LITERATURE REVIEW

Association of Sleep-Disordered Breathing, Sleep Apnea, and Hypertension in a Large Community-Based Study

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Key words: Sleep apnea, hypopnea, hypertension, sleep-disordered breathing, body mass index, United States, obesity, adult.

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Sleep-disordered breathing (SDB) is a condition of repeated episodes of apnea and hypopnea during sleep with an apnea-hypopnea score of 5 or higher. SDB and sleep apnea have both been associated with hypertension in various studies over the last 2 decades. Most of these studies have been criticized for not eliminating several confounding variables, particularly obesity, age, and sex.

SDB and sleep apnea are uncommon in the young or those who are thin in stature. This has led many to postulate that SDB and sleep apnea are simply markers for increased age, obesity, or both. Or, alternatively stated, the presence of hypertension may be secondary to the coexisting risk factors (increased age, obesity, or both) and not due to SDB.

The study of Nieto et al is the largest population study of sleep apnea to date. It is one of many reports originating from data acquired by the Sleep Heart Health Study (SHHS; more information about the SHHS is available on the Internet at http://www.jhsphs.edu/shhs). The SHHS is a multicenter population study with oversight by the National Heart, Lung, and Blood Institute. It is a longitudinal epidemiological investigation that uses population studies to determine whether sleep-related breathing disorders are associated with an increased risk of coronary heart disease, stroke, all-cause mortality, and hypertension.

This study’s stated objective was to “assess the association between SDB and hypertension in a large cohort.” Entrants were aged 40 years or more, had no history of treatment...
of sleep apnea by use of continuous positive airway pressure, had not had a tracheostomy, and were not currently using oxygen at home. By use of the SHHS, 11,053 individuals were screened and 6132 subjects were entered into the study. Entrants had a baseline examination that included a sleep evaluation and history, history of medications, including antihypertensive agents, blood pressure measurement, and an unattended polysomnogram (PSG). The PSG setup was comprehensive and included oximetry, central electroencephalogram, single-lead electrocardiogram, chest excursion, and other measures.

Apnea was defined as a complete or almost complete cessation of airflow. Hypopnea was defined as a decrease in airflow or thoracoabdominal excursion of at least 30% of baseline for 10 seconds or more, accompanied by a 4% or more decrease in oxygen saturation. Other indices of SDB included arousal index (average number of arousals per hour of sleep), percentage of sleep time with oxygen saturation below 90%, and snoring history (self-report of snoring 3 nights a week).

The PSG was used to collect the main outcome measures: apnea-hypopnea index (AHI; the average number of apneas and hypopneas per hour of sleep), arousal index, and percentage of sleep with <90% oxygen saturation. Arbitrary cutoffs for the AHI were set at <1.5 (the reference), 1.5–4.9, 5–14.9, 15–29.9, and ≥30 events per hour. Other indexes included a history of snoring, presence of hypertension (defined as a resting blood pressure of at least 140/90) or the use of antihypertensive medication, smoking history, usual alcohol intake, waist and hip circumference, and body-mass index (BMI).

The authors gave an excellent review of the inherent problems in a cross-sectional study such as this one. Most importantly, they review the reasons that preclude this study and others like it from demonstrating cause and effect; they can only demonstrate association. Other studies, specifically treatment studies, have provided evidence that successful treatment of sleep apnea (eg, continuous positive airway pressure and not weight loss) results in decreased daytime and nighttime blood pressure.

This study supports a linear association of SDB with hypertension. When those individuals on antihypertensive medications were excluded, AHI had a linear association with blood pressure even when BMI was factored in. In the Table (extracted from table 4 in Nieto et al), the odds ratio clearly increases in a linear fashion to as high as 2.27 (95% confidence interval, 1.76–2.92) for an AHI of ≥30 even after age, sex, and obesity were factored in. When BMI, waist-to-hip ratio, alcohol use, and smoking are factored in, the effect persists, with an odds ratio of 1.37 (95% confidence interval, 1.03–1.83).

Other indexes were examined for any association with hypertension. Arousal index per hour was not significant when BMI was factored in (Note that the confidence intervals include the value 1.0.) The percentage of sleep time <90% oxygen saturation was significant only for amounts >12% when adjusted for BMI, waist-to-hip ratio, alcohol use, and smoking.

