# Left Ventricular Morphology and Systolic Function in Sleep-Disordered Breathing

## The Sleep Heart Health Study

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***Background***—Whether sleep-disordered breathing (SDB) is a risk factor for left ventricular (LV) hypertrophy and dysfunction is controversial. We assessed the relation of SDB to LV morphology and systolic function in a community-based sample of middle-aged and older adults.

***Methods and Results***—The present study was a cross-sectional observational study of 2058 Sleep Heart Health Study participants (mean age 65±12 years; 58% women; 44% ethnic minorities) who had technically adequate echocardiograms. A polysomnographically derived apnea-hypopnea index (AHI) and hypoxemia index (percent of sleep time with oxyhemoglobin saturation <90%) were used to quantify SDB severity. LV mass index was significantly associated with both AHI and hypoxemia index after adjustment for age, sex, ethnicity, study site, body mass index, current and prior smoking, alcohol consumption, systolic blood pressure, antihypertensive medication use, diabetes mellitus, and prevalent myocardial infarction. Adjusted LV mass index was 41.3 (SD 9.90) g/m$^{2.7}$ in participants with AHI <5 (n=957) and 44.1 (SD 9.90) g/m$^{2.7}$ in participants with AHI ≥30 (n=84) events per hour. Compared with participants with AHI <5, those with AHI ≥30 had an adjusted odds ratio of 1.78 (95% confidence interval 1.14 to 2.79) for LV hypertrophy. A higher AHI and higher hypoxemia index were also associated with larger LV diastolic dimension and lower LV ejection fraction, with a trend toward lower LV fractional shortening. LV wall thickness was significantly associated with the hypoxemia index but not with AHI. Left atrial diameter was not associated with either SDB measure.

***Conclusions***—In a community-based cohort, SDB is associated with echocardiographic evidence of increased LV mass and reduced LV systolic function. **(*Circulation*. 2008;117:2599-2607.)**

**Key Words:** sleep ■ hypertrophy ■ epidemiology ■ ventricular function, left

Left ventricular hypertrophy (LVH) is an important risk factor for cardiovascular morbidity and mortality.[1] Sleep-disordered breathing (SDB) has been associated with cardiovascular disease in several studies[2,3] and appears to be an independent cause of hypertension.[4–6] SDB is characterized by recurrent episodes of apnea and hypopnea during sleep. The most common form of SDB is obstructive, although in most epidemiology studies, no attempt is made to distinguish central from obstructive forms of SDB. Whereas left ventricular (LV) dysfunction is a known cause of central SDB, it has been postulated that obstructive SDB might be an independent risk factor for LVH and LV dysfunction. Potential mechanisms underlying such an association include recurrent episodes of hypoxemia and arousal from sleep after obstructive respiratory events, both of which cause an increase in sympathetic activity and blood pressure[7] that results in increased LV afterload. Increased sympathetic activity is sustained throughout the day in patients with obstructive SDB and improves after treatment.[8] Furthermore, the forceful inspiratory efforts generated in the face of an obstructed airway result in large negative swings in intrathoracic pressure, which consequently increases transmyocardial pressure (LV afterload).[9–11]

### Clinical Perspective p 2607

In a dog model, 3 months of exposure to severe obstructive SDB resulted in increased LV volume, decreased LV ejection

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fraction (LVEF), and a 10% increase in LV mass (LVM) that was of borderline statistical significance.[11] Whether SDB is an independent risk factor for LVH and LV dysfunction in humans remains controversial. A clinic-based study of 533 subjects found that those with obstructive SDB had greater height-adjusted LVM than those without, but this difference was not significant after adjustment for age, obesity, and hypertension.[12] Several other case-control studies or case series found an association of obstructive SDB with LVH,[13–17] although others did not.[18–20] Continuous positive airway pressure therapy for 6 months resulted in significant regression of LVH as measured by interventricular septal thickness but not LV posterior wall thickness in 1 study,[13] whereas decreased interventricular septal thickness was observed along with improved LV function in another study.[17]

In the present study, we test the primary hypothesis that SDB is associated with increased LVM index as measured by echocardiography in the large, community-based sample of adults participating in the Sleep Heart Health Study (SHHS). We also sought to evaluate the association between SDB and other measures of cardiac morphology and LV function.

## Methods

### Study Sample

Of the total of 6441 SHHS participants, 2850 were drawn from parent cohorts in which echocardiography was performed as part of the parent cohort protocol (1248 from the Cardiovascular Health Study, 1000 from the Framingham Heart Study, and 602 from the Strong Heart Study). An additional 201 subjects initially recruited from those 3 parent cohorts were excluded from the SHHS because of inadequate polysomnography. The study was approved by the institutional review boards at the respective sites, and subjects gave informed consent. The parent cohorts and the SHHS cohort are described elsewhere.[21–24] Briefly, the SHHS is a multicenter study of individuals 40 years or older recruited from participants in several ongoing cohort studies in the United States. Of the 2850 potential subjects, 792 were excluded for missing or technically inadequate echocardiograms (n=714) or missing covariate data (n=78) for age, body mass index (BMI), systolic blood pressure (SBP), antihypertensive therapy, or history of myocardial infarction (MI), which left 2058 subjects for the present investigation.

### Polysomnography

SHHS participants underwent in-home polysomnography between 1995 and 1998 with the Compumedics P-series portable monitor (Abbotsford, Victoria, Australia). The following channels were used: electroencephalogram, electrooculogram, single bipolar ECG, chin electromyogram, pulse oximetry (Nonin Medical, Plymouth, Minn), chest and abdominal excursion, airflow (by thermocouple), and body position. The polysomnography recordings were analyzed and scored centrally at the SHHS reading center (Cleveland, Ohio) with the scoring guidelines and quality assurance and control methods described elsewhere.[25,26] The apnea-hypopnea index (AHI) was defined as the number of episodes of apnea plus hypopnea per hour of sleep. Apnea was defined as a decrease in airflow amplitude to <25% of baseline that lasted for at least 10 seconds. Hypopnea was defined as a decrease in airflow or chest wall movement amplitude to <70% of baseline that lasted for at least 10 seconds. For the present analysis, AHI was obtained with the use of apneas and hypopneas associated with at least 4% oxyhemoglobin desaturation. The intraclass correlation of AHI was 0.75 between unattended home and attended laboratory settings[27] and 0.80 for night-to-night variability in the unattended home setting.[28] The interscorer reliability for scoring AHI in the SHHS was also excellent, with an intraclass correlation of 0.99.[29] Hypoxemia index was defined as the percent of sleep time at oxyhemoglobin saturation <90%.

