

Influence of testosterone on breathing during sleep

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SCHNEIDER, BRENDA K., CHERYL K. PICKETT, CLIFFORD W. ZWILLICH, JOHN V. WEIL, MICHAEL T. McDERMOTT, RICHARD J. SANTEN, LOTTIE A. VARANO, AND DAVID P. WHITE. *Influence of testosterone on breathing during sleep*. J. Appl. Physiol. 61(2): 618–623, 1986.—Apneas and hypopneas during sleep occur more frequently in men than women. Disordered breathing is also reported to increase in hypogonadal men following testosterone administration. This suggests a hormonal influence on sleeping respiratory pattern. We therefore studied respiratory rhythm during sleep in 11 hypogonadal males both on and off testosterone-replacement therapy. In four subjects the anatomy (computerized tomography) and airflow resistance of the upper airway were also determined on both occasions. Sleep stage distribution and duration were unchanged following androgen administration. However, both apneas and hypopneas increased significantly during testosterone replacement so that the total number of disordered breathing events (apneas + hypopneas) per hour of sleep rose from 6.4 ± 2.1 to 15.4 ± 7.0 ($P < 0.05$). This was a highly variable event with some subjects demonstrating large increases in apneas and hypopneas when androgen was replaced, whereas others had little change in respiration during sleep. Upper airway dimensions, on the other hand, were unaffected by testosterone. These results suggest that testosterone contributes to sleep-disordered breathing through mechanisms independent of anatomic changes in the upper airway.

sleep apnea; hypopnea; supraglottic resistance

HYPOVENTILATION and irregular breathing are common events during sleep, and in severe instances frequent and prolonged apnea may occur. Both the common respiratory dysrhythmia and the less common instances of overt sleep apnea are seen more frequently in men than women (3, 6). Furthermore, irregular breathing during sleep is reported to be more common in women following the menopause (4). This association of erratic breathing and apnea with gender and menopause suggests an important potential influence of sex hormones on breathing during sleep. Specifically, the preponderance of respiratory dysrhythmias and apneas in males and the reported development of sleep apnea in patients following testosterone administration (8, 11, 15) suggest that androgens may play a role in determining respiratory rhythm during

sleep.

Despite suggestive evidence that sex hormones, particularly androgens, may have important influences on respiratory events during sleep, this has not, to our knowledge, been systematically evaluated. Therefore, a study of the effect of testosterone on respiratory rhythm during sleep was undertaken. The subjects were hypogonadal men in whom sleep and breathing were evaluated during cessation and following reinstitution of testosterone-replacement therapy. In addition, upper airway size and airflow resistance were determined both on and off testosterone in four of the subjects.

METHODS

Subjects. Eleven hypogonadal males [mean age 48.8 ± 5.7 (SE) yr] were studied. The cause of the hypogonadal status and the physical characteristics of each are given in Table 1. None of the subjects studied had pulmonary disease. All gave informed consent to the protocol which had the approval of the institution's Clinical Investigation Committee.

Each subject was studied on two occasions the sequence of which was randomized. The "off-testosterone" evaluation was conducted at least 30 (mean 52.5 ± 9.6) days after testosterone replacement had been discontinued. The "on-testosterone" study took place 3–7 (mean 3.5 ± 0.4) days after an intramuscular testosterone enanthate injection (200 or 400 mg). All subjects with one exception had received such injections regularly every 2 wk for at least 90 days prior to the on-testosterone study. One subject (*subj 2*, Table 1), however, had received only a single injection prior to the study having never been on androgen previously.

Because hypogonadal males are reasonably rare, we found it necessary to study subjects on medication other than testosterone (Table 1). However, with the exception of the testosterone administration described above, there were no other changes in medication. Subjects were also asked to refrain from the use of alcohol or caffeine for 24 h prior to each study and had fasted for at least 4 h before sleep.

