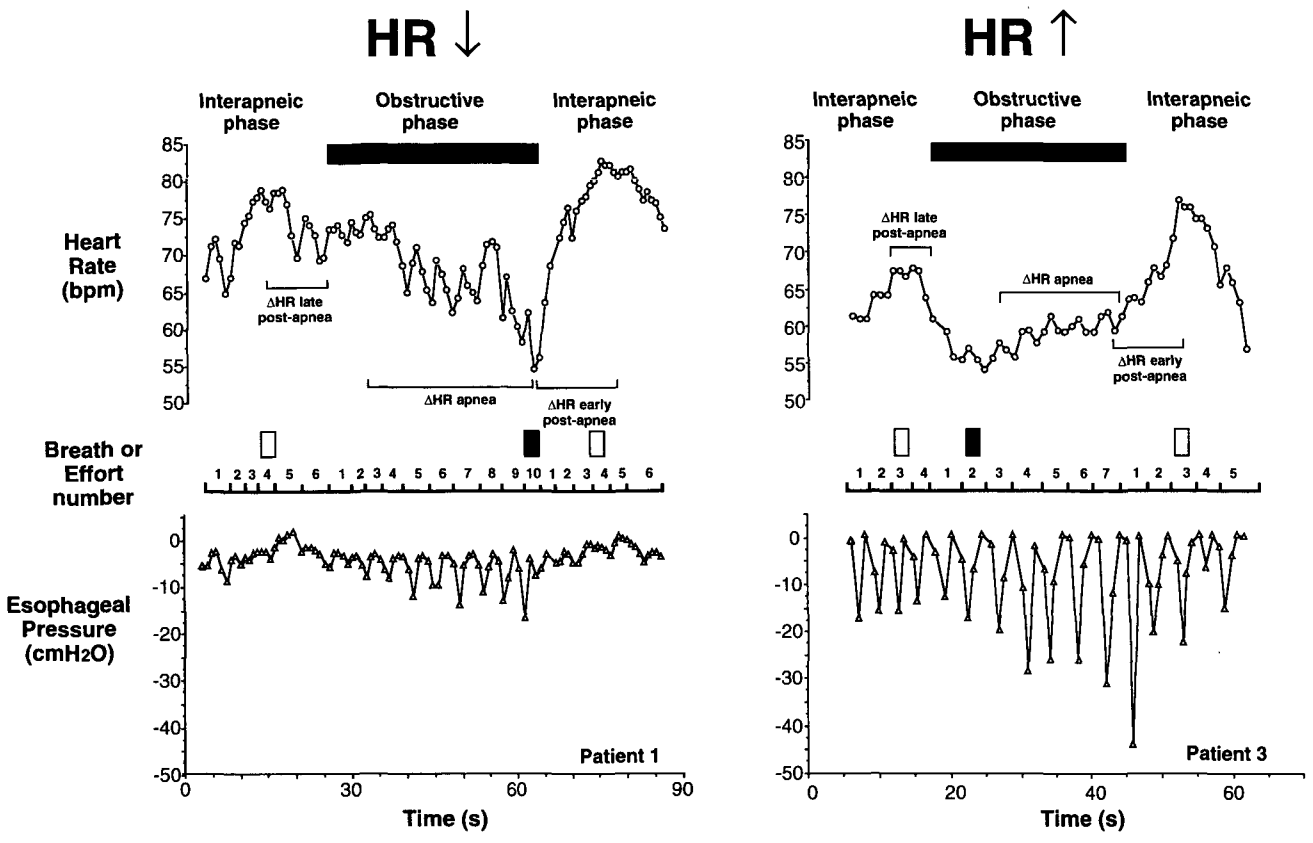

FIG. 1. Analysis of heart rate (HR) trends during obstructive sleep apnea (OSA). Apneas with the decreasing HR (HR↓) pattern (left) and with the increasing HR (HR↑) pattern (right) from patients 1 and 3, respectively. Top: beat-by-beat HR; middle: breath or effort number; bottom: mean esophageal pressure over each cardiac interval. The horizontal black bar helps in identifying the apneic phase. Vertical white bars indicate the breaths where HR_{max} was recorded. Vertical black bars indicate the efforts where HR_{min} was recorded. The figure reports the intervals over which ΔHR is calculated (see text and Table 3).