### Echocardiography

Echocardiography was performed by each parent cohort by use of previously described measurement techniques.[30–32] M-mode measurements were performed according to American Society of Echocardiography recommendations.[33] LVM index was calculated by the necropsy-validated formula described by Devereux and associates[34]:

$$\text{LVM index} = \{0.8 \times [1.04 \times (\text{LVIDd} + \text{IVST} + \text{LVPWT})^3 - (\text{LVIDd})^3] + 0.6\} / \text{height}^{2.7},$$

where LVIDd is LV internal diastolic diameter, IVST is interventricular septal thickness, and LVPWT is LV posterior wall thickness, measured in centimeters. Using previously published thresholds, we defined LVH as an LVM index >49.2 g/m$^{2.7}$ for men and >46.7 g/m$^{2.7}$ for women.[35] Subjects with LVH were further classified as having concentric hypertrophy if relative wall thickness [(LVPWT+IVST)/LVIDd)] was >0.41 or eccentric hypertrophy if it was ≤0.41.[36] The reproducibility of echocardiographic measures has been reported previously and was acceptable.[37–39]

### Covariates

During the SHHS home visit, in advance of the polysomnogram, a study technician collected health history and medication use data using a standardized questionnaire, including history of doctor-diagnosed MI and heart failure, and measured blood pressure and weight using a standardized protocol.[22] Covariates obtained from the parent cohorts included race, height, history of diabetes mellitus, and usual alcohol intake.

### Statistical Analysis

The dependent variable for the primary analysis was LVM index. Dependent variables for secondary analyses included measures of both cardiac morphology and LV systolic function. The morphological measures were LV wall thickness (the mean of interventricular septal thickness plus LV posterior wall thickness), LVIDd, and left atrial diameter (measured at LV end systole). The functional measures were LV fractional shortening, quantitative LVEF (available only for subjects from the Strong Heart Study parent cohort), and categorical LVEF. All dependent variables were continuous except for the categorical variable LVEF, which was categorized with a threshold of 55% as recommended by the American Society of Echocardiography.[40] All statistical analyses were performed with SAS, version 9.1 (SAS Institute Inc, Cary, NC). Relations between echocardiographic and SDB measures, adjusted for covariates, were evaluated with linear regression for continuous measures (Proc GLM) and logistic regression for categorical measures (Proc Logistic for overall LVH and categorical LVEF; Proc CATMOD for LVH categorized as absent, eccentric, or concentric).

Primary exposure variables were the AHI and the hypoxemia index. Secondary exposure variables were the arousal index and habitual snoring. AHI was categorized with the common clinical thresholds of 5, 15, and 30 events per hour of sleep. The hypoxemia index was subdivided into 4 categories by partitions of 0.4%, 4%, and 12% of sleep time, to approximate the frequency distribution of subjects in the AHI categories. Arousal index was categorized by thresholds of 20, 30, and 40 arousals per hour of sleep. Habitual snoring was defined as self-reported snoring 3 or more times per week.

Four models are presented, with adjustment for the demographic variables of age, sex, race, and parent cohort alone (model 1); further adjustment for BMI, an important cause of both SDB and LVH (model 2); further adjustment for hypertension (SBP and antihypertensive therapy) and history of MI, important correlates of LVH that may be caused in part by SDB (model 3); and further adjustment for self-reported history of diabetes mellitus, current smoking, and usual

**Table 1. Characteristics of the Study Sample**

| | AHI | | | |
|---|---|---|---|---|
| | <5 (n=1122) | 5–14.9 (n=596) | 15–29.9 (n=228) | ≥30 (n=112) |
| Age, y (SD) | 64.1 (12.3) | 66.5 (11.7) | 67.6 (11.6) | 67.5 (11.6) |
| Sex, % women | 66.6 | 52.9 | 44.7 | 34.8 |
| Race, % | | | | |
| White | 57.7 | 55.0 | 50.4 | 54.5 |
| Native American | 21.0 | 28.5 | 33.3 | 35.7 |
| Black | 11.0 | 9.4 | 11.4 | 8.0 |
| Hispanic | 7.4 | 5.9 | 4.4 | 0.9 |
| Asian/Pacific Islander/other | 2.9 | 1.2 | 0.4 | 0.9 |
| Parent cohort, % | | | | |
| CHS | 36.4 | 40.9 | 41.2 | 43.8 |
| FHS | 42.7 | 30.7 | 25.4 | 20.5 |
| SHS | 20.9 | 28.4 | 33.3 | 35.7 |
| BMI, kg/m$^2$ (SD) | 27.3 (4.5) | 29.7 (5.6) | 30.58 (6.1) | 32.3 (6.6) |
| Height, cm (SD) | 164.2 (8.9) | 165.3 (9.4) | 166.2 (8.8) | 167.3 (9.4) |
| SBP, mm Hg (SD) | 129.3 (18.6) | 133.6 (18.8) | 133.2 (19.4) | 134.0 (17.1) |
| Antihypertensive therapy, % | 34.9 | 45.3 | 47.4 | 60.7 |
| History of diabetes, % | 12.8 | 18.9 | 25.8 | 30.6 |
| Current smoking, % | 14.7 | 11.9 | 11.0 | 7.1 |
| Former smoking, % | 37.4 | 45.5 | 41.0 | 53.6 |
| Usual alcohol consumption, drinks/wk, median (IQR) | 0 (0–2) | 0 (0–3) | 0 (0–4) | 0 (0–2) |
| History of MI, % | 6.6 | 11.4 | 15.4 | 13.4 |
| History of CHF, % | 1.8 | 3.3 | 4.0 | 6.4 |

CHS indicates Cardiovascular Health Study; FHS, Framingham Heart Study; SHS, Strong Heart Study; and IQR, interquartile range.



alcohol consumption, factors possibly associated with both SDB and LVH for which data were available in a subset of 1689 subjects (model 4).

