Bradycardia during Sleep Apnea

CHARACTERISTICS AND MECHANISM

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ABSTRACT To determine the characteristics of and mechanisms causing the bradycardia during sleep apnea (SA), both patients with SA and normals were studied. Evaluation of six consecutive SA patients demonstrated that bradycardia occurred during 95% of all apneas (central, obstructive, and mixed) and became marked with increased apnea length ($P < 0.01$) and increased oxyhemoglobin desaturation ($P < 0.01$). Heart rate slowed 9.5 beats per minute (bpm) during apneas of 10–19 s in duration, 11.4 bpm during 20–39-s apneas, and 16.6 bpm during 40–59-s apneas. Sleep stage had no effect unexplained by apnea length or degree of desaturation.

Oxygen administration to four SA patients completely prevented the bradycardia although apneas lengthened ($P < 0.05$) in three. Sleeping normal subjects did not develop bradycardia during hypoxic hyperpnea but, instead, HR increased with hypoxia in all sleep stages, although the increase in HR was not as great as that which occurred while awake.

Breath holding in awake normals did not result in bradycardia during hyperoxia (SaO_2 = 99%), but was consistently ($P < 0.01$) associated with heart rate slowing during room air breath-holds (−6 bpm) at SaO_2 = 93%, with more striking slowing (−20 bpm) during hypoxic breath-holds ($P < 0.01$) at SaO_2 = 78%. Breath holding during hyperoxic hypercapnia had no significant effect on rate. Breath holding in awake SA subjects demonstrated similar findings. We conclude that the bradycardia of SA is a consistent feature of apnea and results from the combined effect of cessation of breathing plus hypoxemia.

Dr. Zwillich is a recipient of Research Career Development Award HL 00225. Dr. Douglas is the recipient of Medical Research Council Traveling Fellowship, England.

Received for publication 5 October 1981 and in revised form 14 January 1982.

INTRODUCTION

Apnea during sleep is being recognized with increasing frequency in normal men (1), and is common in those complaining of restless sleep, and daytime hypersomnolence (2). Early observations in these patients showed complex arrhythmias during apneic episodes (3). Subsequent evaluation of a large number of these patients demonstrated that bradycardia is the most common cardiac rhythm abnormality (4). This bradycardia occurs in both the apneic adult and infant and is thought by some to be the probable cause for the increased incidence of sudden death that appears to be present in this illness (3–5).

The present study was undertaken to determine some of the characteristics of, and mechanisms resulting in this bradycardia. We wondered if the bradycardia was related to the type of apnea, the sleep stage in which apnea occurred, and whether this rhythm is a consistent feature of each apneic episode. We also evaluated the role of apnea independent of hypoxemia in causing the bradycardia in sleep apnea patients. Finally, normal individuals were studied in order to determine if bradycardia results from either hypoxemia or cessation of respiration while awake and during sleep.

METHODS

First, we studied six male subjects (Table I) who had the clinical features of the sleep apnea syndrome. Five of the six were referred because of a history of daytime hypersomnolence. All six were obese and had a long history of loud snoring every night but none had a history of heart failure or systemic hypertension. Five of the six had no other known illness and were taking no medication. One (subject F) had had a myocardial infarction and was being treated with propranolol. No rhythm disturbances were present in any subject during a 10-min electrocardiographic analysis while awake. Studies were performed in a laboratory in Denver

TABLE I
Clinical Features of Sleep Apnea Subjects

Subject	Age	Height	Weight	History of snoring	History of hypersomnolence	History of hypertension
		in	*lbs*			
A	23	66	375	Yes	Yes	No
B	33	68	175	Yes	No	No
C	31	68	215	Yes	Yes	No
D	68	69	187	Yes	Yes	No
E	60	69	281	Yes	Yes	No
F	36	69	230	Yes	Yes	No
Mean	41.8	68	244			
SEM	7.30	0.48	30.3			

(altitude 5,200 ft.) designed for sleep with environmental temperature held constant at 21°C and where extraneous noise was eliminated by acoustic insulation. All studies were completed between 10 p.m. and 6 a.m. All subjects (except F) were asked to refrain from the use of any drugs for the 24 h preceding the evaluation.