Alcohol intake and smoking were not found to have any association with SDB in this cohort. And it is of interest that whereas AHI was strongly associated with a self-reported history of snoring, arousal index, and sleep time below 90% saturation, self-reported snoring had little or no association with hypertension.

Controlling for BMI decreased the association of SDB and hypertension (and further supports the association of BMI with SDB). Neck circumference and waist-to-hip ratio added nothing, nullifying criticisms of earlier studies that did not factor in body-fat distribution.
Analysis of Hypertension by Sleep-Disordered Breathing Measures

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of Subjects</th>
<th>Adjusted for Demographics,*</th>
<th>OR (95% CI)</th>
<th>OR Adjusted for Demographics†</th>
<th>OR (95% CI)</th>
<th>OR (95% CI)</th>
<th>OR (95% CI)</th>
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<tbody>
<tr>
<td>Apnea-hypopnea index per hour</td>
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<tr>
<td>&lt;1.5</td>
<td>1691</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
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<tr>
<td>1.5–4.9</td>
<td>1598</td>
<td>1.25 (1.08–1.44)</td>
<td>1.12 (0.96–1.30)</td>
<td>1.11 (0.95–1.29)</td>
<td>1.07 (0.91–1.26)</td>
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<td>5–14.9</td>
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<td>1.28 (1.09–1.48)</td>
<td>1.24 (1.06–1.45)</td>
<td>1.20 (1.01–1.42)</td>
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<td>15–29.9</td>
<td>719</td>
<td>1.73 (1.43–2.10)</td>
<td>1.32 (1.08–1.61)</td>
<td>1.26 (1.03–1.55)</td>
<td>1.25 (1.00–1.56)</td>
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<td>≥30</td>
<td>373</td>
<td>2.27 (1.76–2.92)</td>
<td>1.60 (1.23–2.08)</td>
<td>1.47 (1.12–1.92)</td>
<td>1.37 (1.03–1.83)</td>
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<td>Arousal index per hour</td>
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<td>Percentage of sleep time with &lt;90% of oxygen saturation</td>
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<td>1.25 (1.08–1.46)</td>
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<td>≥12</td>
<td>493</td>
<td>2.03 (1.62–2.53)</td>
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<td>Snoring</td>
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<td>2058</td>
<td>1.21 (1.07–1.38)</td>
<td>1.05 (0.92–1.20)</td>
<td>1.02 (0.89–1.16)</td>
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<td>1.24 (1.08–1.42)</td>
<td>1.25 (1.08–1.43)</td>
<td>1.26 (1.08–1.46)</td>
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* BMI indicates body-mass index; CI, confidence interval; and OR, odds ratio.
† Adjusted for age, sex, and ethnicity.
LITERATURE REVIEW

Heart-Rate Recovery After Submaximal Exercise Testing as a Predictor of Mortality in a Cardiovascularly Healthy Cohort

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Key words: Exercise testing, heart-rate recovery, mortality.

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Many insurers for high-dollar life insurance policies have used exercise testing as a requirement. Some medical directors have been concerned about the specificity and sensitivity of exercise testing done on asymptomatic individuals when these tests are not combined with either thallium or stress echocardiography. This article, by a Cleveland Clinic group of cardiologists, investigates heart-rate recovery after submaximal exercise testing as a predictor of long-term mortality. The group previously looked at heart-rate recovery after a symptom limited exercise treadmill in an intermediate risk group referred for thallium exercise testing. (The initial article was reviewed in this journal recently.1,2) In the first study, a strong relationship was found between a lack of heart-rate recovery and long-term mortality. The current study expanded on the premise and looked at heart-rate recovery after submaximal exercise testing in a population-based cohort of healthy adults with no evidence of coronary artery disease.

METHODS

The study cohort of 5234 adults (mean age, 43 years ±10, 41% women) meeting the inclusion criteria was derived from the Lipid Research Clinics Prevalence Study. The study tried to assure a selection of cardiovascularly healthy asymptomatic adults. Detailed social, family, and medical histories were obtained, as was a lipid profile. The Bruce or Modified Bruce protocols were used. Participants exercised until 85%–90% of age and fitness predicted maximal heart rate for 1 minute was obtained; until they were fatigued; or until medical contraindications to continued exer-
cise were observed. Heart-rate recovery was defined as a change from peak heart rate to that measured after 2 minutes’ recovery. An abnormal value was determined to be ≤42 beats per minute. Mean follow-up time was 12 years. The primary end point was all-cause mortality; follow-up was 100%.

