Altered Cardiac Contractility in Sleep Apnea

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Summary: Adrenergic regulation in sleep apnea is a complex process because adrenergic physiology is difficult to summarize with one measure. Furthermore, the role of the adrenergic system in sleep apnea is often confounded with hypertension, making interpretation difficult in hypertensive apneics. Sixty-six people with and without apnea and/or hypertension (all were off antihypertensive medication) participated in this study. Cardiac β-adrenergic drive, as assessed by systolic time intervals, was examined at rest and in response to a mild laboratory stressor. These measures of cardiac contractility included the pre-ejection period, electrical systole (QT) interval and the cardiac acceleration index. At rest, apneics showed elevated myocardial contractility on all measures (p = 0.001). In response to the laboratory stressor, non-apneics showed an increase in cardiac β-adrenergic drive (p = 0.001), whereas the contractility in apneics did not change or decreased relative to baseline. These findings suggest disrupted cardiac adrenergic regulation in people with sleep apnea. Apnea appears to increase resting sympathetic activity and down regulate β1-adrenergic receptors. The downregulation of cardiac β-adrenergic receptor activity may explain the inability of people with sleep apnea to respond with appropriate cardiac contractility to a mild perturbation.

Key Words: Systolic time intervals—Sleep Apnea—Hypertension—Reactivity—Stress.

The role of the sympathetic nervous system in people with obstructive sleep apnea episodes has been assessed by diverse methods. Patients with sleep apnea frequently show increased sympathetic nerve firing, an elevation in plasma norepinephrine and diminished β-adrenergic receptor sensitivity (1–7). The relationship of this augmented sympathetic tone, however, has not been studied in terms of end-organ responses such as cardiac function. In this study we assessed the relationship of sleep apnea and hypertension with the responsiveness of the cardiac systolic time intervals to a mild laboratory stressor.

Cardiac β-adrenergic drive alters the relationship between electrical and mechanical systole by accelerating both the rate and force of myocardial contractility (8,9). Systolic time intervals are a group of noninvasive measures that reflect cardiac β-adrenergic stimulation or contractility. These measures include the cardiac pre-ejection period (PEP), left ventricular ejection time (LVET), electrical systole (QT) and the cardiac acceleration index (CAI). These measurements are derived from the electrocardiogram (ECG), phonocardiogram (PCG) and/or impedance cardiogram (ICG). PEP and QT interval are two indices of cardiovascular function that may reflect sympathetic drive on the myocardium. These measurements are derived from the ECG, PCG and/or ICG recordings. The PEP interval begins with the onset of electrical systole at the ECG Q-wave and end at the onset of left ventricular ejection. The PCG measures the first heart sound (S1), which begins prior to ejection and aortic opening. S1 is a poor measure of the onset of left ventricular ejection, but the B-waves of the PCG occurs near the time of aortic opening and has been used to signify the end of PEP and the onset of ventricular ejection (10). PIP is an important period in assessing contractility because its length relates to the velocity of isovolumic myocardial contraction (10). Indeed, PEP correlates highly with left ventricular ejection fraction and the rate of ventricular pressure change (11). When there is an increase in β-adrenergic drive, the PEP interval decreases. Thus, PEP is inversely related to β-adrenergic drive on the myocardium. Values for PEP range from 80 to 150 milliseconds in healthy individuals at rest.

QT is inversely related to heart rate (HR) and requires correction for HR (13). Increased β-adrenergic drive shortens the QT interval (13,14). Thus, the QT interval is negatively related to sympathetic myocardial tone. Normal resting values range from 300 to 500 milliseconds.
PEP and QT interval are two indices of sympathetic cardiovascular drive. A third useful measure of cardiac adrenergic drive is the cardiac acceleration index (ACI), which reflects the acceleration of the rapid ventricular ejection phase following the aortic opening (14). It reflects cardiac contractility during the period maximum velocity of left ventricular ejection. Resting values for this ratio range from 20 to 100.

Both CAI and PEP are independent of HR (15). Because the QT interval is affected by HR, QT adjusted for HR, or QT₅₀, is traditionally used for reporting this measure. These measures also provide clues as to when increases in the HR are likely to be related to sympathetic nervous system activity rather than vagal withdrawal. They also provide an estimate of the inotropic forces elicited by adrenergic activation. Many studies have examined the effect of various behavioral challenges on the noninvasive indices of cardiovascular performance used in this study that in turn provide estimates of myocardial sympathetic drive (16–18).