Sleep studies. The sleep studies were conducted in one of two laboratories (Denver, CO, or Hershey, PA), and

the techniques varied slightly between the two as will be described below. However, each individual subject was studied on both occasions, on and off testosterone replacement, in the same laboratory using identical methods on each night. These sleep studies were performed in an acoustically insulated laboratory designed specifically for such studies and were done between 9:30 P.M. and 7:00 A.M., with each subject being allowed to retire at his usual bedtime. Full night electroencephalographic (EEG), electromyographic (EMG), and electrooculographic (EOG) recordings were obtained. Chest and abdominal wall motion were determined with either a circumthoracic mercury strain gauge (Denver) or an inductive phethismograph (Hershey). Nasal and oral airflow was monitored with both heat-sensitive thermistors and an infrared capnograph. Arterial O₂ saturation was continuously recorded using one of two calibrated ear oximeters, the Biox IIA (Boulder, CO) oximeter being used in Hershey and the Hewlett-Packard (Waltham, MA) instrument in Denver. All signals were recorded on a Grass model 78D polygraph (Grass Instruments, Quincy, MA). One-night studies, both on and off testosterone, were completed in Denver, whereas an acclimatization night followed by a study night were conducted in Hershey during both hormonal conditions. Data will be reported only from the study night.

Sleep records were scored using the criteria of Rechtschaffen and Kales (14). Apneas were considered present when respiratory airflow was absent for 10 s or longer. The duration of apneas was scored from breath peak to peak. Absence of both airflow and thoracic movement was considered indicative of a central apnea. Absence of respiratory airflow but persistence of thoracic movement were interpreted as an obstructive apnea.

Mixed apneas were typified by an episode of no air movement that began as a central event but progressed into obstructed ventilatory efforts. Hypopneas were defined as a 50% or greater decrease in the airflow signal (thermistor and capnograph) accompanied by a simultaneous decrease in chest and abdominal wall motion lasting at least 10 s. Some airflow was always present during hypopneas. Arousals were defined as EEG α -activity (wakefulness) for at least 5 but <15 s in association with increased EMG activity. Awakenings were considered to be present when both EEG and EMG signals demonstrated the awake pattern for >15s.

Upper airway. Four of the subjects (*subj 8-11* from Table 1) had supraglottic airway evaluations both on and off testosterone. All subjects had been off testosterone for at least 90 days prior to the off-testosterone study and on hormone replacement for at least 3 mo before the on-testosterone evaluation. The upper airway was evaluated anatomically by computerized tomographic scanning (CT) and physiologically by determining supraglottic airflow resistance (19) while breathing through the nose.

The CT scan (Siemens Somatom 2) was performed with the patient in the supine posture and the neck held in a neutral position, neither flexed nor extended. The uppermost scan was performed at the level of the hard palate, and the imaging was repeated at 0.8-cm intervals caudally until the epiglottis was encountered. All scanning was done during breath holding at functional residual capacity using a 5-s scanning time. The minimal cross-sectional area of the airway at each level was then determined using the software of the scanner. Anatomic landmarks on the scans were used to ensure that the airway locations being examined were comparable on

TABLE 1. *Physical characteristics and cause of hypogonadal status*

Subj No.	Study Site	Age, yr	Ht, cm	Body Wt, kg	Cause of Hypogonadism	Other Medication	Testosterone Level, ng/ml	
							Off	On
1	D	40	170.0	67.0 (95.7)	Klinefelter's syndrome	None	0.4	14.8
2	D	19	182.9	95.5 (117.9)	Delayed adolescence, Klinefelter's mosaic	None	2.4	8.4
3	D	58	172.7	75.9 (106.4)	Idiopathic	None	3.2	12.7
4	D	52	182.9	75.0 (92.7)	Idiopathic	None	2.1	19.0
5	D	55	180.3	84.5 (106.8)	Idiopathic	None	2.0	15.4
6	D	21	170.2	77.3 (110.4)	Kallmann's syndrome	None	1.0	9.4
7	D	55	180.3	95.5 (120.7)	Idiopathic	Insulin	2.8	11.5
8	H	72	176.5	76.8 (103.6)	Pituitary adenoma, postsurgery	Bromocriptine, cortisone acetate, hydrochlorthiazide, phenytoin	0.1	19.7
9	H	72	182.9	81.1 (104.9)	Pituitary adenoma, postsurgery	Phenytoin, digoxin, levothyroxine, cortisone acetate	0.1	7.3
10	H	63	185.4	115.0 (144.6)	Pituitary adenoma, postsurgery	Levothyroxine, cortisone acetate, clonidine, hydrochlorthiazide	0.3	7.3
11	H	30	179.1	69.5 (92.1)	Kallmann's syndrome	None	0.2	19.6
Mean $\pm$ SE		48.8 $\pm$ 5.7	178.5 $\pm$ 1.6	83.0 (108.7) $\pm$ 4.2 $\pm$ 4.5)			1.3 $\pm$ 0.4	13.2* $\pm$ 1.4