History of congestive heart failure (CHF) was not included in the main analytic models to avoid adjustment for a possible effect (CHF) of the exposure of interest. Further analyses that added CHF or height to models 3 and 4 were performed to assess their impact on the observed associations. Additional analyses were performed that excluded subjects with a history of MI or CHF, with stratification by sex, and with the inclusion of a sex-by-SDB interaction term in regression models.

The authors had full access to the data and take full responsibility for its integrity. All authors have read and agree to the manuscript as written.

## Results

Characteristics of the study sample stratified by AHI severity are shown in Table 1. Increasing AHI was associated with male sex, higher mean BMI and SBP, and higher prevalence of treated hypertension, diabetes mellitus, and cardiovascular disease.

### Primary Analysis: LVM Index

In analyses adjusted for age, sex, race, and parent cohort, mean LVM index was progressively higher with increasing AHI or hypoxemia index (Figure 1, model 1). The magnitude of these associations was diminished but remained statistically significant when BMI was added to the model (model 2). Little further diminution in the associations was seen with adjustment for additional covariates (models 3 and 4). The addition of history of CHF to models 3 and 4 did not meaningfully alter the findings (results not shown). Increasing severity of SDB was similarly associated with increased adjusted odds of categorical LVH. Compared with those with AHI <5, those with AHI ≥30 had an adjusted OR of 1.78 (95% confidence interval 1.14 to 2.79) for LVH (Table 2).

Hypoxemia index was highly correlated with AHI, with a Spearman rank correlation of $r=0.72$ for the continuous measures and a contingency coefficient of 0.58 for categorical severity classification by these 2 measures of SDB. Fewer than half of those in the highest AHI category were also in the highest hypoxemia index category, however. In all models, the association of SDB with LVM index appeared somewhat stronger for hypoxemia index than for AHI (Figure 1). When we considered alternative measures of SDB, subjects who reported habitual snoring had a higher LVM index than those who did not in models adjusted for age, sex, race, and parent cohort; however, there was no meaningful difference after adjustment for BMI (42.0 versus 41.7 g/m$^{2.7}$) or other covariates. There was no significant association between the arousal index and LVM index in any model (results not shown).

### Secondary Analyses: LVM Index

The association between AHI (or hypoxemia index) and LVM index persisted in analyses that excluded subjects with

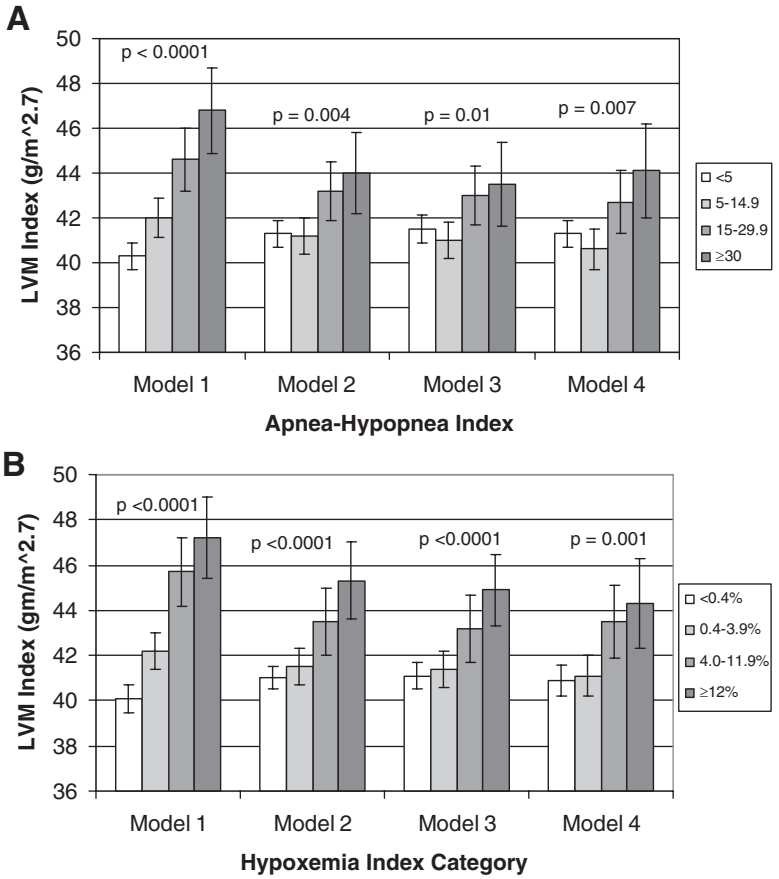


**Figure 1.** Association of LVM index with (A) AHI and (B) hypoxemia index. Model 1 included adjustment for age, sex, race, and parent cohort; model 2, further adjustment for BMI; model 3, further adjustment for SBP, antihypertensive medication use, and history of MI; and model 4, further adjustment for diabetes, current and former smoking, and usual alcohol consumption.

prevalent cardiovascular disease (CHF or MI; Table 3). When analyses were stratified by sex, the association of AHI with LVM index was not significant in women, although the association of hypoxemia index with LVM index persisted in both sexes (Table 3). Inclusion of an SDB-by-sex interaction term in the general linear models indicated that interactions with sex were not statistically significant for either SDB measure, however, whether they were treated as categorical or continuous variables. We did not observe significant effect modification with use of antihypertensive medication in general or $\beta$-blockers in particular (results not shown).

