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The Effect of Sleep Apnea on Plasma and Urinary Catecholamines

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Summary: Numerous studies have suggested an alteration of sympathetic nervous system functioning in sleep apnea. However, most of these studies did not control for confounding factors such as diet, obesity, hypertension and anti-hypertensive medications. We examined plasma and urinary catecholamines in 43 patients, including hypertensive and normotensive individuals with and without sleep apnea. Hypertensive patients were studied at least 3 weeks following tapering of anti-hypertensive medication. All patients consumed similar diets and were of similar age and level of obesity.

Twenty-four-hour urinary norepinephrine levels were significantly higher in apneics (58.2 ng vs. 40.2 ng in nonapneics, $p < 0.002$). Urinary norepinephrine in apneics was increased during both day and night. Plasma norepinephrine levels were not significantly elevated in apneic patients but were elevated in hypertensive patients both during sleep and in the morning ($p < 0.05$). **Key Words:** Hypertension—Norepinephrine—Sleep apnea—Sympathetic nervous system.

Although originally characterized as a rare disorder, sleep apnea is increasingly recognized as a prevalent illness. Recent estimates suggest that 9% of men and 4% of women have sleep apnea (1). In older populations these numbers are higher (2), and there is a beginning literature suggesting that apnea may be even more common among blacks (3,4). Sleep apnea is frequently associated with hypertension; indeed, it is estimated that approximately 25% of patients with hypertension have undiagnosed sleep apnea (5).

There is considerable interest in defining possible mechanisms underlying sleep apnea and its links to hypertension. One of the more frequently invoked mechanisms is a hypothesized increase in sympathetic nervous system (SNS) activity. Hypoxia is known to increase SNS activity (6), and, during sleep, apneics repeatedly undergo epochs of oxygen desaturation. Other evidence suggesting SNS involvement comes from studies of plasma and urinary catecholamines. We recently reviewed the literature and found 13 studies examining plasma catecholamines and an additional 9 studies on urinary catecholamines in sleep apnea (7–27). The literature suggests that plasma and urinary norepinephrine levels are increased in apnea. Unfortunately, this conclusion rests on shaky ground. Few studies examined more than a handful of apneics. Comparisons were generally made between SNS functioning of apneics and nonapneics without considering the possibility that a comorbid diagnosis of hypertension might account for the observed relationship. Given the increased level of norepinephrine found in hypertensive patients (28) and the fact that hypertension is overrepresented among apneics (5), it is possible that the increased norepinephrine levels found among the apneics may be attributable primarily to their underlying hypertension. In addition, many of these studies examined patients while they were receiving their antihypertensive medications, despite the fact that such medications can have a powerful effect on catecholamine levels (29,30). Finally, few studies controlled for factors such as diet, age or obesity, that also have prominent effects on SNS activity (30,31).

We examined SNS activity in a group of 43 indi-

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viduals, including apneics and nonapneics, with and without hypertension. Anti-hypertensive medications were tapered 3 weeks prior to study.

METHODS

Subjects

Subjects were recruited from diverse sources: The major source of referral was from public service advertisements or word of mouth referrals from other participants. We specifically sought patients who would presumably fall into one of the following four groups: normotensive individuals with no history of apnea, normotensive individuals with a history suggestive of apnea, hypertensive individuals with no history suggestive of apnea and hypertensive individuals with a history suggestive of apnea. Individuals with histories suggestive of other sleep disorders were excluded.

After giving informed consent, all subjects were screened for hypertension and were admitted to the Clinical Research Center at the University of California San Diego (UCSD). Subjects were eligible if they were between 40 and 60 years of age and if their weight was between 0.90 and 1.6 times ideal body weight (32). Seated blood pressure (BP) was measured multiply on two occasions, separated by about 1 week. Individuals with BPs averaging <140/90 mm Hg on both occasions were considered normotensive. Individuals with BPs averaging >140/90 mm Hg but less than 180/110 mm Hg were considered hypertensives who were eligible to participate in the protocol. Anti-hypertensive medications were tapered, and the patients were admitted approximately 3 weeks after such medications were stopped.

Procedures

Patients were admitted for 2.5 days to the UCSD Clinical Research Center, where they received a standardized isocaloric diet providing 160 meq Na and 100 meq K/day. Polysomnography was performed on two successive nights. We monitored central and occipital electroencephalogram, bilateral electrooculogram, submental and tibialis electromyogram, and electrocardiogram. Respiration was assessed with nasal/oral airflow, abdominal and thoracic respiratory effort and oximetry. Sleep was scored according to standard criteria (33). The respiratory disturbance index (RDI) was quantified as the average number of hypopneas plus apneas per hour of sleep. Individuals with an average RDI (over the 2 nights) ≥20 were considered to have sleep apnea. Two successive 12-hour urine samples were collected for catecholamines and stored at −70°C until assayed. The samples were collected from 6 a.m. to 6 p.m. on the second day and from 6 p.m. until 6 a.m. the next morning. Urinary catecholamines were measured using a radioenzymatic assay (34). An indwelling intravenous line was inserted the second night, and blood was drawn during stage 2. An additional plasma sample was obtained in the morning after the subject had rested quietly. The samples were collected in ethylenediaminetetraacetic acid (EDTA)-treated tubes, placed on crushed ice, and promptly spun down in a refrigerated centrifuge. The plasma was stored at −70°C until assayed (34).