Full night's sleep electroencephalographic recordings were obtained using standard silver disk electrodes placed in the usual position. Three electro-oculogram electrodes were attached, one lateral to each eye, and one near the nasion. Two electromyogram electrodes were placed under the chin. Electrocardiograph (EKG) tracings were recorded from three chest electrodes. A mercury strain gauge with suitable bridge balancing was placed around the lower chest and was used to record respiratory excursions. Nasal and oral thermistors were used to detect airflow. We previously determined that this strain gauge was as sensitive to respiratory movement of either the chest or abdomen as a thoraco-abdominal impedance vest (Respitrace Corp., Ardsley, NY). Continuous measurement of oxygen saturation was recorded using a calibrated ear oximeter (47201A, Hewlet-Packard Co., Palo Alto, CA). Signals from the electroencephalograph, EKG, electromyogram, electrooculogram, respiratory strain gauge, ear oximeter and thermistors were recorded on an electroencephalograph polygraph (Grass model 78D, Grass Instrument Co., Quincy, MA). Sleep recordings were scored using conventional criteria (6). Apneas were considered present when there was no air flow for >10 s. These were considered central in origin when cessation of air flow was accompanied by no thoracic movement as measured by the strain gauge. Obstructive apneas were considered present when apneas were associated with positive strain gauge deflections indicating thoracic movement. Mixed apneas were typified by an episode of no air movement resulting from central, followed by obstructive mechanisms.

In each subject, we randomly sampled 20 apneas of each type (central, obstructive, and mixed), and also when possible apneas of short (10–19 s), medium (20–39 s), and long duration (40–59 s). The effects of apnea on heart rate was assessed by measuring the EKG rate for 10 s preceding the onset of apnea, and comparing this with the heart rate during the final 10 s of an apnea. Since, in some cases, heart rate was decelerating during the final 10 s of apnea our measures of the bradycardia may be an underestimate. We reasoned that using a 10-s interval is preferable to a single R-R interval because of the additional amount of data evaluated and because there is an expected variability in R-R intervals due to respiratory cycling (7). We then evaluated heart rate for the 10 s following the termination of each apnea. At no time during an apnea was any rhythm other than sinus found. The variability in rate independent of apneas was measured in three subjects during random periods in stage 1, 2 and rapid eye movement (REM)[1] sleep during intervals where no apneas occurred in the previous minute. Heart rate was measured over a 10-s period and compared with the rate found during a subsequent 10-s period. This second period of measurement was separated from the first by 5 s in order to duplicate the conditions for measurement during the most common (10–19-s) apneas. Of the 56 apnea-free intervals tested, 30 demonstrated identical rates during the two 10-s periods, whereas 20 showed a random change in rate of between 3 and 6 bpm. The remaining six periods showed random variability in rate of between 7 and 10 bpm. Sleep stage had no effect on variability.

To determine whether bradycardia found during apnea was related to the apnea itself or its resultant hypoxemia, four additional subjects with predominantly obstructive sleep apnea were studied before and during the administration of supplemental oxygen. Informed consent was obtained from each after approval by the Human Research Committee. These subjects were similar to the first group in age, height, and weight distribution. Two differences were present in this second group. The first is that there was one postmenopausal female subject and the second was that the effects of oxygen administration was assessed during a 1-h daytime period of sleep. In this group all comparisons were made using this 1-h sleeping period of 2 separate d with or without supplemental oxygen administration (mask). Oxygen administration varied in quantities sufficient to maintain $SaO_2 \geq 90\%$ during apneas.

In order to determine the effects of hypoxemia alone (independent of apnea) on heart rate, six normal male subjects had their heart rate responses to hypoxemia measured during all sleep stages. Informed consent was given by each. Four of these six were studied previously and had no apneas during full night recording. Hypoxemia and heart rate was assessed using the previously described methods. Hypoxemia was induced by the administration of 100% nitrogen to an air filled bag connected to the inspiratory port of a sealed face mask. Isocapnia was maintained using techniques that

[1] *Abbreviations used in this paper:* FRC, functional residual capacity; REM, rapid eye movement.

we have previously reported (8). Hypoxemia was progressive over a period of ~4 min during which time SaO_2 decreased from 95 to 82%. Data was used only if the subject remained in the same sleep stage during the 4 min. Subject safety was enhanced by having two physicians present at all times during these studies. In addition, oxygen sensing alarms were constructed on the inhaled gas bag and in the mask (end tidal PO_2) to signal dangerous levels of hypoxemia (PaO_2 < 40 mm Hg).