To assess whether the observed association of SDB with LVM index might be driven by LVH-associated central SDB, the main analyses were repeated with the exclusion of 96 subjects with a central apnea index greater than the obstructive apnea index or with a central apnea index >5 per hour (regardless of obstructive apnea index) and an additional 573 subjects for whom either central or obstructive apnea indices were not reported separately from the overall AHI. Compared with the main analysis, the association with LVM index in these models was slightly stronger for the hypoxemia index and was not meaningfully altered for the AHI. Similarly, the associations of other outcomes with SDB measures were not meaningfully altered by exclusion of these subjects (results not shown).

## Secondary Analyses: Morphology and Function

Because inclusion of smoking status, alcohol use, and history of diabetes mellitus did not meaningfully alter the analyses but led to the exclusion of 369 subjects owing to missing data,

**Table 2. Adjusted* OR (95% CI) for LVH and Decreased LVEF by SDB Category**

| | AHI | | | | | Hypoxemia Index | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | <5 | 5–14.9 | 15–29.9 | ≥30 | P† | <0.4% | 0.4–4.0% | 4–11.9% | ≥12% | P† |
| LVEF <55% | 1 (Referent) | 0.86 (0.57–1.30) | 1.51 (0.93–2.44) | 1.61 (0.86–3.00) | 0.074 | 1 (Referent) | 0.96 (0.65–1.42) | 1.00 (0.55–1.82) | 1.49 (0.85–2.62) | 0.50 |
| LVH | 1 (Referent) | 0.99 (0.76–1.28) | 1.18 (0.83–1.66) | 1.78 (1.14–2.79) | 0.060 | 1 (Referent) | 1.00 (0.77–1.29) | 1.35 (0.93–1.96) | 2.03 (1.35–3.05) | 0.003 |
| Eccentric LVH | 1 (Referent) | 0.81 (0.60–1.11) | 1.10 (0.73–1.64) | 1.84 (1.12–3.03) | 0.04 | 1 (Referent) | 0.93 (0.70–1.27) | 1.13 (0.72–1.76) | 2.25 (1.44–3.52) | |
| Concentric LVH | 1 (Referent) | 1.33 (0.92–1.92) | 1.30 (0.78–2.18) | 1.59 (0.80–3.15) | | 1 (Referent) | 1.09 (0.75–1.59) | 1.81 (1.08–3.02) | 1.50 (0.79–2.84) | 0.003 |

*Adjusted for age, sex, race, parent cohort, BMI, SBP, antihypertensive medication use, and history of MI.
†Overall significance level of the effect of SDB on LV geometry or function by likelihood ratio test.

**Table 3. Adjusted Mean LVM Index (95% CI) by SDB Category, Excluding Subjects With CHF or History of MI* and Stratified by Sex†**

| | LVM Index, g/m$^{2.7}$ | | | | | |
|---|---|---|---|---|---|---|
| | Excluding CHF and MI | | Men | | Women | |
| | n | Mean (CI) | n | Mean (CI) | n | Mean (CI) |
| AHI | | | | | | |
| <5 | 1040 | 41.0‡ (40.4–41.6) | 375 | 42.4‡§ (41.4–43.5) | 747 | 40.8‡ (40.1–41.5) |
| 5–14.9 | 515 | 40.4‡ (39.6–41.2) | 281 | 41.1‡ (39.9–42.3) | 315 | 41.1‡ (40.0–42.1) |
| 15–29.9 | 188 | 42.5§ (41.1–43.8) | 126 | 44.3§‖ (42.5–46.1) | 102 | 41.8‡ (40.0–43.7) |
| ≥30 | 92 | 43.3§ (41.4–45.3) | 73 | 45.4‖ (43.1–47.8) | 39 | 41.5‡ (38.5–44.5) |
| Total | 1835 | $P$=0.008 | 855 | $P$=0.002 | 1203 | $P$=0.79 |
| Hypoxemia index | | | | | | |
| <0.4% | 1086 | 40.5‡ (40.0–41.1) | 426 | 41.9‡ (40.9–42.9) | 751 | 40.6‡§ (39.9–41.3) |
| 0.4–3.9% | 491 | 40.7‡ (39.9–41.5) | 266 | 42.2‡ (41.0–43.4) | 297 | 40.7‡§ (39.6–41.8) |
| 4.0–11.9% | 147 | 43.5§ (42.0–45.1) | 79 | 42.7‡ (40.4–45.0) | 98 | 43.6‖ (41.7–45.5) |
| ≥12% | 107 | 45.1§ (43.4–46.9) | 82 | 46.6§ (44.4–48.8) | 55 | 43.0§‖ (40.4–45.5) |
| Total | 1831 | $P$<0.0001 | 853 | $P$=0.002 | 1201 | $P$=0.02 |

*Adjusted for age, sex, race, parent cohort, BMI, SBP, and antihypertensive medication use. Nine subjects with missing data for history of CHF are excluded from this analysis.

†Adjusted for age, race, parent cohort, BMI, SBP, antihypertensive medication use, and history of MI.

‡,§,‖Groups that do not differ significantly from one another.

further analyses are presented with adjustment for age, sex, race, site, BMI, hypertension, and history of MI. When concentric and eccentric LVH were considered separately, the prevalence of eccentric LVH increased across all categories of AHI, whereas the prevalence of concentric hypertrophy was similar across higher AHI categories (Figure 2). Although the magnitude of these associations was diminished with covariate adjustment, the overall association of SDB with eccentric and concentric hypertrophy remained significant (Table 2). Mean LVIDd differed significantly across categories of AHI and hypoxemia index (Table 4). Mean LV wall thickness was slightly higher in subjects with a higher hypoxemia index but was not significantly associated with AHI (Table 4). These associations were not meaningfully affected by further adjustment for history of CHF or for height. There was no significant association between either measure of SDB and left atrial diameter (Table 4).

Although decreased LVEF was more prevalent in higher AHI categories (Figure 2), the adjusted ORs of decreased LVEF in the higher SDB quartiles were not significantly different from the referent category for either SDB measure (Table 2). Quantitative LVEF as a continuous measure was available in the subset of participants from the Strong Heart Study and was significantly associated with both AHI and hypoxemia index (Table 4). In the total sample, a trend toward lower LV fractional shortening with increasing AHI and hypoxemia index did not reach statistical significance (Table 4).