The study site designations are D for Denver, CO, and H for Hershey, PA. Body weights in parentheses indicate percent of ideal weight. A normal serum testosterone level is 3–10 ng/ml. * $P < 0.05$ different from Off-testosterone value.

and off testosterone. Results for each individual will be reported in two ways: 1) as the mean cross-sectional area of the entire airway and 2) as the minimal cross-sectional area encountered for the entire airway.

Supraglottic resistance was determined using a technique previously described by our laboratory (19). Briefly, the pharynx was lightly anesthetized with lidocaine, and a small calibrated balloon-tipped catheter was inserted through the mouth to about 2–3 cm below the level of the posterior tongue (at the level of the epiglottis). Pressure was determined with a Validyne differential pressure transducer. Flow was measured using a sealed face mask and pneumotachometer. The subjects were studied in the supine position breathing exclusively through the nose. Both signals were recorded on a Grass model 78D polygraph, and airflow resistance was determined on inspiration at a flow rate of 0.3 l/s.

Testosterone assay. A venous blood sample was obtained prior to sleep under both hormonal conditions. Serum testosterone concentrations were measured using a radioimmunoassay technique (1) and are expressed as nanograms per milliliter.

Statistical analysis. Because of the large variability and skewed distribution of the response to testosterone administration, a nonparametric paired *t* test (the Wilcoxon signed rank) was used for data analysis of sleep and breathing values (17). Because the original hypothesis was directional, i.e., adverse effects on sleep events were anticipated during testosterone replacement, a one-tailed test was used. For all other comparisons a Student's *t* test (2 tailed) was employed. The statistical confidence intervals selected for all analysis was $P < 0.05$.

RESULTS

As is shown in Table 1 there was a large increase in testosterone concentration following hormone replacement. There was, however, no change in weight (83.0 ± 4.2 kg off and 82.2 ± 4.2 kg on testosterone). The duration of sleep and sleep stage distribution was also unaffected by testosterone (Table 2). The total number of arousals (brief return to wakefulness), however, increased significantly (21.3 ± 3.9 to 55.6 ± 25.9 per night, $P < 0.05$) following testosterone administration, but more prolonged awakenings remained unchanged.

Disordered breathing events during sleep (apneas and

hypopneas) were increased following testosterone replacement (Table 3, Fig. 1). Apneas rose from 3.5 ± 1.9 to 9.2 ± 6.2 per hour ($P < 0.05$), and hypopneas increased from 3.0 ± 1.0 to 6.2 ± 1.9 per hour ($P < 0.05$). As a result there was a significant increment in total disordered breathing events (apneas + hypopneas) from 6.4 ± 2.1 to 15.4 ± 7.0 per hour ($P < 0.05$) with testosterone. These dysrhythmic events (apneas and hypopneas) tended to occur primarily during stage 2 sleep but also occurred during stage 1 and rapid-eye-movement (REM) sleep. Little stage 3/4 sleep occurred (Table 2), and few apneas were encountered during this slow-wave sleep. The type of apnea varied between subjects, with some demonstrating primarily obstructive events and others central or mixed apneas. However, the type of apnea did not change following hormone replacement. A subject with obstructive apneas prior to testosterone continued to have obstructive events after replacement. The same principle applied to central and mixed events. The mean arterial O_2 desaturation that occurred during both apneas and hypopneas did not change following testosterone administration (apnea: on $4.5 \pm 1.0\%$, off $4.7 \pm 1.0\%$; hypopnea: on $3.4 \pm 0.6\%$, off $3.6 \pm 0.6\%$).

