The Role of Sleep-Disordered Breathing in Essential Hypertension*

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In recent years, there have been numerous reports addressing the relationship between sleep-disordered breathing (SDB) and hypertension (HTN). This study investigated the relationship between SDB and BP after controlling for age, gross obesity, and notably, antihypertensive medications. Sixty-seven men and women between 30 and 60 years of age and between 0.90 to 1.5 times ideal body weight were studied. SDB was assessed over two nights of polysomnographic monitoring, and BP was measured over repeated visits to the hospital. The results indicate that respiratory disturbance index (RDI) independently predicts diastolic BP (DBP), accounting for 15% of the variance in DBP (p=0.02). In subjects with severe levels of SDB (RDI >30), RDI uniquely accounted for 36% of the variance in DBP (p=0.003). Interestingly, SDB was not independently related to systolic BP. The physiologic mechanisms responsible for these findings are currently being explored. (CHEST 1996; 108:890-95)

A number of reports have analyzed the association between sleep-disordered breathing (SDB) and essential hypertension (HTN). Roughly one third of hypertensive individuals have SDB, and 40 to 60% of patients with SDB have HTN. Causal links between the two disorders have been suggested, such that when SDB is successfully treated, BP decreases. The physiologic mechanisms that link these two disorders may be related to an arousal of the sympathetic nervous system secondary to nocturnal hypoxia, arousals from sleep, and changes in intrapleural pressure.

However, a cause-effect relationship between SDB and HTN has not been clearly demonstrated. After controlling for obesity and age, which are common to both disorders, some investigators concluded that excess body weight and increasing age may be confounding the relationship between SDB and HTN. However, recent studies have reported a link between SDB and HTN independent of obesity and age, even when SDB is mild and asymptomatic. Other potentially confounding variables have not received careful attention. For example, much of the research in this area has not controlled for the use of antihypertensive medications among hypertensive subjects. This is an important issue since antihypertensives may alter the severity of SDB, therefore obscuring the true relationship between the two disorders.

Even with full experimental control over possible confounding variables, the association between SDB and HTN may be influenced by severity of these conditions. For example, the question of whether SDB is independently related to HTN may be overly simplistic and dependent on the severity of SDB (ie, are only those with severe SDB at risk for HTN?). Likewise, if SDB increases BP, at what point should one consider this increase HTN? Because the clinical cut-off levels for SDB and HTN vary from study to study, it remains difficult to make firm conclusions about their relationship.

This study examined the relationship between SDB and HTN after controlling for age, gross obesity, and antihypertensive medications. We studied this association separately among those with (1) no SDB, (2) mild-moderate SDB, and (3) severe SDB.

**Materials and Methods**

Sixty-seven paid volunteers were studied as part of an ongoing study examining sympathetic activity in SDB. Subjects were referred by their physicians or recruited by word of mouth and/or

Key words: age; antihypertensives; blood pressure; body mass index; hypertension; obesity; respiratory disturbance index; sleep apnea; sleep-disordered breathing
local advertising. Many participants were concerned about suspected HTN, sleep apnea, or loud snoring because of previous diagnoses and/or bedpartner complaints. All subjects were between 30 and 60 years old. Fifty-six subjects were male; 11 were female. Height and weight were measured to compute body mass index (BMI) and ideal body weight. To eliminate the effects of gross obesity, only subjects between 0.90 and 1.5 times ideal body weight as determined by Metropolitan Life tables were studied (Metropolitan Life Foundation, 1983). All subjects were free from major medical illness, substance abuse, and sleep disorders other than SDB. Eighty-four percent reported a history of snoring. Informed consent was obtained from all subjects and procedures were approved by the committee on human subjects.

BP was measured with a BP monitor (Dinamap 1846 SX) on two different occasions, approximately 1 week apart. After subjects had rested quietly for 10 to 15 min, BP was measured once every minute for 3 min and averaged. Subjects were considered to be hypertensive if systolic BP (SBP) was greater than 140 mm Hg and/or diastolic BP (DBP) was greater than 90 mm Hg on both occasions in the absence of antihypertensive medications. Treatment with all antihypertensive medications was withdrawn slowly over a period of 1 to 2 weeks. Hypertensive subjects whose BP exceeded 180/110 mm Hg during the tapering period were returned to their medication regimen and excluded from the study. Subjects were admitted to the Clinical Research Center for two nights of sleep monitoring after HTN status was determined. Subjects previously taking antihypertensive medications were not admitted to the Clinical Research Center for at least 2 weeks after treatment with all antihypertensive medications was withdrawn.