## Discussion

In the present study of a large, community-based sample of middle-aged and older adults, SDB as measured by AHI or hypoxemia index was associated with a significantly higher LVM index after adjustment for age, sex, race, parent cohort, BMI, hypertension, history of MI, diabetes mellitus, current or former smoking, and usual alcohol consumption. The adjusted LVM index was ≈7% greater and the adjusted

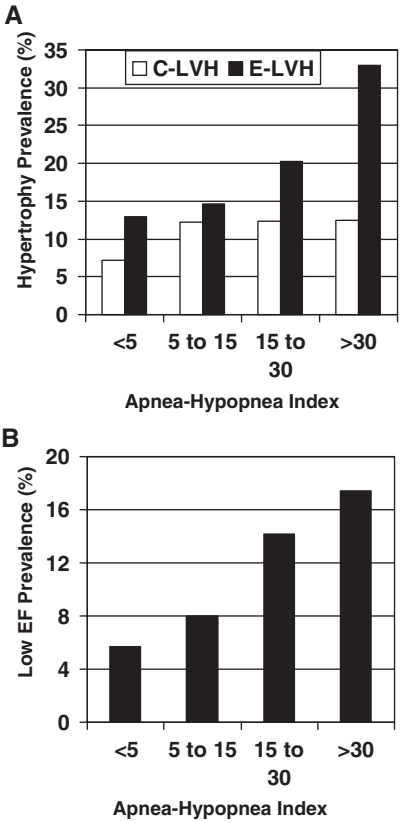


**Figure 2.** Association of AHI with (A) concentric (C-LVH) and eccentric (E-LVH) LVH and (B) LVEF <55%. EF indicates ejection fraction.

**Table 4. Adjusted Mean Echocardiographic Measures (95% Confidence Interval) by SDB Category**

| | LV Fractional Shortening, %† | Quantitative LVEF, %* | Mean LV Wall Thickness, cm† | LVIDd, cm† | LA Diameter, cm† |
|---|---|---|---|---|---|
| AHI | | | | | |
| <5 | 38.3 (37.9–38.7) | 62.5 (61.4–63.7) | 0.92 (0.91–0.93) | 4.83 (4.80–4.86) | 3.88 (3.85–3.91) |
| 5–14.9 | 38.3 (37.8–38.9) | 62.9 (61.5–64.3) | 0.93 (0.92–0.94) | 4.76 (4.73–4.80) | 3.90 (3.86–3.94) |
| 15–29.9 | 37.6 (36.7–38.5) | 59.7 (57.7–61.6) | 0.93 (0.92–0.95) | 4.85 (4.79–4.92) | 3.95 (3.88–4.01) |
| ≥30 | 37.5 (36.2–38.8) | 61.2 (58.4–64.0) | 0.93 (0.90–0.95) | 4.91 (4.82–5.0) | 3.90 (3.80–3.99) |
| n | 2003 | 560 | 2058 | 2058 | 2027 |
| *P* | 0.37 | 0.04 | 0.44 | 0.002 | 0.38 |
| Hypoxemia index | | | | | |
| <0.4% | 38.4 (38.0–38.8) | 62.1 (61.0–63.2) | 0.92 (0.91–0.93) | 4.81 (4.78–4.84) | 3.89 (3.86–3.92) |
| 0.4–3.9% | 38.2 (37.6–38.8) | 62.8 (61.4–64.1) | 0.93 (0.92–0.94) | 4.78 (4.74–4.82) | 3.90 (3.86–3.95) |
| 4.0–11.9% | 38.1 (37.1–39.1) | 62.8 (60.6–65.1) | 0.94 (0.93–0.96) | 4.89 (4.82–4.96) | 3.91 (3.83–3.98) |
| ≥12% | 36.8 (35.7–38.0) | 58.9 (56.3–61.4) | 0.94 (0.92–0.96) | 4.98 (4.90–5.06) | 3.92 (3.83–4.01) |
| n | 1999 | 559 | 2054 | 2054 | 2023 |
| *P* | 0.12 | 0.05 | 0.04 | <0.0001 | 0.85 |

*Adjusted for age, sex, BMI, SBP, antihypertensive medication use, and history of MI.

†Adjusted for age, sex, race, parent cohort, BMI, SBP, antihypertensive medication use, and history of MI.

relative odds of LVH 78% higher in subjects with AHI ≥30 than in those with AHI <5. Although an increase in LVM index was seen across all categories of SDB in minimally adjusted models, in more fully adjusted models, this association was only seen at AHI ≥15 or hypoxemia index ≥4% of sleep time. Increasing SDB severity was also associated with larger LVIDd and lower LVEF.

Although in the main analysis, we do not discriminate between central and obstructive SDB, few subjects in the present cohort had predominantly central SDB. The exclusion of those subjects did not meaningfully alter the associations with LV morphology and function; we therefore concluded that obstructive SDB was driving the observed associations. The number of subjects with central SDB was too small to meaningfully evaluate its association with LV morphology and function in the present cohort.

Previous clinic-based studies of the relation of SDB to LV morphology and function have generally found an association between SDB and increased LVM or wall thickness, although the association was often not significant after adjustment for obesity and other relevant covariates.[12,18,20] The present study confirms that although obesity does explain some of the association of SDB with LVM index and LV function, a significant association persists after adjustment for BMI in a large, community-based cohort not selected on the basis of either suspected LV dysfunction or presence of SDB. This association was not diminished by the exclusion of subjects with a history of CHF or MI. Although this history was by self-report, which makes misclassification of the history of CHF or MI possible, the lack of any diminution in the effect estimate indicates that the observed association of SDB with LVM index was not driven by those conditions.