As can be seen in Fig. 1 and Table 3, the response to testosterone was variable. Five of the subjects demonstrated either little change or a small decrement in apneas plus hypopneas, whereas six of the subjects had a substantial increase in disordered breathing events during sleep when androgen was replaced. Four of these subjects (Table 3, *subj 1, 4, 6, and 10*) had considerable sleep-disordered breathing in the hypogonadal state, but these events clearly increased following hormonal administration. The duration of testosterone administration did not appear to play a role in determining an individual's response to the hormone. *Subject 2* (Table 1) demonstrated an increase in disordered breathing events from 0.9 to 4.2/h after a single injection of testosterone. This increment was similar to that observed in a number of the other subjects receiving more chronic hormone replacement.

TABLE 3. Effect of testosterone on disordered breathing events (apneas and hypopneas) during sleep

Subj No.	Apneas/h		Hypopneas/h		Total Apneas + Hypopneas/h	
	Off	On	Off	On	Off	On
1	21.5	69.8	1.2	10.0	22.7	79.8
2	0.6	1.7	0.3	2.4	0.9	4.2
3	0.8	0.2	3.0	3.1	3.2	3.3
4	0.4	1.0	5.2	18.3	5.6	19.3
5	0.3	0.0	0.3	0.5	0.7	0.5
6	3.5	8.2	0.3	1.1	3.8	9.3
7	0.5	0.6	0.0	0.9	0.5	1.6
8	0.3	2.1	9.2	6.1	9.6	8.2
9	2.3	1.5	3.3	2.1	5.6	3.6
10	8.2	14.0	7.6	16.8	15.8	30.8
11	0.4	1.8	2.5	7.2	2.9	9.1
Mean	3.5	9.2*	3.0	6.2*	6.4	15.4*
±SE	±1.9	±6.2	±1.0	±1.9	±2.1	±7.0

Values are given per hour of sleep. Off and On indicate presence or absence of testosterone replacement. * $P < 0.05$ different from off testosterone.

TABLE 2. Effect of testosterone on sleep

	Testosterone	
	Off	On
Total sleep time, min	385.0±16.8	370.4±14.9
% Awake	15.8±2.9	15.3±2.5
% Stage 1	6.9±1.0	6.6±1.8
% Stage 2	53.5±2.6	53.0±4.3
% Stage 3	4.1±1.0	4.8±1.4
% Stage 4	4.5±2.1	4.2±2.1
% REM	15.2±2.4	16.2±1.2
Total arousals	21.3±3.9	55.6±25.9*
Total awakenings	29.9±3.9	26.5±3.1

Values are means ± SE. REM, rapid-eye movement sleep. Arousals and awakenings are defined in METHODS. * $P < 0.05$ different from off testosterone.