METHODS

Subjects

Sixty-six subjects were recruited through advertisement and referral from sleep-disorders clinics. Subjects were studied after obtaining written informed consent. Forty-one subjects were normotensive, and 25 were classified as mildly hypertensive [blood pressure (BP) >140 mm Hg systolic or >90 mm Hg diastolic]. Three of the hypertensive subjects had been on antihypertensive therapy at the time of recruitment (one on a β blocker, one on a diuretic and one on a calcium channel blocker), were tapered off antihypertensive medication and were free of medication for at least 2 weeks prior to the study. Given the effects of weight on sympathetic physiology, only subjects whose weight was between 0.9 and 1.6 times ideal body weight were studied. The protocol was approved by the University of California–San Diego (UCSD) Institutional Review Board. All subjects were studied at the UCSD Clinical Research Center.

Procedures

Subjects were admitted to the Clinical Research Center (CRC) of the UCSD Medical Center and placed on an isocaloric diet providing 200 mmol Na⁺ and 100 mmol K⁺ per day. Sleep polysomnography was performed on both nights the subject was in the CRC. Sleep polysomnography included central and occipital electroencephalogram (EEG), bilateral electrooculogram (EOG), submental and tibialis electromyogram (EMG) and ECG. Respiration was assessed with nasal/oral air-flow, abdominal and thoracic respiratory effort and oximetry. Sleep was scored according to standard criteria (19). The respiratory disturbance index (RDI) was quantified as the average number of hypopneas plus apneas per hour of sleep; individuals with an RDI ≥20 were classified as apneic.

Cardiovascular reactivity testing, as a way to perturb the heart and sympathetic nervous system, was performed the morning of the second hospital day. Subjects were brought to the testing laboratory at 0830 hours. After arrival in the laboratory, instrumentation was applied. Impedance cardiography electrodes were applied in a standard fashion (18).

After instrumentation, the subjects sat quietly for 30 minutes to allow for habituation to the instrumentation and testing environment. A 3-minute baseline was determined at the end of the habituation period. Following the baseline period, the subjects were given instructions for a speaking task. This task involved preparing and presenting a speech in response to being falsely accused of shoplifting. Instructions were given that the performance would be videotaped and rated by experts on poise and articulation. The video camera was displayed prominently during the procedure. Subjects were given 3 minutes to prepare their speech and told that the speech should cover certain points. Immediately following the preparation period, subjects talked for 3 minutes. If subjects stopped speaking before the end of the period, they were reminded to continue the talk by reiterating or summarizing the main points.

Apparatus

Impedance cardiography (Minnesota Impedance Cardiograph no. 304B) signals were relayed to an analog/digital converter (Data Translations no. DT2801), sampling at 1 kHz per channel, and stored in a computer. The calibration signals were also stored in a computer for later conversion of the dZ/dt to ohm/second.

The hemodynamic data were collected in 30-second epochs, at 1-minute intervals during baseline and each phase of the speech task. These samples were ensemble averaged by a computer program that summed the digitized beat-by-beat (R-R) waveforms, time-synchronized to the R-wave of the ECG and divided by the number of cardiac cycles. The ensemble average was then graphically displayed, and the waveform events were scored by computer signal processing techniques (University of Miami Behavioral Medicine Research Center).
TABLE 1. Subject characteristics and baseline measurements

<table>
<thead>
<tr>
<th></th>
<th>Non-apneic normotensive (n = 23)</th>
<th>Non-apneic hypertensive (n = 11)</th>
<th>Apneic normotensive (n = 18)</th>
<th>Apneic hypertensive (n = 14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>Mean 44.9 ± 5.2</td>
<td>Mean 47.2 ± 4.2</td>
<td>Mean 51.0 ± 6.0</td>
<td>Mean 50.3 ± 7.9</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>26.6 ± 3.3</td>
<td>28.9 ± 3.6</td>
<td>29.2 ± 2.5</td>
<td>32.0 ± 14.9</td>
</tr>
<tr>
<td>Respiratory disorder index</td>
<td>7.1 ± 1.1</td>
<td>6.2 ± 1.8</td>
<td>43.9 ± 6.2</td>
<td>77.3 ± 9.3</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>120.0 ± 11.7</td>
<td>149.3 ± 10.7</td>
<td>129.0 ± 14.0</td>
<td>151.4 ± 10.8</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>77.0 ± 8.6</td>
<td>96.7 ± 7.5</td>
<td>82.7 ± 9.5</td>
<td>93.0 ± 6.5</td>
</tr>
<tr>
<td>Heart rate (BPM)</td>
<td>67.0 ± 10.7</td>
<td>65.7 ± 10.7</td>
<td>74.3 ± 12.8</td>
<td>75.8 ± 9.2</td>
</tr>
<tr>
<td>Pre-ejection period (milliseconds)</td>
<td>117.9 ± 15.2</td>
<td>109.5 ± 28.0</td>
<td>94.56 ± 22.6</td>
<td>92.79 ± 17.33</td>
</tr>
<tr>
<td>QT interval (milliseconds)</td>
<td>385.4 ± 8.0</td>
<td>402.2 ± 50.4</td>
<td>383.7 ± 33.6</td>
<td>357.9 ± 35.7</td>
</tr>
<tr>
<td>Cardiac acceleration index (β/second²)</td>
<td>8.0 ± 3.6</td>
<td>10.8 ± 8.4</td>
<td>11.3 ± 6.2</td>
<td>12.3 ± 6.4</td>
</tr>
</tbody>
</table>