Analysis

Catecholamine levels were not normally distributed and, as a result, we used a natural log transformation on these values. To ensure that differences in age and body mass index did not confound analysis, these factors were entered as covariates. We then used a two-way repeated measures analysis of covariance (ANCOVA) to examine urinary catecholamine levels, with apnea and hypertension as grouping variables and urinary sample (first vs. second 12-hour collection) as the repeated measure. For the plasma samples, we employed a similar analysis with apnea and hypertension as grouping variables and sample time (during stage 2 sleep vs. morning awake) as the repeated measure.

RESULTS

We studied 43 individuals. Table 1 provides the patient characteristics. Because of differences in age and level of obesity, these variables were included as covariates in subsequent analyses. In certain instances samples were not collected because of technical problems or assay difficulties.

Analysis of covariance revealed that plasma epinephrine levels were not significantly influenced either by the diagnosis of hypertension ($F_{1,25} = 1.32$, $p = 0.26$) or sleep apnea ($F_{1,25} = 0.01$, $p = 0.92$). Plasma norepinephrine levels were greater in hypertensives both during stage 2 sleep and morning wakefulness ($F_{1,30} = 6.01$, $p = 0.02$). However, plasma norepinephrine levels were not significantly increased in apneics ($F_{1,30} = 0.46$, $p = 0.50$).

A different picture emerged from analyzing urinary catecholamine levels. Across both 12-hour urine collections, apneic patients had higher norepinephrine excretion ($F_{1,32} = 11.55$, $p = 0.002$). A similar observation held when the relationship between urinary norepinephrine and RDI was plotted. Figure 1 portrays this significantly positive relationship ($r = 0.39$, $p < 0.05$). Hypertensive and normotensive subjects did not have significantly different levels of urinary norepinephrine.

TABLE 1. *Subject characteristics (mean ± standard deviation)*[a]

Variable	Apneic hypertensive	Apneic normotensive	Nonapneic hypertensive	Nonapneic normotensive
n	10	15	6	12
Age (years)	50.1 ± 8.4	51.3 ± 6.2	47.5 ± 4.37	45 ± 6.02
Range	40–60	42–60	42–53	40–59
BP (mm Hg)	152.6/95.3 ± 10.4/5.5	127.1/81.4 ± 9.3/7.0	149.8/98.1 ± 9.2/3.9	121.2/77.1 ± 8.5/7.4
% Ideal body weight, range	125 ± 7 120–140	125 ± 16 91–160	129 ± 12 120–150	117 ± 15 100–140
12-Hour urinary norepinephrine (collection 1) (ng)[b]	34.4 ± 11.5	27.6 ± 13.0 (n = 11)	24.4 ± 14.9	18.9 ± 5.4 (n = 11)
12-Hour urinary norepinephrine (collection 2) (ng)	28.3 ± 7.7	26.4 ± 13.9 (n = 11)	20.3 ± 7.4	18.8 ± 7.0 (n = 11)
12-Hour urinary epinephrine (collection 1) (ng)	10.7 ± 3.8	7.8 ± 3.1 (n = 11)	10.1 ± 3.7	9.7 ± 4.0 (n = 11)
12-Hour urinary epinephrine (collection 2) (ng)	8.2 ± 1.9	7.2 ± 3.0 (n = 11)	8.4 ± 2.8	9.1 ± 3.9 (n = 11)
Stage 2: plasma norepinephrine (pg/ml)	232 ± 80 (n = 8)	191 ± 62 (n = 12)	228 ± 114 (n = 5)	167 ± 60 (n = 11)
Stage 2: plasma epinephrine (pg/ml)	7.3 ± 2.7 (n = 6)	8.3 ± 4.3 (n = 11)	7.1 ± 3.9 (n = 5)	8.6 ± 4.47 (n = 9)
a.m.: plasma[c] norepinephrine	523 ± 163 (n = 8)	397 ± 133 (n = 12)	483 ± 222 (n = 5)	362 ± 113 (n = 11)
a.m.: plasma epinephrine	48.8 ± 48 (n = 6)	60.1 ± 73 (n = 11)	32.6 ± 27.1 (n = 5)	61.2 ± 31.3 (n = 9)

[a] For statistical tests catecholamine values were natural log transformed. Some samples were not obtained or were lost and thus the sample size varies for some catecholamine variables. In such instances, the sample size is indicated in parentheses.
[b] Collection 1 spans from 6 a.m. to 6 p.m., and collection 2 spans from 6 p.m. to 6 a.m.
[c] a.m. plasma samples were drawn around 9 a.m.