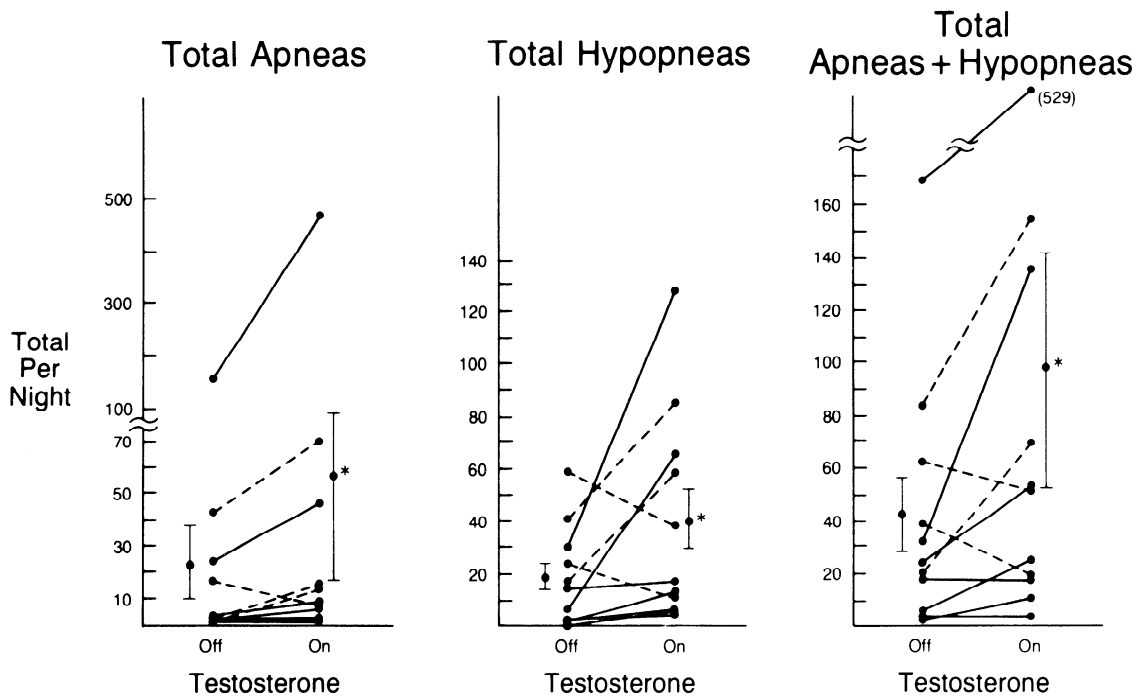


FIG. 1. Total number of apneas, hypopneas, and apneas plus hypopneas per night on and off testosterone replacement are demonstrated. Means $\pm$ SE are also depicted. There was a significant increase in all 3 events during testosterone replacement. *Solid lines*, subject studied in Denver, CO; *dotted lines*, subject studied in Hershey, PA. * $P < 0.05$, On different from Off testosterone.

The results of the upper airway evaluations are shown in Table 4. There was no difference in airway size or supraglottic airflow resistance in these four subjects on and off testosterone.

DISCUSSION

This study indicates that the administration of testosterone to hypogonadal men leads to a significant increase in disordered breathing during sleep. This applies to both apneas and hypopneas. This effect was quite variable in that some individuals demonstrated a large increase in dysrhythmic breathing episodes, whereas others had little change. This is not to say that testosterone is the primary mediator of sleep-disordered breathing inasmuch as several subjects persisted in having apneas and hypopneas even when androgen was withheld (Table 3). However, testosterone is likely to be one of many factors that are important in the development of disordered

breathing during sleep.

It should be noted that, following testosterone administration, many of the subjects demonstrated small increases in the number of sleep-disordered breathing events (Table 3) without large changes in arterial O_2 saturation. Therefore, in most subjects, the effects of testosterone are not dramatic and the syndrome of sleep apnea does not develop. However, the changes observed were consistent and statistically significant and are unlikely to represent random variability in breathing pattern during sleep.

Although there has been little systematic investigation of the influence of testosterone on respiratory events during sleep, considerable evidence points to the possibility that the male hormone may exert important effects. Snoring, obstructive sleep apnea, and disordered breathing during sleep are all far more frequent in men than in premenopausal women (3, 6). These gender differences could relate either to the adverse effects of male hormones (androgens) or possible beneficial effects of female hormones such as progestins. Several lines of evidence suggest that androgenic effects may be of primary importance. First, although progestins are capable of stimulating ventilation and increasing ventilatory drives during wakefulness (10, 21), they have not been shown to be therapeutically useful in sleep apnea (13). Alternatively, there are case reports which suggest that testosterone may have adverse effects on breathing during sleep. In a study of seven morbidly obese males (7), all but one showed arterial O_2 desaturation or disordered breathing during sleep, the exception being a hypogonadal patient. This led the authors to speculate that decreased testosterone levels may protect an individual