a Apneics were significantly older, p = 0.004.
b Hypertensives were significantly higher, p = 0.0001.
c Apneics were significantly higher, p = 0.0001.
d Apneics were significantly higher, p = 0.0004.
e Apneics were significantly lower, p = 0.0003.
f Apneics were significantly higher, p = 0.0041.

Data analysis

Subject characteristics and raw baseline data were assessed with a 2 [apnea (non-apneic, apneic)] × 2 [blood pressure level (normotensive, hypertensive)] analysis of variance. A 2 [apnea (non-apneic, apneic)] × 2 [blood pressure level (normotensive, hypertensive)] × 3 [task (baseline, preparation, talk)] mixed model analysis of variance, with task as the repeated measures variable, was performed on HR, PEP, QT, and CAl to determine reactivity (because of the difference in age, it was used as a covariate in these analyses). QT was calculated by dividing the QT interval by the square root of the R-R interval (in seconds). Geisser–Greenhouse corrections for repeated measure analyses are reflected in the reported significance levels. Post hoc assessments of differences in the repeated measures were determined with Bonferroni-corrected paired t tests. All data analyses were performed using BMDP statistical software.

RESULTS

The apneic subjects were significantly older and, as expected, had significantly higher RDI scores than the non-apneic subjects. The hypertensive subjects had significantly higher screening blood pressure than the normotensive subjects. The diastolic blood pressure of the normotensive apneics was significantly higher than that of the normotensive non-apneics (Table 1)

Heart rate (HR)

There was a significant apnea × blood pressure level × task interaction [F(2,124) = 3.99, p = 0.027] for HR; this is summarized in Fig. 1. The analyses of simple effects for HR follow.

Apnea effects

At each task level, apneics had a significantly higher HR than non-apneics [F(1,64) = 10.87, p = 0.002; F(1,64) = 11.4, p = 0.001; F(1,64) = 8.81, p = 0.004 at baseline, preparation, and talk, respectively].

Blood pressure level effects

There were no significant differences in HR during baseline, preparation or speaking as a function of blood pressure level.
Task

HR increased significantly from baseline to speech preparation to speaking in all four groups \[F(2,44) = 21.23, p = 0.001\] for normal subjects; \[F(2,20) = 34.62, p = 0.001\] for hypertension; \[F(2,34) = 7.52, p = 0.002\] for apnea; \[F(2,24) = 34.65, p = 0.001\] for hypertension plus apnea].

Summary

HR increased as a result of the stressor in all groups. Its levels were not significantly different between normotensive and hypertensive subjects. Apneic patients had significantly higher heart rates than non-apneic subjects.

QT\textsubscript{c} interval (shorter duration of this measure indicates increased \(\beta\)-adrenergic activity)

There was a significant main effect of task \[F(2,122) = 11.68, p = 0.001\] for QT\textsubscript{c} interval that is reflected in Fig. 2. Tukey post hoc analysis showed that QT\textsubscript{c} decreased significantly from baseline to preparation and from preparation to talking.

Pre-ejection period (PEP) (smaller values of this measure indicate increased \(\beta\)-adrenergic activity)

There was a significant apnea \(\times\) blood pressure level \(\times\) task interaction \[F(2,124) = 4.27, p = 0.016\]; this relationship is summarized in Fig. 3.

Apnea effects

PEP was significantly shorter in apneics than non-apneics at baseline \[F(1,64) = 18.52, p = 0.001\], prep-
ALTERED CARDIAC CONTRACTILITY

FIG. 4. Cardiac acceleration index (CAI) (mean ± SEM) during
baseline, speech preparation and speech talk periods. CAI is directly
related to cardiac β-adrenergic activity. Normal = non-apneic nor­
motensive subjects; Apnea = apneic normotensive subjects; Hyperten­
sion = non-apneic hypertensive subjects; Apnea + Hypertension =
apneic hypertensive subjects.

There was a significant apnea × blood pressure × task interaction for CAI [F(2,124) = 3.47, p = 0.034].

Apnea effects

Apneic subjects had significantly higher CAI at baseline
[F(1,64) = 11.53, p = 0.001] and during preparation
[F(1,64) = 8.34, p = 0.005]. CAI was significantly
lower in the apneics while talking [F(1,64) = 4.91, p
= 0.03] compared to non-apneics.