Two successive nights of sleep were recorded by standard polysomnography, including central and occipital EEG, bilateral electro-oculogram, submental and tibialis electromyogram, ECG, nasal/oral airflow, and respiratory effort. Cutaneous pulse oximetry was recorded for measurement of arterial oxygen saturation (SaO2). Signals were recorded on a Nihon Koden Model 4412P. Sleep was scored by standard criteria. Apneas were defined as a cessation of airflow, as measured by a nasal/oral thermistor, for at least 10 s; hypopneas were defined as at least a 50% reduction in airflow for at least 10 s. Respiratory disturbance index (RDI) was calculated as the average number of apneas plus hypopneas per hour of sleep. RDI, percent time less than 90% SaO2, mean number of desaturations greater than 4%, and mean SaO2 were determined and averaged over nights. Subjects with an RDI less than 10 were considered to have no SDB. Those with an RDI between 10 and 30 and more than 30 were considered to have mild-moderate and severe SDB, respectively. These categories were determined partly by clinical experience, and partly because these cutoffs divided our total subject pool into three near equally sized groups.

Pearson correlations were performed to examine the associations among RDI, oximetry indexes, SBP, DBP, age, and BMI among all subjects, and among those with SDB (RDI ≥10). Hierarchical multiple regression analyses were performed to examine the independent effect of RDI on BP after controlling for age and BMI (age, BMI, and RDI were predictors; SBP and DBP served as outcome variables). Regressions were run among all subjects, and individually among each of our three SDB subgroups as described above.

### Results

Tables 1 through 3 summarize the characteristics of the subjects. Mean age was 47 years (SD=6.7). Mean BMI was 28.1 (SD=3.4). The mean RDI over both nights was 29.9 (SD=34.3). Night 1 and 2 RDIs were significantly correlated with each other (r=0.93; p<0.001). Twenty-eight subjects had an RDI less than 10 (mean RDI=3.9, SD=2.3). Eighteen subjects were considered to have mild-moderate SDB (mean RDI=20.1, SD=5.7); 21 had severe SDB (mean RDI=72.7, SD=29.8). Those with RDI less than 10 were younger than those with mild-moderate and severe SDB. In addition, those with RDI less than 10 had a lower BMI compared with the severe SDB group.

The overall mean SBP and DBP was 134.5 (SD=15.8) and 85.5 (SD=10.3), respectively. Twenty-seven subjects had HTN (mean SBP and DBP was 150.5 [SD=8.1] and 95.3 [SD=4.9], respectively). Among the hypertensive and normotensive subjects, mean RDIs were 38.7 (SD=42.1) and 24.2 (SD=27.3), respectively.

### Significant Correlations Among All Subjects

RDI correlated with SBP (r=0.31, p=0.01), DBP (r=0.34, p=0.005), and age (r=0.33, p=0.006). Number of desaturations greater than 4% and mean time less than 90% SaO2 correlated with DBP (r=0.29, p=0.03;
Multiple Regressions Among Subjects With RDI of 10 or More

In only those subjects considered to have SDB, significant correlations were obtained between RDI and SBP (r=0.31, p=0.05) and DBP (r=0.47, p=0.002). DBP correlated with number of desaturations greater than 4% (r=0.46, p=0.003) and mean time less than 90% SaO2 (r=0.37, p=0.02) (Table 4).

Multiple Regressions Among All Subjects

SBP: BMI, age, and RDI significantly predicted SBP, accounting for 16% of the variance in SBP (p=0.01). RDI uniquely accounted for 5% of this variance, but was not a significant predictor. BMI was the only significant independent predictor of SBP, accounting for 6% of the variance in SBP (p=0.05).

DBP: BMI, age, and RDI significantly predicted DBP, accounting for 14% of the variance in DBP (p=0.02) (Fig 1; Table 5). RDI uniquely accounted for 11% of this variance, and was the only significant individual predictor in our model (p=0.02).