which occurs when upper airways are obstructed (11), may increase mean HR. Because parasympathetic activity is low or absent during inspiration (12), prolongation of inspiration may concur to increase mean HR, so that a seventh variable, ΔTi, i.e. the difference between $Ti_{last\ effort}$ and $Ti_{effort3}$, was included in the analysis. Four additional variables were considered: age, apnea/hypopnea index (AHI), body mass index (BMI) and HR during wakefulness of each patient. Because the quoted variables were highly correlated, a stepwise backward regression analysis was performed, with ΔHR_{apnea} as the dependent variable and the other 11 variables as independent regressors. The variables were discarded each at a time, according to their increasing contribution to the explanation of ΔHR_{apnea}. The total adjusted R^2 obtained was 0.422. The final relationship found was (R = 0.667, adjusted R^2 = 0.419, p = 0.000001) $\Delta HR_{apnea} = 15.3 + 0.21\ \Delta HR_{late\ postapnea} - 0.31\ HR_{first\ effort} - 0.08\ Pes_{last\ effort} + 3.55\Delta Ti$, with $\Delta HR_{late\ postapnea}$ as the most significant variable, followed by $HR_{first\ effort}$, $Pes_{last\ effort}$, and ΔTi. Therefore, taking into account all the relevant variables, the partial contribution of the degree of hypoxemia (ΔSaO_2) was not significant: in fact, even if simple linear regression between ΔSaO_2 and ΔHRapnea showed a significant direct relationship (R^2 = 0.246, R = 0.48, p < 0.01; Fig. 3, upper panel), the partial linear correlation, i.e. the one obtained by keeping constant all other 10 variables, showed a partial R^2 of 0.10 (ns). This finding indicates that the contribution of ΔSaO_2 to ΔHR_{apnea} was due to a spurious correlation, induced by the simultaneous influence of other variables.

Three HR patterns could be roughly identified in our sample: HR↓ OSA with a $\Delta HR_{apnea} < -4$ bpm (mean = −7.9 ± 3.7 bpm); HR= OSA with ΔHR_{apnea} between −4 and 4 bpm (mean = 0.5 ± 2.1 bpm); HR↑ OSA with a $\Delta HR_{apnea} > 4$ bpm (mean = 8.6 ± 3.5 bpm). According to this subdivision, 21 HR↓ OSAs, 38 HR=

TABLE 3. *Definitions*

$HR_{first\ effort}$ = HR at the beginning of apnea
HR_{min} = lowest HR during apnea
$HR_{last\ effort}$ = HR at the end of apnea
HR_{max} = highest HR in the interapneic period
$\Delta HR_{apnea} = HR_{last\ effort} - HR_{effort\ 3}$
$\Delta HR_{early\ postapnea} = HR_{max} - HR_{last\ effort}$
$\Delta HR_{late\ postapnea} = HR_{max} - HR_{last\ breath}$

HR, heart rate.