A prior study of subjects with cardiomyopathy found that those who had SDB had greater LV wall thickness than those without, whereas the LVIDd was not different.[41] Another study excluding subjects with diagnosed cardiomyopathy also found an unadjusted association of SDB with concentric hypertrophy.[14] In contrast to these studies, the present study found SDB to be associated with eccentric LVH, characterized by higher LVIDd with little difference in LV wall thickness. This is consistent with a prior study of adolescents and children with SDB in which most subjects with LVH had eccentric hypertrophy.[15] Eccentric LVH occurs primarily in response to volume overload and may reflect mild LV dilatation as a compensation for decreased LVEF. It is also observed in mild to moderate uncomplicated hypertension, associated with mildly increased cardiac output.[42,43] In the present sample, prevalence of both decreased LVEF and treated hypertension increased across SDB categories, and this may have contributed to the observed association with eccentric hypertrophy. Previous studies have shown that airway occlusion during sleep is associated with a reduced LVEF and increased LV end-systolic volume in a canine model of obstructive sleep apnea.[9,44] The mechanism by which recurrent acute increases in LV volume might lead to eccentric remodeling remains to be elucidated.

Eccentric hypertrophy has been observed in patients with anemia, decreased renal function, or increased cardiac output demand due to higher fat-free body mass. Severe anemia and renal failure are expected to be rare in a general community sample and are therefore unlikely to account for the observed association of SDB measures to LVIDd. Although there was a trend toward increasing mean height with increasing AHI category, which suggests a higher fat-free body mass, this reflected the higher proportion of men in the higher AHI categories; adjustment for height did not alter the observed association.

The present study provides only weak evidence for an association between SDB and decreased LVEF. Although SDB was associated with lower quantitative LVEF in subjects recruited from the Strong Heart Study, for which this measure was available, SDB was not a significant predictor of categorically low LVEF or LV fractional shortening, measurements of which were available for all 3 parent cohorts.

In general, the hypoxemia index was more strongly associated with measures of LV morphology than was AHI, consistent with a recently published correlative study.[45] Although observational studies have a limited ability to explore pathophysiological mechanisms, this finding may reflect a primary role for hypoxemia in the mechanisms by which SDB influences LV morphology. This may be mediated by alterations in expression of myosin heavy chain isoforms, as animal studies suggest.[46]

Prior studies of cardiac morphology and function in SDB have generally included few[13,15] or no[16,18] women. In the present study, more than half of the subjects were women. In sex-stratified analyses, the evidence for an association of SDB with LVM index appeared stronger in men than in women, although an independent association with the hypoxemia index was observed in women. Fewer women than men have moderate-to-severe SDB, which results in lower power to detect significant associations of SDB with LV morphology, and a formal test of interaction between SDB measures and sex was not significant. The low power of such tests of interaction does not exclude an effect modification by sex, however, and this finding suggests that caution should be taken in generalizing from the results of studies that include men only.

The present study has several limitations. It is cross-sectional in design. Although LVH and LV systolic dysfunction are not known to contribute to the pathogenesis of pure obstructive SDB, LV systolic dysfunction is known to result in central SDB, which may trigger obstructive events in individuals with a predisposing anatomy.[47] It is unlikely, however, that this explains the present findings, because analyses that excluded subjects with evidence of central SDB did not alter the results. Although echocardiographic measures were standardized for each parent cohort,[29–31] systematic differences in measurements may have occurred between parent cohorts; we therefore adjusted for parent cohort in the present analysis. Balancing these limitations are several strengths, including the large, ethnically and geographically diverse sample drawn from well-defined community-based cohorts with detailed, prospective ascertainment of covariates and rigorously standardized echocardiographic and polysomnographic measures that were obtained according to strict protocols and with the use of explicit quality control measures.

In conclusion, we found that SDB at a severity commonly encountered in the general population is associated with increased LVM index, an increased prevalence of LVH, and modestly reduced global LV systolic function. This association has important clinical implications, because LVH is a known predictor of subsequent cardiovascular morbidity and mortality.[1] The association of SDB with a pattern of eccentric, rather than concentric, hypertrophy requires further investigation to define the mechanism and its clinical implications.



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## Disclosures

None.

## References

1. Levy D, Garrison RJ, Savage DD, Kannel WB, Castelli WP. Prognostic implications of echocardiographically determined left ventricular mass in the Framingham Heart Study. *N Engl J Med*. 1990;322:1561–1566.
2. Shahar E, Whitney CW, Redline S, Lee ET, Newman AB, Javier Nieto F, O'Connor GT, Boland LL, Schwartz JE, Samet JM. Sleep-disordered breathing and cardiovascular disease: cross-sectional results of the Sleep Heart Health Study. *Am J Respir Crit Care Med*. 2001;163:19–25.
3. Peker Y, Hedner J, Norum J, Kraiczi H, Carlson J. Increased incidence of cardiovascular disease in middle-aged men with obstructive sleep apnea: a 7-year follow-up. *Am J Respir Crit Care Med*. 2002;166:159–165.
4. Nieto FJ, Young TB, Lind BK, Shahar E, Samet JM, Redline S, D'Agostino RB, Newman AB, Lebowitz MD, Pickering TG. Association of sleep-disordered breathing, sleep apnea, and hypertension in a large community-based study: Sleep Heart Health Study. *JAMA*. 2000;283:1829–1836.
5. Peppard PE, Young T, Palta M, Skatrud J. Prospective study of the association between sleep-disordered breathing and hypertension. *N Engl J Med*. 2000;342:1378–1384.
6. Brooks D, Horner RL, Kozar LF, Render-Teixeira CL, Phillipson EA. Obstructive sleep apnea as a cause of systemic hypertension: evidence from a canine model. *J Clin Invest*. 1997;99:106–109.
7. Somers VK, Dyken ME, Clary MP, Abboud FM. Sympathetic neural mechanisms in obstructive sleep apnea. *J Clin Invest*. 1995;96:1897–1904.
8. Fletcher EC, Miller J, Schaaf JW, Fletcher JG. Urinary catecholamines before and after tracheostomy in patients with obstructive sleep apnea and hypertension. *Sleep*. 1987;10:35–44.
9. Tkacova R, Rankin F, Fitzgerald FS, Floras JS, Bradley TD. Effects of continuous positive airway pressure on obstructive sleep apnea and left ventricular afterload in patients with heart failure. *Circulation*. 1998;98:2269–2275.