Then, in order to determine if voluntary apnea (breath-holding) with or without hypoxemia results in bradycardia in normals, we studied six normal subjects on two different occasions while awake. During these studies the subjects rested in the supine position while EKG, oxygen saturation, and respiratory excursions were measured using the techniques previously described. When heart rate was stable, each subject was asked to breath-hold at functional residual capacity (FRC) for as long as possible after breathing room air. Breath holding at reproducible levels of FRC was easily achieved using the strain gauge signal as a guide. The subjects were then made hypoxemic by breathing a low oxygen gas for ~5 min with isocapnia maintained by the addition of CO_2 to the inspired gas. Once a stable saturation of 85% had been achieved, the subject was asked to breath-hold at FRC for as long as possible. Electrocardiographic analysis during these maneuvers were identical to those used previously.

To determine whether the heart rate changes during breath-holds were related to hypoxemia or the breath-holding maneuver itself, these subjects breath-held after breathing 100% oxygen. Because of the hyperoxia, long breath-holding (90 s) was easily achieved. The possible role of hypercapnia causing bradycardia was evaluated by having these subjects breath-hold after rebreathing a hyperoxic gas mixture when end tidal carbon dioxide was elevated ~10 mm Hg and SaO_2 was >97%.

Because patients with obstructive sleep apnea tend to breathe against an obstructed upper airway we duplicated this maneuver by instructing our subjects to attempt to maximally inhale against the voluntarily closed upper airway (Mueller maneuver) every 5 s during a 30-s breath-hold. This was done at FRC to duplicate what is seen in obstructive SA patients. Strain gauge deflection without air flow was easily achieved in each subject.

To determine the reproducibility of these findings and the previously reported role of increased vagal efferent activity as the cause for the bradycardia (4) three of these subjects were restudied in an identical fashion on a 2nd d before and after the intravenous administration of 1.5 mg of atropine sulphate. Each breath-holding maneuver was repeated at least four times in each subject during every experimental condition. The reproducibility was excellent.

To determine if those with sleep apnea responded similarly to normal individuals, four previously studied obstructive sleep apnea subjects underwent evaluation of heart rate during breath holding after breathing room air and 100% oxygen. The conditions of study were the same as those used in the normal subjects.

The paired and two population *t* test were used to compare the results before and after high oxygen, and low oxygen administration. The analysis of variance was used when multiple comparisons were made such as on heart rate be-