RESULTS

Heart-rate recovery was related to all-cause mortality by using univariable and multivariable Cox regression analysis. During the 12 years of follow-up, 325 people died (6.2%). Abnormal heart-rate recovery was strongly predictive of death; relative risk was 2.58 (95% confidence interval, 2.06–3.20; \( P < .001 \)). Of those who died, 116 (36%) were thought to have died of cardiovascular causes. Abnormal heart-rate recovery was even more predictive of death from cardiovascular cause than death in general; relative risk was 3.06 (95% confidence interval, 2.0–4.44; \( P < .001 \)). An abnormal heart-rate recovery was predictive of death in all subgroups divided by age, sex, chronotropic response to exercise, regular exercise habits, smoking, resting hemodynamics, and cholesterol level. The only subgroup where it was not predictive was in those patients who used vasodilators.

DISCUSSION

In this population-based cohort of healthy adults adjusted for multiple potential confounding factors, an abnormal heart-rate recovery after submaximal exercise was a powerful predictor of all-cause mortality. The authors of this study noted, “Furthermore, because an abnormal heart rate recovery accounted for 15% of deaths, this measure may be useful for insurance underwriting assessments.”

This study suggests there is an additional and easily obtained mortality predictor in a test commonly used for risk assessment. An abnormal heart-rate recovery may also provide information we can use in our attempt to separate the patients who truly test positive on the treadmill test from false-positive results in asymptomatic people seeking insurance.

REFERENCES


LITERATURE REVIEW

The Effects of Physical Activity on Mortality in the Jerusalem 70-Year-Olds Longitudinal Study

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Key Words: Physical activity, mortality.

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There has recently been a significant amount of literature attempting to address the effect of physical activity on longevity. There is ample evidence to suggest that in middle-age men even low-intensity physical activity reduces mortality. The authors reviewed 1014 studies that addressed this question and found that only 9 of the studies considered the implications of the elderly population. This study was designed to include a homogenous age population (70-year-olds) in a single locale, Jerusalem.

The study enrolled Jerusalem residents who were born in 1920–21. They contacted 40% of all of the eligible persons. Of the 759 people sampled, 20% refused to participate. The 605 enrollees were interviewed and seen in a geriatric clinic setting. The study population was felt to be representative of the Jerusalem population as previously published in the European Journal of Epidemiology.

PHYSICAL ACTIVITY

Participants were asked to describe their own physical activity and were placed into 4 categories (Table 1). Group A comprised those who were considered sedentary with less than 4 hours of walking per week. Group B consisted of those who walked approximately 4 hours per week. Group C comprised those who were involved in a sporting activity (jogging, cycling, and others) at least twice a week. Group D comprised those who were considered to have at least 1 hour of walking a day.

RESULTS

The end point of the study was death as measured by a review of death certificates (Table 2). The incidence of death was measured at 1, 3, and 6 years. Crude mortality
Table 1. Baseline Physical Activity by Gender

<table>
<thead>
<tr>
<th></th>
<th>Male (%)</th>
<th>Female (%)</th>
</tr>
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<tbody>
<tr>
<td>Group A (&lt;4 hrs/wk)</td>
<td>44</td>
<td>51</td>
</tr>
<tr>
<td>Group B (4 hrs/wk)</td>
<td>20</td>
<td>15</td>
</tr>
<tr>
<td>Group C (sports part.)</td>
<td>16</td>
<td>20</td>
</tr>
<tr>
<td>Group D (&gt;1 hr/day)</td>
<td>20</td>
<td>14</td>
</tr>
</tbody>
</table>

Table 2. Six-Year Mortality Rates Versus Physical Activity

<table>
<thead>
<tr>
<th></th>
<th>All (%)</th>
<th>Male (%)</th>
<th>Female (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A (&lt;4 h/wk)</td>
<td>23</td>
<td>30</td>
<td>16</td>
</tr>
<tr>
<td>Group B (4 h/wk)</td>
<td>13</td>
<td>18</td>
<td>6</td>
</tr>
<tr>
<td>Group C (sports part.)</td>
<td>12</td>
<td>15</td>
<td>10</td>
</tr>
<tr>
<td>Group D (&gt;1 h/d)</td>
<td>4</td>
<td>4</td>
<td>3</td>
</tr>
</tbody>
</table>

Mortality rates at 6 years decreased considerably with increased physical activity.