TABLE 4. Effect of testosterone on upper airway

Subj No.	Supraglottic Resistance, $\text{cmH}_2\text{O} \cdot \text{l}^{-1} \cdot \text{s}$		Mean Pharyngeal Airway Size, mm		Minimal Pharyngeal Airway Size, mm	
	Off	On	Off	On	Off	On
8	3.1	4.2	320	319	215	241
9	5.4	5.6	165	194	145	114
10	9.4	6.8	78	93	0	0
11	12.9	7.9	175	192	101	147
Mean $\pm$ SE	7.7 $\pm$ 2.2	6.2 $\pm$ 0.7	184.5 $\pm$ 50.1	199.5 $\pm$ 46.3	115.3 $\pm$ 45.0	125.8 $\pm$ 49.7

Off and On indicate presence or absence of testosterone replacement. Airway size was determined by computerized tomography.

from respiratory dysrhythmias during sleep. Subsequently Sandblom et al. (15) reported the case of a moderately obese male who developed symptomatic obstructive sleep apnea several months after the administration of testosterone. Symptoms and obstructive apneas improved with discontinuation of the drug on two occasions and recurred with its resumption.

More recently, Johnson, Anch, and Remmers (8) reported the development of loud snoring and obstructive sleep apnea in a 54-yr-old woman after several months of high-dose androgen administration. Symptoms and sleep findings resolved when the androgens were withdrawn, recurred with rechallenge, and subsided again with subsequent discontinuation of the hormone. Finally Matsumoto et al. (11) reported a study of sleep in five hypogonadal men on and off testosterone. They found two of the subjects to have a large increase in sleep-disordered breathing following testosterone administration, whereas three demonstrated little change. These findings are similar to our results. This group of studies would suggest that testosterone could be important in the development of disordered breathing during sleep and may explain the male predominance in sleep apnea.

Although this study and others have indicated that the administration of testosterone in physiological doses produces an increase in disordered breathing during sleep in some individuals, it provides no clear insight into the mechanism of this effect. However, several possibilities must be considered. First, could the anabolic effects of testosterone lead to anatomic reduction in patency of the upper airway predisposing the individual to airway closure and apnea during sleep? The previously described study by Johnson et al. (8) would suggest this may be the case. They observed an increase in supraglottic resistance in a woman following high-dose androgen administration coincident with the development of obstructive sleep apnea. Our data, however, indicate that pharyngeal anatomy is unlikely to explain how physiological testosterone replacement produces disordered breathing for several reasons. First, we were unable to demonstrate a change in either upper airway patency (CT scan) or supraglottic resistance in four subjects following testosterone administration. Although the number of subjects studied, four as stated, is too small for meaningful statistical analysis, there was no trend or indication that the awake airway was changing during hormone replacement. Second, we observed an increase in dysrhythmic breathing episodes during sleep in *subject 2* following a single injection of testosterone 3 days prior to study, a time period likely to be too short to produce anatomic changes. Neither of these observations, however, rule out the possibility that the neuromuscular control of upper airway patency during sleep could be influenced by testosterone.

Testosterone could also produce changes in sleep state such as increases in REM sleep and thereby yield more disordered breathing. However, for the group as a whole there was no difference in any sleep stage on and off testosterone replacement (Table 2). Also, when the subjects who demonstrated an increase in sleep-disordered breathing are examined separately, there is actually a small statistically insignificant drop in the percentage of

REM sleep during androgen administration. Therefore, sleep state does not seem to explain testosterone's effect on breathing.