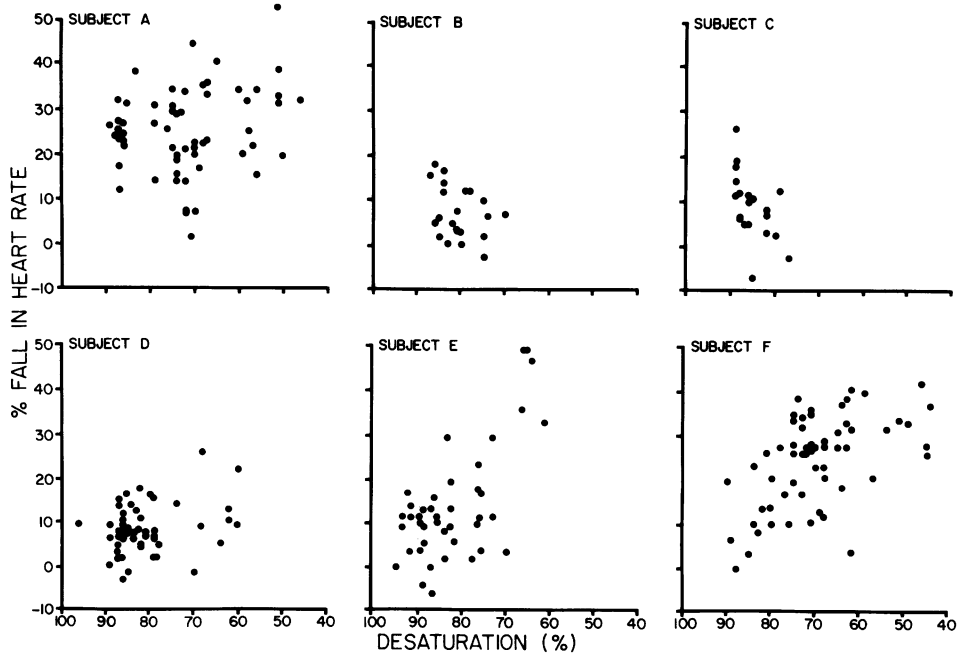

FIGURE 1 The relationship between arterial saturation (SaO_2) and fall in heart rate during apneas in the six subjects is demonstrated. A significant relationship was found in four of six subjects. In B and C no relationship between fall in SaO_2 and heart rate is evident but in these two subjects apnea length was short and desaturation relatively minor compared to that found in the others. Subject A, $P < 0.03$, $r^2 = 0.07$; B, P = NS, $r^2 = 0.11$; C, P = NS, $r^2 = 0.30$; D, $P < 0.03$, $r^2 = 0.08$; E, $P < 0.01$, $r^2 = 0.43$; F, $P < 0.01$, $r^2 = 0.30$.

fore, during, and after apneas. Correlation coefficients were analyzed by linear regression for each subject.

RESULTS

In the six sleep apnea subjects studied breathing room air, a total of 3,070 apneas were recorded (range, 197–1,174). Central, obstructive, and mixed apneas were seen in five, the remaining subject having only obstructive apneas. Each subject had short (10–19-s duration) and medium (20–39 s) length apneas and five of the six had apneas of long duration (40–59 s). These longest apneas always represented <10% of their total number of apneas. 10 apneas of >60 s were seen and these occurred in three patients.

Of the 256 randomly selected apneas, only 15 demonstrated no decrease in heart rate as defined by a fall of at least 1 bpm. These 15 apneas were of short duration, 11 being of 10–19 s, whereas 4 were of 20–39 s in duration. 118 apneas of short duration were evaluated suggesting that only a minority (11 of 118) were not associated with bradycardia. These apneas not accompanied by bradycardia were associated with only mild desaturation (11 of 15 had minimum SaO_2 of >80%) but were represented by all mechanisms (six obstructive, eight central, and two mixed). Overall, the 15 apneas not accompanied by bradycardia were significantly shorter and resulted in less desaturation than the overall average (both $P < 0.05$). As apneas lengthened there was an increasingly greater degree of bradycardia ($P < 0.01$, $r^2 = 0.30$). Heart rate slowed 9.5 bpm during 10–19-s apneas, 11.4 bpm during 20–39-s apneas, and 16.6 bpm during 40–59-s apneas (all changes were $P < 0.01$). Also, using data from all six subjects, a highly significant ($P < 0.01$, $r^2 = 0.36$) relationship between the maximum degree of desaturation and bradycardia found during each apnea was present. This relationship is demonstrated in Fig. 1 where data collected from individual subjects is shown. It should be noted that apnea subjects B and C did not show this effect. These two subjects also had the shortest apneas with least desaturation. A highly significant relationship was found (Fig. 2) between the length of apnea and the maximal degree of desaturation seen during an apnea ($P < 0.01$).

100 obstructive, 78 central, and 78 mixed apneas comprised the total number evaluated. On the average, the obstructive apneas were shorter than the central apneas, while mixed apneas were longest. Mean duration for each apnea type was significantly different from the other two types ($P < 0.05$ by nonparametric multiple comparisons) (9). Mean decrease in heart rate found for all obstructive apneas was −9.3 while the decrease in heart rate during central apneas was −10.6 bpm and −14.4 bpm for the mixed apneas. The significantly greater decrement ($P < 0.05$) in heart rate found during mixed apneas was associated with their greater duration and desaturation when compared with the central and obstructive types.

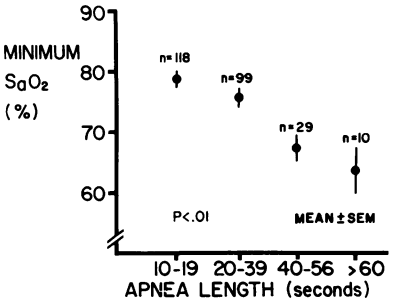

FIGURE 2 The length of apnea is compared to the lowest SaO_2 reached during an apnea. The overall effect was that of longer apneas resulting in more striking desaturation ($P < 0.01$, $r^2 = 0.36$ pooled analysis from each individual). The average minimal SaO_2 reached during the 10 apneas of >60 s in duration was 64%.