10. Hall MJ, Ando S, Floras JS, Bradley TD. Magnitude and time course of hemodynamic responses to Mueller maneuvers in patients with congestive heart failure. *J Appl Physiol*. 1998;85:1476–1484.
11. Parker JD, Brooks D, Kozar LF, Render-Teixeira CL, Horner RL, Douglas Bradley T, Phillipson EA. Acute and chronic effects of airway obstruction on canine left ventricular performance. *Am J Respir Crit Care Med*. 1999;160:1888–1896.
12. Niroumand M, Kuperstein R, Sasson Z, Hanly PJ. Impact of obstructive sleep apnea on left ventricular mass and diastolic function. *Am J Respir Crit Care Med*. 2001;163:1632–1636.
13. Cloward TV, Walker JM, Farney RJ, Anderson JL. Left ventricular hypertrophy is a common echocardiographic abnormality in severe obstructive sleep apnea and reverses with nasal continuous positive airway pressure. *Chest*. 2003;124:594–601.
14. Noda A, Okada T, Yasuma F, Nakashima N, Yokota M. Cardiac hypertrophy in obstructive sleep apnea syndrome. *Chest*. 1995;107:1538–1544.
15. Amin RS, Kimball TR, Bean JA, Jeffries JL, Willging JP, Cotton RT, Witt SA, Glascock BJ, Daniels SR. Left ventricular hypertrophy and abnormal ventricular geometry in children and adolescents with obstructive sleep apnea. *Am J Respir Crit Care Med*. 2002;165:1395–1399.
16. Hedner J, Ejnell H, Caidahl K. Left ventricular hypertrophy independent of hypertension in patients with obstructive sleep apnoea. *J Hypertens*. 1990;8:941–946.
17. Shivalkar B, Van de Heyning C, Kerremans M, Rinkevich D, Verbraecken J, De Backer W, Vrints C. Obstructive sleep apnea syndrome: more insights on structural and functional cardiac alterations, and the effects of treatment with continuous positive airway pressure. *J Am Coll Cardiol*. 2006;47:1433–1439.
18. Davies RJ, Crosby J, Prothero A, Stradling JR. Ambulatory blood pressure and left ventricular hypertrophy in subjects with untreated obstructive sleep apnoea and snoring, compared with matched control subjects, and their response to treatment. *Clin Sci (Lond)*. 1994;86:417–424.
19. Alchanatis M, Paradellis G, Pini H, Tourkohoriti G, Jordanoglou J. Left ventricular function in patients with obstructive sleep apnoea syndrome before and after treatment with nasal continuous positive airway pressure. *Respiration*. 2000;67:367–371.
20. Kraiczi H, Peker Y, Caidahl K, Samuelsson A, Hedner J. Blood pressure, cardiac structure and severity of obstructive sleep apnea in a sleep clinic population. *J Hypertens*. 2001;19:2071–2078.
21. Kannel WB, Feinleib M, McNamara PM, Garrison RJ, Castelli WP. An investigation of coronary heart disease in families: the Framingham offspring study. *Am J Epidemiol*. 1979;110:281–290.
22. Quan SF, Howard BV, Iber C, Kiley JP, Nieto FJ, O'Connor GT, Rapoport DM, Redline S, Robbins J, Samet JM, Wahl PW. The Sleep Heart Health Study: design, rationale, and methods. *Sleep*. 1997;20:1077–1085.
23. Fried LP, Borhani NO, Enright P, Furberg CD, Gardin JM, Kronmal RA, Kuller LH, Manolio TA, Mittelmark MB, Newman A; for the CHS collaborative research group. The Cardiovascular Health Study: design and rationale. *Ann Epidemiol*. 1991;1:263–276.
24. Lee ET, Welty TK, Fabsitz R, Cowan LD, Le NA, Oopik AJ, Cucchiara AJ, Savage PJ, Howard BV. The Strong Heart Study: a study of cardiovascular disease in American Indians: design and methods. *Am J Epidemiol*. 1990;132:1141–1155.
25. Redline S, Sanders MH, Lind BK, Quan SF, Iber C, Gottlieb DJ, Bonekat WH, Rapoport DM, Smith PL, Kiley JP; Sleep Heart Health Research Group. Methods for obtaining and analyzing unattended polysomnography data for a multicenter study. *Sleep*. 1998;21:759–767.
26. Whitney CW, Gottlieb DJ, Redline S, Norman RG, Dodge RR, Shahar E, Surovec S, Nieto FJ. Reliability of scoring respiratory disturbance indices and sleep staging. *Sleep*. 1998;21:749–757.
27. Iber C, Redline S, Kaplan Gilpin AM, Quan SF, Zhang L, Gottlieb DJ, Rapoport D, Resnick HE, Sanders M, Smith P. Polysomnography performed in the unattended home versus the attended laboratory setting: Sleep Heart Health Study methodology. *Sleep*. 2004;27:536–540.
28. Quan SF, Griswold ME, Iber C, Nieto FJ, Rapoport DM, Redline S, Sanders M, Young T; Sleep Heart Health Study (SHHS) Research Group. Short-term variability of respiration and sleep during unattended nonambulatory polysomnography: the Sleep Heart Health Study. *Sleep*. 2002;25:843–849.
29. Whitney CW, Gottlieb DJ, Redline S, Norman RG, Dodge RR, Shahar E, Surovec S, Nieto FJ. Reliability of scoring respiratory disturbance indices and sleep staging. *Sleep*. 1998;21:749–757.
30. Gardin JM, Wong ND, Bommer W, Klopfenstein HS, Smith VE, Tabatznik B, Siscovick D, Lobodzinski S, Anton-Culver H, Manolio TA. Echocardiographic design of a multicenter investigation of free-living elderly subjects: the Cardiovascular Health Study. *J Am Soc Echocardiogr*. 1992;5:63–72.
31. Devereux RB, Roman MJ, de Simone G, O'Grady MJ, Paranicas M, Yeh JL, Fabsitz RR, Howard BV. Relations of left ventricular mass to demographic and hemodynamic variables in American Indians: the Strong Heart Study. *Circulation*. 1997;96:1416–1423.
32. Dhingra R, Pencina MJ, Benjamin EJ, Levy D, Larson MG, Meigs JB, Rifai N, D'Agostino RB Sr, Vasan RS. Cross-sectional relations of urinary sodium excretion to cardiac structure and hypertrophy: the Framingham Heart Study. *Am J Hypertens*. 2004;17:891–896.
33. Sahn DJ, DeMaria A, Kisslo J, Weyman A. Recommendations regarding quantitation in M-mode echocardiography: results of a survey of echocardiographic measurements. *Circulation*. 1978;58:1072–1083.
34. de Simone G, Daniels SR, Devereux RB, Meyer RA, Roman MJ, de Divitiis O, Alderman MH. Left ventricular mass and body size in normotensive children and adults: assessment of allometric relations and impact of overweight. *J Am Coll Cardiol*. 1992;20:1251–1260.
35. de Simone G, Devereux RB, Daniels SR, Koren MJ, Meyer RA, Laragh JH. Effect of growth on variability of left ventricular mass: assessment of allometric signals in adults and children and their capacity to predict cardiovascular risk. *J Am Coll Cardiol*. 1995;25:1056–1062.
36. de Simone G, Daniels SR, Kimball TR, Roman MJ, Romano C, Chinali M, Galderisi M, Devereux RB. Evaluation of concentric left ventricular geometry in humans: evidence for age-related systematic underestimation. *Hypertension*. 2005;45:64–68.
37. Gardin JM, Siscovick D, Anton-Culver H, Lynch JC, Smith VE, Klopfenstein HS, Bommer WJ, Fried L, O'Leary D, Manolio TA. Sex, age, and disease affect echocardiographic left ventricular mass and systolic function in the free-living elderly: the Cardiovascular Health Study. *Circulation*. 1995;91:1739–1748.
38. Sundstrom J, Sullivan L, Selhub J, Benjamin EJ, D'Agostino RB, Jacques PF, Rosenberg IH, Levy D, Wilson PW, Vasan RS. Relations of plasma homocysteine to left ventricular structure and function: the Framingham Heart Study. *Eur Heart J*. 2004;25:523–530.
39. Palmieri V, Dahlöf B, DeQuattro V, Sharpe N, Bella JN, de Simone G, Paranicas M, Fishman D, Devereux RB. Reliability of echocardiographic assessment of left ventricular structure and function: the PRESERVE Study. *J Am Coll Cardiol*. 1999;34:1625–1632.
40. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise J, Solomon SD, Spencer KT, Sutton MS, Stewart WJ; Chamber Quantification Writing Group; American Society of Echocardiography's Guidelines and Standards Committee; European Association of Echocardiography. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr*. 2005;18:1440–1463.
41. Usui K, Parker JD, Newton GE, Floras JS, Ryan CM, Bradley TD. Left ventricular structural adaptations to obstructive sleep apnea in dilated cardiomyopathy. *Am J Respir Crit Care Med*. 2006;173:1170–1175.
42. Devereux RB, Case DB, Alderman MH, Pickering TG, Chien S, Laragh JH. Possible role of increased blood viscosity in the hemodynamics of systemic hypertension. *Am J Cardiol*. 2000;85:1265–1268.
43. Bella JN, Wachtell K, Palmieri V, Liebson PR, Gerdts E, Ylitalo A, Koren MJ, Pedersen OL, Rokkedal J, Dahlof B, Roman MJ, Devereux RB. Relation of left ventricular geometry and function to systemic hemodynamics in hypertension: the LIFE Study: Losartan Intervention For Endpoint Reduction in Hypertension Study. *J Hypertens*. 2001;19:127–134.
44. Schneider H, Schaub CD, Chen CA, Andreoni KA, Schwartz AR, Smith PL, Robotham JL, O'Donnell CP. Effects of arousal and sleep state on systemic and pulmonary hemodynamics in obstructive apnea. *J Appl Physiol*. 2000;88:1084–1092.
45. Avelar E, Cloward TV, Walker JM, Farney RJ, Strong M, Pendleton RC, Segerson N, Adams TD, Gress RE, Hunt SC, Litwin SE. Left ventricular