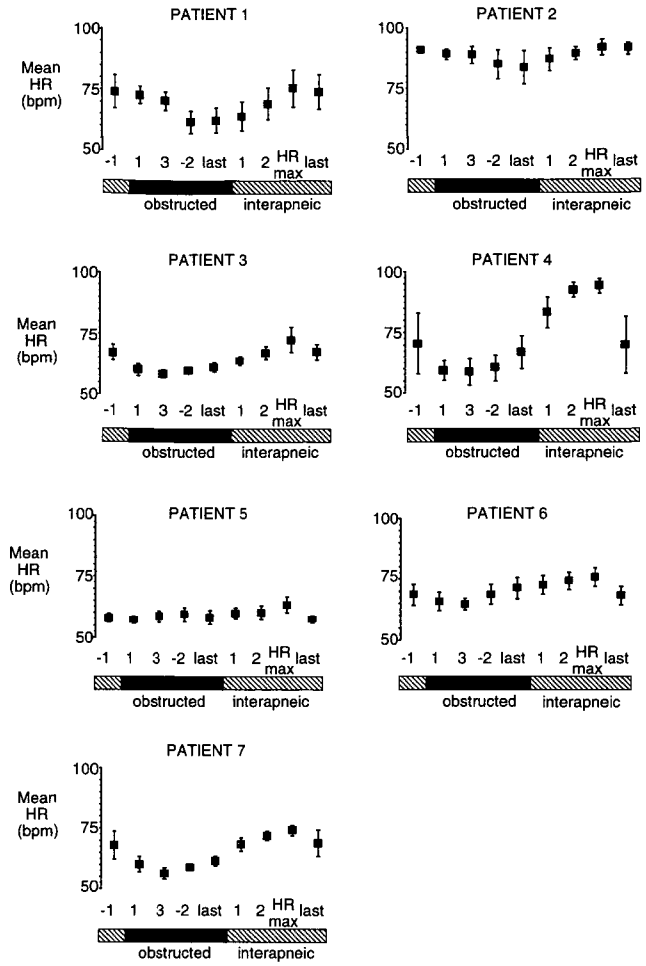

FIG. 2. Time course of heart rate (HR) in each patient during the apneic cycle while breathing room air. Symbols indicate mean HR ± SD at selected breaths/respiratory efforts.

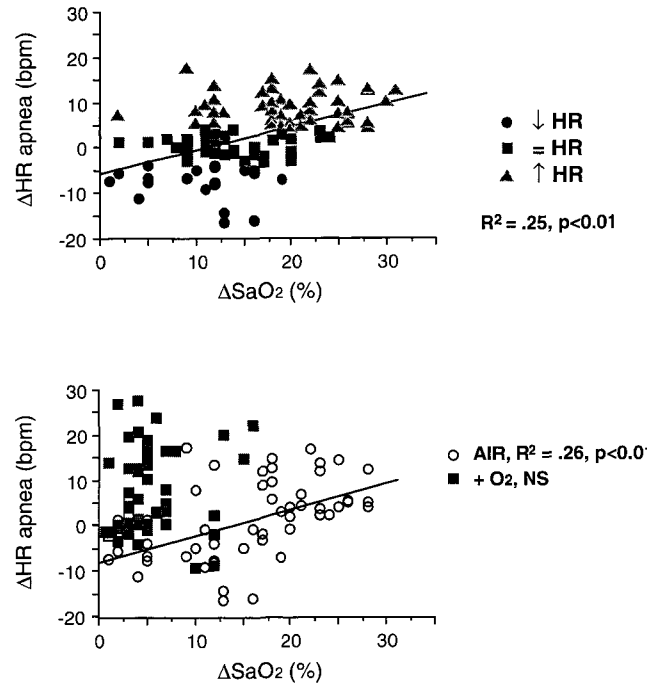

FIG. 3. Simple linear regression between ΔSaO_2 during apnea and ΔHR_{apnea}. Each point indicates one apnea. Upper panel: series while breathing room air (AIR); lower panel: series while breathing room air and supplemental oxygen ($+O_2$). Lines indicate regression on all points in AIR in both series (regression for $+O_2$ data ns, line not shown).

OSAs, and 47 HR↑ OSAs (19.8, 35.9, and 44.3% of total sample, respectively) were recorded. In the individual patient, OSA with either HR↑ or HR↓ prevailed, coupled with variable percentages of HR= OSA (Fig. 4, left panel). In summary, the major difference between HR↓-OSA and HR↑-OSA concerned the late interapneic HR fall and initial HR: HR↓-OSA began with a high HR, due to a small HR fall in the late interapneic phase, whereas the opposite occurred in HR↑-OSA. Mechanical changes and lengthening of inspiration significantly contributed to increased ΔHR_{apnea}. The degree of hypoxemia increased from HR↓-OSA to HR↑-OSA but did not appear independently related to HR behavior during apnea.

HR in OSA during oxygen administration

In the patients studied under both AIR and $+O_2$ conditions, mean lowest SaO_2 was 81.2 ± 9.0% in AIR and 91.8 ± 1.8% during $+O_2$ ($p = 0.0001$ by unpaired *t* test). Patient 2 did not desaturate during AIR, and his lowest SaO_2 was similar in AIR and $+O_2$ due to an increase in apnea duration in this subject (Table 1). Table 2 reports the features of OSA analyzed during AIR (n = 54) and $+O_2$ (n = 53). Mean lowest Pes and apnea duration were similar in AIR and $+O_2$, whereas interapneic phase was longer during $+O_2$ (16.7 ± 8.3 seconds) than in AIR (13.5 ± 4.9 seconds, $p = 0.02$ by unpaired *t* test).