Blood pressure level effects

There were no significant hypertensive–normotensive
differences observed in CAI at any of the task levels.

Task effects

CAI increased significantly in the normal subjects
[F(2,44) = 5.83, p = 0.0093] and in the hypertensive
patients to the stressor [F(2,20) = 4.51, p = 0.024].
In the apnea patients and hypertension plus apnea pa­
tients, CAI decreased significantly [F(2,34) = 7.31, p
= 0.0023; F(2,26) = 4.13, p = 0.028, respectively].

Summary

Apneic subjects (with or without hypertension) had
larger CAIs than non-apneic subjects. CAI was not sig­nificantly different between normotensive and hy­pertensive subjects. Normal and hypertension-only
subjects showed a significant increase in CAI to the
stressor, whereas CAI values of hypertension plus ap­nea patients decreased during stress. In apnea-only pa­tients, no significant change in CAI was observed.

DISCUSSION

End-organ responses are some of the more inter­pretable measures relating function to morbidity. In
understanding the cardiovascular system, the basic
measures of HR and BP provide clinical information.
These measures, however, represent different func­tions. BP is the product of cardiac output and vascular
resistance. Changes in HR represent the effects of both
sides of the autonomic nervous system. By focusing
on systolic time interval measures we examined the
sympathetic, inotropic forces on the myocardium.

HR and QT interval are easily obtained and widely
used measures. QT interval is affected by a number of
factors, such as preload and afterload (10–13). Group
differences were not detected in QT; probably because
of these effects. PEP is also affected by afterload (10–
13), but it is a more sensitive measure. As such it was
able to detect differences in between apneics and non­apneics as well as inotropic responses to the stressor
in normotensive individuals. It could be argued that
the increased contractility observed at rest in the ap­neics was the result of decreased afterload in these
patients. This argument does not hold up on two ac­counts: 1) no differences were observed between hy­pertensive and normotensive subjects, and 2) CAI,
which is free from the effects of preload and afterload
(14), also revealed increased contractility in the apneic
patients.

At rest, patients with sleep apnea have been shown
to have increased sympathetic nerve firing and in some
studies increased catecholamine levels (1,2,4–7).
These studies, however, have failed to control for the
blood pressure status of the apneic subjects and have
used more obese individuals than were used in our
study. In addition, previous studies of adrenergic phys­iology in apnea examined subjects at rest and not in
response to behavioral provocation. Apneic subjects in
this study do indeed show heightened cardiac β-adren­ergic activity at rest; however, their response to a be­havioral challenge was decidedly unusual.

Repeated nocturnal airway obstruction may result in
generalized neurohumoral activation. The mechanisms
linking obstruction to neurohumoral activation could
include: 1) decreased input from inhibitory barorecep­tor afferent vessels, and 2) increased input from ex­citatory afferent vessels arising from arterial chemore­ceptors in the skeletal muscle metaboreceptors or the
lungs (20–22). We hypothesize that the repeated sym­pathetic stimulation is directly impinging on the heart
(viz. the increased contractility at rest). There appears,
however, to be an additional consequence of this ad­
ergic stimulation; the heart is unable to respond to behavioral challenge with the appropriate increases in contractility (23–27).

This action may be explained by our observation of downregulated β-adrenergic receptors (4). The increased sympathetic activity occurring with the apneic episodes resulted in decreased receptor number and sensitivity. Therefore we observe that individuals with sleep apnea are not able to respond to a mild perturbation with increased cardiac β-adrenergic responses, as reflected in PEP and CAI measures of cardiac contractility. HR did increase, but this may reflect vagal withdrawal rather than increased cardiac sympathetic tone. A study with a larger sample size and the addition of measures that assess vagal tone would clarify some of these questions. This assessment performed before and after treatment for apnea would provide an interesting replication of these findings.

Although many investigators have examined adrenergic function in apnea, we know of no prior work concerning cardiac sympathetic tone in such patients. We observed an association between sleep apnea and altered cardiac β-adrenergic drive at rest and during a behavioral challenge. Apneic subjects had higher resting HR values and cardiac contractility than non-apneic subjects. Whereas HR continued to increase in the apneic subjects during a laboratory stressor, contractility decreased. In this study we found complex interactions between apnea and hypertension. These interactions between apnea and hypertension affected virtually all of these measures of cardiac sympathetic tone. This study suggests that a better understanding of the comorbidity of sleep apnea and hypertension will result from studying the factors associated with cardiac-specific as well as generalized activation of the sympathetic nervous system. Thus, we feel it is crucial for future studies to note the BP status of their apneic patients.

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