hypertrophy in severe obesity: interactions among blood pressure, nocturnal hypoxemia, and body mass. *Hypertension*. 2007;49:34–39.
46. Hashimoto T, Yamasaki S, Taguchi S. Alterations in the expression of myosin heavy chain isoforms in hypoxia-induced hypertrophied ventricles in rats. *Comp Biochem Physiol B Biochem Mol Biol*. 2003;136:139–145.
47. White DP. Pathogenesis of obstructive and central sleep apnea. *Am J Respir Crit Care Med*. 2005;172:1363–1370.

## CLINICAL PERSPECTIVE

The present study evaluates the association of obstructive sleep-disordered breathing with left ventricular morphology and function in a community-based sample of adults drawn from the Cardiovascular Health Study, Framingham Heart Study, and Strong Heart Study. The primary outcome measure was left ventricular mass index, an important predictor of cardiovascular mortality and morbidity. There was a significant association between sleep-disordered breathing at a severity commonly encountered in the general population and increased left ventricular mass index, after adjustment for known and potential causes of left ventricular hypertrophy, including age, sex, body mass index, hypertension, history of diabetes mellitus and myocardial infarction, smoking, and alcohol consumption. Left ventricular hypertrophy in subjects with sleep-disordered breathing had a pattern of eccentric rather than concentric hypertrophy. Modestly reduced global left ventricular systolic function was also observed. The results of the present study add to the growing literature supporting an association of sleep-disordered breathing and cardiovascular disease and suggest that obstructive sleep-disordered breathing should be considered as a possible causative factor in the development of left ventricular hypertrophy and dilated cardiomyopathy.