There was no effect of diagnosis of hypertension or apnea on urinary epinephrine levels.

DISCUSSION

Our study has certain limitations. The sample size, although typical for studies of apnea and SNS activity, is certainly not large. It is conceivable that we lacked statistical power to perceive differences in plasma norepinephrine levels among apneics. Nonetheless, our sample size was sufficient to perceive a significant increase in plasma norepinephrine levels in the hypertensive subjects. Given the comorbidity between sleep apnea and essential hypertension, one implication of these observations is that previously reported increases in plasma norepinephrine levels in apneics may have been confounded by the association of apnea with hypertension. Similarly, other sample characteristics (e.g. weight and age) that are known to exert a powerful influence on plasma catecholamines could powerfully confound observations. We felt it would be perilous to extrapolate on the basis of a single resting plasma catecholamine value and thus examined the plasma catecholamine levels obtained during a waking resting condition and during stage 2 of sleep. It is difficult to examine catecholamine levels at other sleep stages because apneics have so little rapid eye movement (REM) sleep and deep sleep, and, of course, nonapneics have relatively little apnea. Plasma norepinephrine levels are quite pulsatile (30), and thus it is possible that apneics may have increased norepinephrine levels under different blood sampling conditions.

Another potential issue relates to our cutpoint for defining apnea. We used an RDI cutpoint of 20 to diagnose significant apnea. The cutpoint is arbitrary, but it resulted in two clearly differentiated groups. The

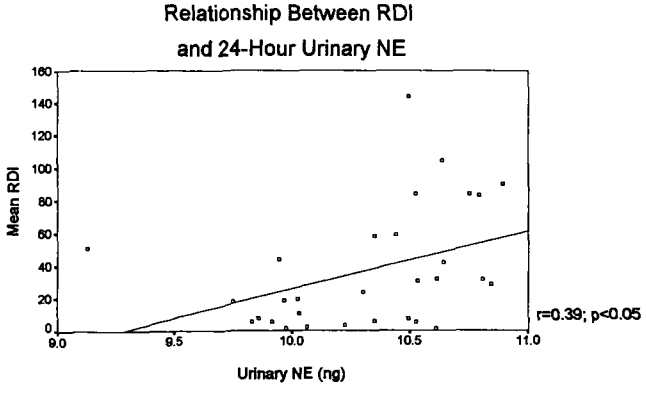

FIG. 1. Relationship between 24-hour urinary norepinephrine levels ($\log_e$) and respiratory disturbance index.

RDIs of our nonapneic subjects ranged from 1.7 to 19.5 (average 7.7). The RDIs among our apneic subjects ranged from 22.5 to 143.5 (mean = 65); thus it is clear that we studied individuals with clinically significant apnea.

Twenty-four-hour urinary norepinephrine levels were increased by approximately 45% in apneic patients. It was interesting to note that these levels were increased in both 12-hour urine collections. In retrospect, it would have been more interesting to compare the levels more precisely corresponding to "sleep" vs. "awake," i.e. 10 p.m.–6 a.m. vs. 6 a.m.–10 p.m. Nonetheless, it is evident that the increase in apneics' urinary norepinephrine is not confined only to the interval containing sleep; the collection from 6 a.m. to 6 p.m. was also increased among the apneic subjects. The mechanism for this continued increase in SNS activity continues to be elusive. Like BP, norepinephrine might be expected to be elevated during apneic events; however, why BP and norepinephrine both remain elevated in the daytime is a crucial question for the field.

In some respects we have confirmed prior observations of increased SNS activity in patients with sleep apnea. However, the design of this study adds considerably to the confidence in these observations. No confounding of age, obesity, dietary sodium, hypertension or anti-hypertensive medication could explain these findings. We did not find evidence for increased sympathoadrenomedullary activity, as would be inferred by epinephrine levels. Instead, we found increased urinary norepinephrine levels, which are markers (admittedly crude) of SNS neural transmission (30).

The SNS does not respond in an all-or-none fashion. Indeed, fine-grained studies have demonstrated clearly the dissociation between SNS nerve firing rates in different areas of the body (35). We are uncertain about the explanation for the discrepancy between plasma and urinary measures but offer two possibilities. The urinary levels, by virtue of their integration throughout 24 hours of monitoring, may be a more valid index of enduring SNS "tone" (36) than plasma levels, which are greatly influenced by the preceding few minutes prior to sampling (37). Alternatively, plasma norepinephrine levels represent a summation of all norepinephrine released throughout the body, but most prominently the vasculature and the peripheral muscle beds (38). It may well be that the SNS alterations in apnea are more notable in the kidney (as tracked by urinary norepinephrine excretion).

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