During O_2 administration, bradycardia at the end of apneas was attenuated in patient 1, whereas in patients 3 and 4 HR at the beginning of apnea was higher than in AIR despite similar HR_{max} values in the two experimental conditions (Fig. 5, two-way ANOVA on HR: $p < 0.001$ for both obstructed efforts vs. interapneic breaths and AIR vs. $+O_2$). In both AIR and AIR/O_2 series, the higher the degree of hypoxia during apnea, the larger the $\Delta HR_{late\ postapnea}$ ($R^2 = 0.251$ for AIR, $p < 0.01$; $R^2 = 0.185$ for AIR/O_2, $p < 0.01$), suggesting that hypoxia may potentiate the HR fall following HR_{max} in the subsequent postapneic phase. Thus, the main effect of O_2 was to blunt HR fall, irrespective of the portion of apneic cycle where it occurred, i.e. end of apneas in HR↓-OSA or beginning of apneas in HR= or HR↑-OSA. Meanwhile, O_2 had no major effect on ΔHR_{apnea}. Actually, the prevailing HR trend tended to remain unchanged, as in patient 4, or to shift toward the HR= pattern, as in the other patients.

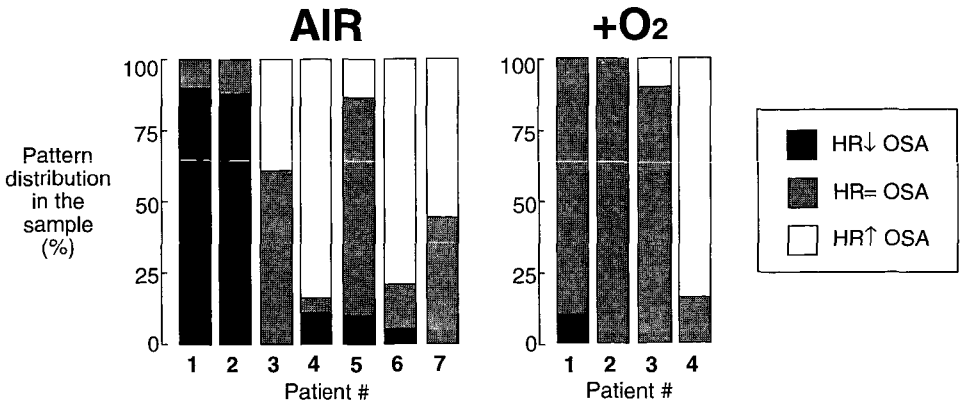

FIG. 4. Percentage distribution of heart rate patterns in each patient sample while breathing room air (left) and during administration of supplemental oxygen (right).

DISCUSSION

The analysis of HR in NREM OSA cycles performed in this study confirms and extends previous results (2,4). It shows that HR behavior is characterized by some intraindividual and by a large interindividual variability. In fact, in the sequence of respiratory efforts, HR may tend to increase, remain unchanged, or decrease, i.e. ΔHR_{apnea} has either a positive or negative sign. Although HR trends in our sample correlated directly with ΔSaO_2 during apnea (i.e, small ΔSaO_2 in HR↓ apneas, large ΔSaO_2 in HR↑ apneas), multiple regression failed to indicate ΔSaO_2 as a variable significantly affecting ΔHR. Although supporting that HR at the beginning of apnea significantly affects the subsequent HR behavior (4), our data suggest that the initial HR may mostly depend on HR behavior in the preceding interapneic period. In fact, the early interapneic tachycardia was followed in some patients by a prompt return to a low HR, in others by a slow HR decline. Our analysis also pointed out the role of mechanical changes and respiratory timing in HR modulation during apnea. Therefore, the pathogenesis of OSA-induced HR changes appears more complex than previously suggested (2,4).