Table 4—Correlates of BP

<table>
<thead>
<tr>
<th></th>
<th>Among All Subjects</th>
<th>Among Those With SDB*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SBP</td>
<td>DBP</td>
</tr>
<tr>
<td>RDI</td>
<td>r=0.31</td>
<td>r=0.34</td>
</tr>
<tr>
<td></td>
<td>(p=0.01)</td>
<td>(p=0.005)</td>
</tr>
<tr>
<td>Mean SaO2</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Time &lt;90% SaO2</td>
<td>NS</td>
<td>r=0.29</td>
</tr>
<tr>
<td></td>
<td>(p=0.04)</td>
<td>(p=0.03)</td>
</tr>
<tr>
<td>No. of desaturations</td>
<td>r=0.25</td>
<td>r=0.29</td>
</tr>
<tr>
<td></td>
<td>(p=0.05)</td>
<td>(p=0.03)</td>
</tr>
<tr>
<td>BMI</td>
<td>r=0.28</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>(p=0.02)</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

*RDI ≥10.

r=0.26, p=0.04, respectively. Number of desaturations greater than 4% correlated with SBP (r=0.25, p=0.05). BMI correlated with SBP (r=0.28, p=0.02) but not DBP.

Table 5—Regression Analyses of DBP

<table>
<thead>
<tr>
<th>Variable</th>
<th>B</th>
<th>Standard Error B</th>
<th>Beta</th>
<th>t Test</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regression analysis of DBP on BMI, age, and RDI among all subjects</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>BMI</td>
<td>0.497539</td>
<td>0.362844</td>
<td>0.164699</td>
<td>1.37</td>
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</tr>
<tr>
<td>Age</td>
<td>-0.081004</td>
<td>0.188263</td>
<td>-0.053264</td>
<td>-0.43</td>
<td>NS</td>
</tr>
<tr>
<td>RDI</td>
<td>0.094198</td>
<td>0.037910</td>
<td>0.315779</td>
<td>2.49</td>
<td>0.020</td>
</tr>
<tr>
<td>Regression analysis of DBP on BMI, age, and RDI among subjects with RDI &gt;30</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>1.250816</td>
<td>0.518741</td>
<td>0.427335</td>
<td>2.41</td>
<td>0.028</td>
</tr>
<tr>
<td>Age</td>
<td>-0.052174</td>
<td>0.234419</td>
<td>-0.039272</td>
<td>-0.22</td>
<td>NS</td>
</tr>
<tr>
<td>RDI</td>
<td>0.183048</td>
<td>0.051947</td>
<td>0.608979</td>
<td>3.52</td>
<td>0.003</td>
</tr>
</tbody>
</table>
BMI

Figure 2. The predicted BP on the basis of multiple regression analysis was compared with the observed BP. The top figure is based on BMI and age ($r^2=0.14; p=NS$). The bottom figure also included RDI ($r^2=0.50; p=0.006$).

nor were any of the individual predictors associated with SBP.

DBP: BMI, age, and RDI significantly predicted DBP among subjects with severe SDB, accounting for 50% of the variance in DBP ($p=0.02$) (Fig 2; Table 5). RDI uniquely accounted for 36% of this variance, and was the most significant predictor in our model ($p=0.003$).

Discussion

Among all of our subjects, RDI was moderately correlated with BP. Some, but not all, of the oximetry indexes were also related to BP. Moreover, RDI accounted for a significant percentage of variance in DBP, but not SBP, independent of gross obesity, age, and antihypertensive medications. In subjects with SDB only (RDI $\geq 10$), the relationship between RDI and BP was stronger, and some of the oximetry indexes correlated with DBP. In subjects with severe SDB, RDI accounted for a 36% of the variance in DBP independent of gross obesity and age. However, RDI did not independently contribute to SBP in this group of subjects.

Others have noted the independent contribution of SDB on BP after controlling for other factors. Some investigators found that SDB accounted for significantly more variance in BP as compared with the findings in this study. For example, Mendelson performed a stepwise regression in which minimum $\text{SaO}_2$ explained 92% of the variance in DBP. Similarly, Kiselak et al reported that RDI accounted for nearly 60% of the variance in mean BP. While we found a greater independent relationship of RDI on BP among subjects with severe SDB, the strength of this association did not approach that reported by others. Our subjects, however, differed from those in the above studies. Kiselak et al examined only subjects who were obese, in which the overall mean ideal body weight was 183%. Our study, in contrast, recruited only subjects between 0.90 and 1.5 times ideal body weight. Mendelson also examined subjects more obese than ours (a mean of nearly 22.5 kg heavier), and used minimum $\text{SaO}_2$, rather than RDI, as a regression predictor. Finally, because our subjects were not taking antihypertensive medications, this may have weakened the association between SDB and HTN.