Confounding variables included in the logistic regression analyses included malignancies, diabetes mellitus, hypertension, coronary artery disease, cerebrovascular disease, respiratory disease, renal disease, anemia, body mass index, and smoking.

The authors concluded that “after adjustment for these variables, daily exercise remains the most protective form of exercise.” Sport activities were found to have no statistically significant effect on mortality.

Mortality-odds ratios were calculated using Group A as the standard (1.00). For males, Group B experienced an odds ratio of 0.41. This decreased to 0.14 in Group D. For females in Group B, an odds ratio of 0.28 fell to 0.17 in Group D.

Data for Group C is inconstant, likely because of the nondescript inclusion of sports participation. It is difficult to delineate whether the self-description of sport participation has had any quantitative value in aerobic activity. Be that as it may, increased physical activity in a 70-year-old cohort does decrease mortality. The authors repeatedly state the following: “accounting for the effects of preexisting major illness and cardiovascular risk factors” on the mortality implications of physical activity. They did not include the raw data in this review of their study, so it is difficult to accept the conclusions. For example, in the Group A men, 22% were diabetics compared with only 14% in Group D men. Furthermore, 46% suffered from hypertension compared with only 20% in Group D. Ischemic heart disease was noted in 36% of the Group A men compared with 24% of the Group D men. These differences obviously would have profound implications on the survival of an elderly population. The regression analyses of these variables was simply stated as “after adjustment,” and it was not well delineated.

The study also did not include any data on length of this physical activity (i.e., whether it began a month or 10 years ago).

This study was an attempt to understand the mortality implications of physical activity on a homogenous elderly population. One should be hesitant, however, to develop mortality ratios based on these groupings without a thorough review of the confounding variables.
LITERATURE REVIEW

Effects of Physiologic Pacing Versus Ventricular Pacing on the Risk of Stroke and Death Due to Cardiovascular Causes

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Key words: Pacing, physiologic pacing, ventricular pacing, stroke, mortality.

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As the science and technology of cardiac pacing has improved and advanced in the past number of years, it has been assumed (and shown in a few small studies) that atrioventricular (AV) sequential pacing offers a substantial improvement over the more simple ventricular pacemaker. It was thought that duplicating the natural AV sequence would lead to less secondary complications such as stroke and cardiovascular mortality. However, a large study to confirm or deny this hypothesis had never been carried out.

In this study from Canada, a total of 2568 patients undergoing pacemaker implantation were randomized to receive either a ventricular or AV sequential pacemaker. This group was then followed for 3 years in order to study the annual rate of stroke or death from cardiovascular causes. In addition, the patients were monitored for death from any cause, development of atrial fibrillation, or hospitalization for heart failure.

RESULTS

The statistics failed to show a significant difference in the annual rates of stroke or death from cardiovascular causes between the ventricular-paced group (5.5%) and the physiologically-paced group (4.9%).

Atrial fibrillation was significantly lower in the AV-paced group, but this only became apparent 2 years after implantation. There was also a very small decrease in overall death rate for the AV-paced group and fewer hospitalizations for heart failure, although the differences were not statistically different. It
is noteworthy that the AV-paced group did have a significantly higher rate of perioperative complications (9.0% vs. 3.8%), reflective of the complexity of this newer technology.

CONCLUSIONS

The findings of this large randomized study suggest that despite the intuitive notion that duplicating the body’s natural AV sequence during pacing is beneficial, the results do not show a statistically significant improvement in preventing stroke or death from cardiovascular causes over simple ventricular pacing. There is a slight improvement in the incidence of atrial fibrillation in the AV-paced group 2 years following implantation. It is also noted that, because of the complexity of AV pacing, the perioperative complications are significantly higher.