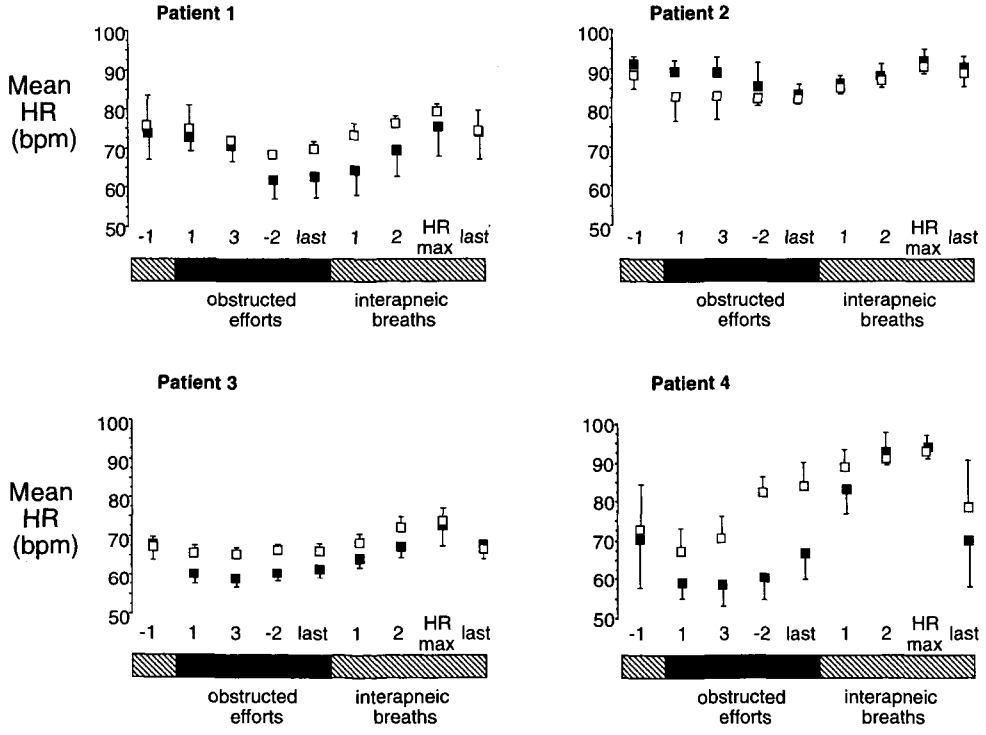

FIG. 5. Time course of heart rate while breathing room air (black symbols) and supplemental oxygen (open symbols) in each of the four patients studied. Data are expressed as mean ± standard deviation at selected time points (same as in Fig. 2).

The effects of O_2 administration clarified the meaning of the multiple correlation analysis results. Oxygen blunted HR oscillations in the apneic cycle but did not affect the interapneic tachycardia and ΔHR_{apnea}, suggesting that hypoxia may potentiate the parasympathetic "brake" during the late interapneic period and contribute to set a low HR in the following apnea (Fig. 5). A tonic modulating effect of hypoxia is also suggested by the finding that the patient with the smallest ΔSaO_2 (patient 2) also showed the highest mean HR during the apneic cycle. The interpretation of parasympathetic potentiation over the entire apneic cycle agrees with a model of cardiocirculatory oscillations in OSA based on chemoreceptor activity (12). Therefore, our data suggest a tonic rather than phasic effect of hypoxia on HR during OSA, which, combined with other factors, may account for the variable HR behavior in the apneic phase.

As for the role of hypoxia, during OSA in NREM sleep HR was reported either to decrease as hypoxia developed (2) or to decrease initially and increase thereafter (4,5). Our results confirm and extend these conclusions, because choosing consecutive rather than isolated apneas allowed analysis of HR during the entire apneic cycle. However, the relationship between HR and ΔSaO_2 differed from the hypoxia-induced bradycardia found in previous studies (2,4), as simple linear regression applied on ΔHR_{apnea} and $\Delta SaO2$ data showed a direct linear relationship between these two variables (Fig. 3). At least part of these discrepancies may be due to differences in methods among studies. For example, one study examining HR during OSA found bradycardia in the large majority of apneas (2), whereas we found it in only 20% of our sample. However, had we calculated the difference in HR between beginning and end of apneas, about two-thirds (66.7%) of OSAs in our sample would have shown "bradycardia". In addition, HR analysis on sequences of apneas may give results different from samples of isolated apneas collected at different times during the night. On the other hand, as others reported (1,2), O_2 administration blunted HR oscillations in the apneic cycle.