The 80 apneas evaluated in stage 1 sleep had a mean decrease in heart rate of 13 bpm ($P < 0.05$) from 65.9±0.91 to 52.9±0.98. A similar mean decrement in heart rate of 11 bpm ($P < 0.05$) was found in the 95 apneas evaluated in stage 2. The 27 apneas that occurred during REM sleep resulted in the greatest ($P < 0.01$) decrease in heart rate (−17.8 bpm) and was accounted for by the greatest length and most severe desaturation that occurred in these apneas. Accordingly, the degree of bradycardia appeared to be best explained by apnea length and desaturation, and not apnea type or sleep stage. The other 54 apneas were scattered between stages 3 and 4 or occurred where sleep stages spontaneously changed.

In the four sleep apnea subjects studied before and during oxygen administration each developed bradycardia without supplemental oxygen during every one of the 10 obstructive apneas randomly selected for evaluation in each (Table II). No mean decrease in heart rate was found in any subject during O_2 administration when apneas of all duration were evaluated (Fig. 3). However, slowing did occur in 14 of the 40 apneas evaluated during oxygen. Interestingly, the most marked slowing found in any apnea during oxygen was 6 bpm, as compared with a mean decrease of 13 bpm breathing room air. The mean length of apnea increased during oxygen in three of the four subjects (Table II). In the third, apnea length decreased while breathing oxygen from 21 to 14 s, which was also significant ($P < 0.03$). As in the first group of sleep apnea subjects, a direct relationship between O_2-hemoglobin desaturation and the degree of bradycardia during apnea was found ($P < 0.01$).

The relationship between O_2-hemoglobin desatu-

TABLE II

Effects of Oxygen Administration on Apnea Length and Heart Rate

Subject		Apnea length	Apnea heart rate			Lowest oxyhemoglobin saturation
			Before		During	
		s				
	Room air	15±1.1*	71±0.6	($P < 0.01$)	65±0.6	89±0.8
1		($P < 0.01$)				($P < 0.01$)
	Oxygen	23±2.5	67±0.8	(P = NS)	67±0.6	98±0.2
	Room air	15±0.5	90±0.9	($P < 0.01$)	78±1.6	86±0.5
2		($P = 0.08$)				($P < 0.01$)
	Oxygen	21±3.3	79±2.2	(P = NS)	79±2.2	98±0.3
	Room air	21±1.5	76±1.0	($P < 0.01$)	70±0.9	88±0.7
3		($P = 0.03$)				($P < 0.01$)
	Oxygen	14±2.7	72	(P = NS)	72	98±0.2
	Room air	29±1.1	90±2.1	($P < 0.01$)	61±1.9	65±0.9
4		($P = 0.02$)				($P < 0.01$)
	Oxygen	56±10.9	100±1.1	(P = NS)	96±1.1	98±0.2

* All values are means±SEM.

ration and bradycardia during breath-holding in normals is shown in Fig. 4. Breath-holding after breathing room air or hypoxic gas resulted in bradycardia. The degree of bradycardia was much greater during hypoxic than during room air breath-holds ($P < 0.01$). This bradycardia was completely blocked by previous atropine administration. In contrast, prolonged breath holds following 100% oxygen breathing eliminated any bradycardia. Mueller's maneuver did not significantly affect heart rate during room air breath-hold (62.4±3.74 before and 62.4±4.21 at the end of the 30-s maneuver). The Mueller's maneuver during hypoxic breath-hold resulted in bradycardia that was no different in degree from that of hypoxic breath-hold alone. The presence of hyperoxic hypercapnia before breath-hold did not result in bradycardia (heart rate before breath-hold 60±2.6 and 59±3.1 at termination).

The sleep apnea subjects responded similarly to the controls during hyperoxic breath-holding. Mean heart rate was not significantly lower after a 1-min breath-hold during hyperoxia (90±3.5 before and 83±9.4 during, P = NS). Room air breath-holding resulted in oxyhemoglobin desaturation <90% at or before 30 s in each subject. This rapid desaturation is also seen during apneas and was associated with a marked heart rate fall from 92±4.0 before to 47±7.8 during breath-hold ($P = 0.01$). Breath-holding following hypoxic gas breathing not considered a safe maneuver in these subjects.

A referred sleep apnea subject was also tested during breath-holding. Unlike any previously evaluated subject, he demonstrated no bradycardia even though his SaO_2 fell below 90% at breath-hold termination. Our review of his sleep polygraph, which was recorded at another institution, demonstrated no bradycardia during apneas even when SaO_2 fell below 70%. Of interest is the fact that 10 yr prior to our evaluation he underwent a craniotomy for a pituitary tumor. However, he had no present symptoms of dysautonomia.