Interestingly, RDI and oximetry were more strongly related to DBP than SBP among our subjects. This was most striking in the multiple regression analyses, in which RDI and SBP were not related after controlling for age and BMI. While others have also found a stronger relationship between DBP and SDB, the reason(s) for this is unclear. Mendelson only reported the relationship between minimum $\text{SaO}_2$ and DBP, but it is unclear whether minimum $\text{SaO}_2$ did not correlate with SBP or whether this relationship was not examined. Others have also only considered DBP as it relates to SDB. Some investigators reported the relationship between SDB and HTN, but this diagnosis could have been based on either an elevated SBP or DBP. Still, others have examined mean arterial pressure as it relates to SDB. Thus, as it now stands, more studies are needed before the relationship between SDB and both DBP and SBP is more clearly understood.

We found BMI to be an independent predictor of SBP, but not DBP. Some investigators have reported a relationship between BMI and BP, while others have not. In addition, we did not find age to be a significant correlate of BP in either the univariate or multivariate analyses. This is contrary to the findings of others who have performed similar studies. One explanation for these discrepancies is that we intentionally recruited subjects within a limited age range (30 to 60 years of age) and body weight (0.90 to 1.5 times ideal body weight). This was done to help restrict the effects of age and obesity on BP physiology in the subject recruitment process. By way of controlling range of age and weight via re-
stricted recruitment criteria, there may have been less variability to account for statistically.

It should be emphasized that our subjects are not representative of the population at large. Most of our subjects volunteered for the study because they suspected they had SDB, were concerned about their HTN, or were attracted to a paid research protocol. As noted above, we intentionally selected subjects who were not grossly obese (>1.5 times ideal body weight) and who were between 30 and 60 years of age. The range of BPs among our hypertensive subjects was restricted between the ranges of 140/90 and 180/110 mm Hg. In addition, our sample had a small number of females (n=11). For this reason, we were not able to include gender as a predictor in our regression model. Smoking may be another risk factor for SDB,21 but due to the limited number of smokers in our sample, we could not confidently assess its relationship to SDB.

Importantly, these results were obtained in subjects not currently taking antihypertensive medications. It is not clear how antihypertensive medications affect SDB, but they have known effects on respiration and sleep.22 For example, antihypertensive drugs may affect muscle tone in the upper airway, increasing the likelihood of SDB.12 Conversely, a recent study reported that metoprolol and cilazapril reduced apnea severity.23

Rauscher et al24 examined the relationship between SDB and HTN in subjects not receiving antihypertensive medications. No direct relationship was found, but rather HTN was linked to obesity.24 Although these results differ from those reported in the present study, there are apparent differences between the populations studied. Rauscher et al24 compared individuals with sleep apnea to snorers, not normal subjects as in the present study. Snorers have increased upper airway resistance and may be prone to HTN.25 Although many of our subjects did report snoring on a sleep questionnaire, objective snoring assessment was not performed during polysomnography.

To help clarify the relationship between SDB and HTN, it is critical that both breathing disturbances during sleep and BP are reliably measured. Some studies have relied on self-report to diagnose HTN,15 others considered history of HTN with no current assessment,13 while still others do not specify how HTN was assessed.26 However, BP is quite variable. We obtained six BP readings over two visits to the hospital before a diagnosis of HTN was made.

Differences in the assessment and definition of SDB over studies may have been partly responsible for the discrepant findings in the literature regarding BP and SDB. Some investigators have relied solely on oximetry recordings with no airflow or respiratory effort recordings to assess SDB.12,13 Although oximetry is a time- and cost-saving method of screening for SDB, it may not be a sensitive tool in the diagnosis of milder cases of SDB, resulting in false-negatives.27,28 In addition, there is significant night-to-night variability in SDB.29,30 This study assessed SDB with a nasal/oral thermistor and respiratory effort bands over two consecutive nights.

In conclusion, we found RDI to be an independent, although modest, predictor of DBP after controlling for age and gross obesity among a group of nonmedicated hypertensive and normotensive subjects. Among subjects with an RDI of 30 or greater, the independent relationship between RDI and DBP was even stronger. The physiologic mechanisms responsible for this relationship are not well understood, but may relate to sympathetic arousal. This possibility is currently being explored.31,32

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