The behavior of HR during the apneic cycle could yield information on parasympathetic modulation in OSA patients during sleep. However, this issue is complicated by two features of OSA: 1) the frequent state shifts from sleep to arousal, and 2) the continuous alternation of apneas and hyperventilatory phases. As for the effects of sleep and arousals, our present (Fig. 1) and previous observations (13) suggest that parasympathetic activity undergoes a marked inhibition at resumption of breathing. In the early interapneic period, HR increased and respiratory sinus arrhythmia disappeared, in agreement with experimental and clinical studies (7,8,14–16). It is conceivable that the opposite state shift, from arousal to sleep, may increase parasympathetic tone and cause bradycardia, and that the features of this increase may affect HR behavior. We speculate that when re-establishment of parasympathetic activity was rapid and effective, HR declined immediately after the peak, and HR values at the beginning of OSA were low, as in the HR↑ pattern. Conversely, when re-establishment of parasympathetic activity was less effective, little or no HR fall occurred after the peak, and HR values at the beginning of OSA were high, as in the HR↓ pattern. Re-establishment of parasympathetic tone was variable, as all three identified patterns occurred in some of the subjects examined. As for a role for resumption of ventilation, HR increased very slowly in a bilaterally vagotomized patient with OSA (17), supporting the possibility that postapneic tachycardia may be the same as the "pulmonary inflation reflex" (2,3). Other studies, however, tend to deny this possibility (6). Our results support the role of arousal in postapneic tachycardia (7,8), because neither HR_{max} or transient disappearance of respiratory sinus arrhythmia were affected by O_2 (Fig. 5).

The intriguing questions as to why some patients showed predominance of one or the other HR trend, and which factors determine bradycardia or tachycardia during apneas, are difficult to answer. We speculate that HR↓ OSAs result from a low initial parasympathetic tone, that possibly increased during apnea as result of hypoxia. In fact, HR↓ OSA disappeared during O_2 administration, as in previous studies (1,2). The subjects with prevalence of HR↓ OSA were less overweight than the rest of the sample, but no relationship was found between anthropometric variables and HR behavior during OSA. In HR↑ apneas, parasympathetic tone appeared strong initially, to decrease during apnea. One can hypothesize that the HR↑ trend reflected a relative increase in sympathetic (18) over parasympathetic activity during apnea. This hypothesis agrees with the small ΔSaO_2 observed in HR↓ apneas, possibly involving a low degree of sympathetic activation. Similarly, fewer HR↑-OSAs should occur during O_2 administration, because preventing hypoxia blunted sympathetic activation during apnea (19). However, O_2 did not affect frequency of HR↑-OSA in patient 4. Therefore, additional factors likely contribute to the pathogenesis of HR↑-OSA, like large Pes swings, in agreement with data reported in awake subjects during the Mueller maneuver (20,21), and/or lengthening of inspiration during apnea (11). Ti prolongation may delay the onset of parasympathetic activity at expiration (22), thereby increasing mean HR as efforts become progressively greater during apnea.

Apneas with stable HR (HR=, ΔHR_{apnea} between −4 and +4 bpm) can be interpreted as representing a mixed OSA population. For example, the HR= pattern

may occur in apneas too short for any HR trend to develop, as already suggested (2). Alternatively, predominance of OSA with the HR= pattern may reflect the balance between limited hypoxia and small intrathoracic pressure swings. HR_{max} after HR= OSA was lower than after HR↑-OSA or HR↓-OSA (data not shown), suggesting light arousals and less sleep disruption, possibly related to limited Pes swings compared with OSA with HR↑ or HR↓ trends. Finally, a shift to HR= is favored by O_2 administration. Together, our data suggest a complex HR modulation during apnea, resulting from the interplay of several factors (level of parasympathetic activity in state shifts and at the onset of apnea, hypoxia-induced increase in sympathetic activity, mechanical and timing changes) acting in similar or opposite directions.

Because each patient showed a predominant HR pattern, the interindividual variability observed may reflect differences in autonomic HR control during sleep. In other words, parasympathetic activity may be more effective in subjects showing brisk HR falls than in subjects with slow and/or small HR changes in the interapneic period. In agreement with the possibility that HR↑ in OSA may be a sign of good autonomic function, the HR↑ trend was rarely found in hypertensive OSA patients (Bonsignore, unpublished data). It is possible that, as for other neurologic diseases (23), nocturnal HR alterations precede abnormally low parasympathetic responses during wakefulness (24,25). This hypothesis, however, needs further study. Age may affect HR variability (26) but did not correlate with the development of HR trends during apnea, as well as BMI, AHI, or HR during wakefulness.

In conclusion, our data indicate a multifactorial modulation of HR during apnea and suggest that hypoxia may tonically potentiate the parasympathetic "brake". Further studies are needed to ascertain whether HR changes in the apneic cycle can yield clinically important information on the effectiveness of parasympathetic cardiovascular control during sleep in OSA patients.

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