Isocapnic hypoxia induced in the six normal subjects during sleep resulted in a significant increase ($P < 0.01$) in heart rate in each sleep stage studied. While awake the slope of the heart rate response to decreasing SaO_2 was calculated and demonstrated a mean increase of 1.25±0.19 bpm/SaO_2%. During sleep the mean increase in rate was 0.77±0.14 in stage 2, 0.72±0.09 in stage 3/4 and 0.26±0.20 bpm/SaO_2% in REM. The heart rate response to hypoxia was greater ($P < 0.05$) awake then during any sleep stage, and was least during REM ($P < 0.01$). A mean increase in rate of 1.30±0.60 bpm/SaO_2 percent was present in the three sleep apnea subjects studied during wakefulness. This heart rate response to hypoxemia hyperpnea was similar to the mean value of 1.25±0.19 found in the awake normals.

DISCUSSION

The present study demonstrates that bradycardia occurs during almost all apneas. Furthermore, the oc-

currence and degree of bradycardia does not vary with the type of apnea but instead depends upon the degree of hypoxemia resulting from these apneas. The magnitude of bradycardia appears to be related to the length of the apnea through the apnea-related hypoxemia. Thus, bradycardia was most marked during REM sleep where apneas were longest and desaturation greatest. The importance of hypoxemia causing bradycardia is suggested by the findings during oxygen administration where the degree of bradycardia was diminished or completely eliminated even when apneas lengthened. Prolongation of apneas during oxygen administration has been reported previously (10).

This study provides several lines of evidence supporting the idea that cessation of breathing combined with hypoxemia are required together to cause bradycardia. First, apnea during sleep without hypoxemia (supplemental oxygen) markedly attenuates or eliminates bradycardia. Second, bradycardia occurs when breathing is voluntarily stopped (breath-hold) and hypoxemia ensues. This effect is accentuated by more severe hypoxemia being present before or during the breath-hold. Here also oxygen administration prevents bradycardia even when voluntary breath-hold is prolonged. Third, hypoxemia during sleep unaccompanied by apnea results in tachycardia and not bradycardia. Fourthly, normal breathing excursions seem important in the prevention of bradycardia during hypoxemia because mixed and obstructive apneas (respiratory efforts against the closed upper airway) did not prevent or even diminish the degree of bradycardia. Furthermore, the same respiratory abnormality produced during wakefulness (the Mueller maneuver during hypoxemia) also resulted in bradycardia. Taken together, these data suggest that whether asleep or awake bradycardia will result from the combined effects of cessation or diminution of respiratory movement and its accompanying hypoxemia. As can be seen in Fig. 1, there was a direct relationship between the

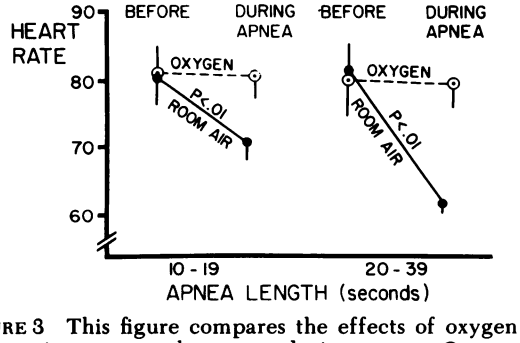

FIGURE 3 This figure compares the effects of oxygen administration on mean heart rate during apneas. Oxygen did not alter heart rate preceding apneas, but it did eliminate desaturation and the bradycardia resulting from apneas.

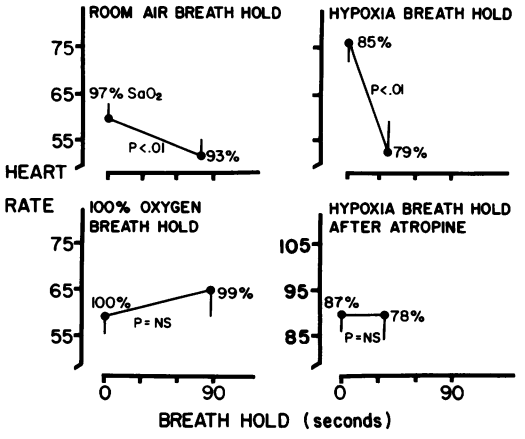

FIGURE 4 The results of breath-holding under the different experimental conditions that headline each panel is displayed. Each response represents at least four repeated maneuvers in the three normal subjects studied. The panels show that as oxy-hemoglobin saturation (SaO_2) reaches a lower value, bradycardia becomes more pronounced with breath-holding. 100% oxygen breathing before a 90-s breath-hold resulted in neither desaturation or decrease in heart rate. The lower right panel demonstrates that pretreatment with atropine eliminated the heart rate slowing found during hypoxic breath-holding.