The other possible explanation for testosterone's effect on breathing during sleep relates to its influence on the control of breathing. We, in 12 subjects (20), and Sandblom et al (15), in a single subject, found testosterone to elevate metabolic rate and produce an increase in hypoxic ventilatory responsiveness with little change in hypercapnic sensitivity. Matsumoto et al. (11), on the other hand, found no change in metabolic rate and a decrease in the hypoxic response following testosterone administration. It is difficult to explain this discrepancy. However, a number of older studies suggest that O_2 consumption increases in hypogonadal men following testosterone replacement (9, 18) and increases in metabolic rate are often associated with increased hypoxic sensitivity (22, 23). On balance, therefore, it seems likely that an individual's hypoxic response will increase with testosterone administration. To the extent that the hypoxic drive is augmented by testosterone, the associated apneas and hypopneas might be analogous to those seen at high altitude or with laboratory induced hypoxia (2), where it appears that increased ventilatory chemosensitivity may act to drive CO_2 tensions below levels required to sustain regular breathing (16). If so, CO_2 tension during sleep should be reduced following testosterone, especially prior to episodes of hypopnea or apnea. Regrettably, such values are unavailable from this study.

In an attempt to determine whether the changes in hypoxic sensitivity induced by testosterone correlate with changes in breathing rhythm during sleep, we compared these variables in the nine subjects in whom both waking hypoxic ventilatory responses (from a previous study, Ref. 20) and sleep studies were completed on and off testosterone. No correlation between either absolute or percent changes in these measurements could be found. This does not rule out an association between the two, since most subjects demonstrated an increase in both variables. Also one determination was made during wakefulness and the other during sleep, which would detract from our ability to show a relationship. However, no direct correlations could be detected.

Our observation that testosterone's effect on breathing during sleep was highly variable is also of interest. Some individuals demonstrated a large increase in apneas and hypopneas during hormone replacement, whereas others had little or no change. Why this occurred is unclear but may relate to the size or patency of the individual's upper airway. Of the four subjects undergoing upper airway evaluation, two had large increases in sleep-disordered breathing events following testosterone and two demonstrated little effect. The two subjects who increased their dysrhythmic breathing episodes (*subj 10* and *11*, Table 3 and 4) tended to have a higher supraglottic resistance and lower mean pharyngeal airway size than the other two subjects (*subj 8* and *9*, Tables 3 and 4), although such small numbers prohibit statistical evaluation. As stated previously, testosterone did not influence the size or airflow resistance of the pharynx. However, an individual with a small airway initially whose hypoxic sensitivity is enhanced by androgen administration may

have more disordered breathing due to interactions between an unstable ventilatory controller (5) and variable upper airway patency (12).

Although our observations regarding the upper airway are of interest, the small number of subjects studied does not exclude the possibility that changes in upper airway resistance or anatomy could occur secondary to testosterone. Also the reproducibility of the CT measurements has not been determined by either ourselves or others. However, there was no evidence that large changes in the pharynx were occurring with androgen administration.

It is important that our results be interpreted with some caution due to potential pitfalls in study design. The availability of hypogonadal males forced us to conduct the study at two medical centers with slightly different protocols. However, it is unlikely that this critically influenced our findings, because each subject was studied in an identical manner, both on and off testosterone. Although some subjects were acclimatized to the sleep laboratory, and others not, each was studied similarly both before and after testosterone replacement and the sequence of study was randomized. Therefore, the "first-night" effect in the unacclimatized subjects is unlikely to have altered our observations. The slight differences in equipment used in the two sleep laboratories seems inconsequential. Therefore, the use of two study centers probably did not affect our results.

Finally, it should also be noted that the testosterone levels observed during replacement therapy (mean 13.2 ± 1.4 ng/dl) at the time sleep studies were conducted frequently exceeded the upper limit of the normal range (10 ng/dl). Therefore, any effects testosterone may have on breathing during sleep may have been exaggerated by these high serum concentrations. However, a number of subjects with testosterone levels in the normal range demonstrated large increases in apneas and hypopneas. Therefore, the effect of the male hormone on respiration during sleep may be greater at slightly supraphysiological levels but clearly occurs in the physiological range.

We conclude that testosterone in physiological amounts may cause or act to accentuate episodes of apnea and hypopnea during sleep. This seems to occur without changes in upper airway patency or airflow resistance. Neither the site of action nor mechanism by which this effect is mediated is understood, but these observations may explain, in part, hormonal and gender influences on the incidence of respiratory disorders during sleep.

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