lowest oxyhemoglobin saturation reached during apnea and the severity of the bradycardia. However, this relationship was not present in two (B and C) of the original group of six sleep apnea patients. These two had the fewest and least severe apneas with SaO_2 only once falling below 75%. These exceptions when added to the variability of the bradycardia response to apneic hypoxemia suggests that other mechanisms may also play a role. Hypercapnia during sleep apnea may play a role in bradycardia even though we were unable to demonstrate bradycardia during awake hypercapnic breath-holding.

Several previous studies have convincingly demonstrated the occurrence of bradycardia during sleep apnea. This has been profound in some patients (3, 4). The present study is the first, we believe, to demonstrate the pivotal role of hypoxemia and the permissive role of apnea as the cause of bradycardia in such patients. The attenuation or prevention of bradycardia during supplemental oxygen administration in four patients should not be considered evidence for its therapeutic role in this syndrome. It must be emphasized that only oxygen's effects on bradycardia and apnea length were evaluated in these patients, and only four patients were evaluated. Therefore, no overall therapeutic conclusions should be made from our study.

Previous experiments suggest a possible explanation for our current findings. Carotid body stimulation by hypoxemic blood results in bradycardia when anes-

thetized and paralyzed dogs are mechanically ventilated at a controlled rate (11, 12). Cutting the carotid body's nerve eliminates the bradycardia (11, 13). If, however, the animals are not paralyzed and are allowed to hyperventilate in response to hypoxemia, tachycardia usually occurs (11). A similar tachycardic response to hypoxemia is found during paralysis if mechanical ventilation is increased to match the usual reflex hyperventilation (11). That lung inflation attenuates the bradycardia of carotid body stimulation is demonstrated by cutting the pulmonary vagal afferent fibers during hypoxemia in paralyzed ventilated dogs. This results in immediate bradycardia (11). These experiments may explain the bradycardia in man during hypoxemia that occurs when respiratory excursions are eliminated by either breath-holding or apnea. The respiratory movement of either the Mueller's maneuver or that which results during upper airway obstruction in sleep apnea appears insufficient in combating the carotid body-induced bradycardia. The bradycardia of voluntary breath-holding after room air breathing has been well studied (14, 15) and the finding consistent. In the present study, bradycardia always resulted from breath-holds where any degree of desaturation occurred and was particularly marked during low oxygen gas breathing followed by a breath-hold. The pivotal role of hypoxemia is suggested by the elimination of bradycardia during hyperoxic breath-holding. We know of no previous study that has evaluated heart rate changes during breath-hold with varying degrees of desaturation. The finding that hyperoxia eliminates the bradycardia of breath-holding is controversial in that Mithoefer (16) has shown a fall in heart rate during apnea following hyperoxic hyperventilation (PaO_2 = 503, $PaCO_2$ = 22 mm HG) in paralyzed dogs. The initial heart rate of 160 bpm decreased slowly over 10 min of apnea during which time arterial oxygen tension fell to normal. However, when the PaO_2 dropped below 80 mm Hg heart rate decelerated rapidly. It is possible that the initial tachycardia resulted from the combined effects of anesthesia and hyperventilation (16), and that the subsequent rapid fall in heart rate was due to apnea and hypoxemia. Increasing $PaCO_2$ probably plays little or no role in causing bradycardia because the hyperoxic hypercapnia resulting from apnea or prolonged breath-hold after oxygen breathing diminished or eliminated cardiac slowing.

Increased vagal efferent activity appears to cause the bradycardia seen in these patients. Tilkian et al. (4) demonstrated that intravenous atropine prevented the heart rate slowing resulting from sleep apnea. A similar mechanism appears to cause bradycardia during breath-hold as our normal subjects showed complete abolition of the bradycardia during both room air and hypoxic breath-holds following atropine administration.

ACKNOWLEDGMENTS

This work was supported in part by National Institutes of Health program project grant HL 14985, and Buffington Research Foundation.

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