Echocardiographic Features of the Right Heart in Sleep-Disordered Breathing

The Framingham Heart Study

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The effect of sleep-disordered breathing (SDB) on right heart structure and function is controversial. Studies of patients referred for evaluation of possible sleep apnea have yielded conflicting results, and the impact of SDB on the right heart has not been investigated in the general population. We examined the echocardiographic features of subjects with SDB at the Framingham Heart Study site of the Sleep Heart Health Study. Of 1,001 polysomnography subjects, 90 with SDB defined as a respiratory disturbance index (RDI) score > 90th percentile (mean RDI = 42) were compared with 90 low-RDI subjects (mean RDI = 5) matched for age, sex, and body mass index. Right heart measurements, made without knowledge of clinical status, were compared between groups. The majority of the subjects were male (74%). After multivariable adjustment, right ventricle (RV) wall thickness was significantly greater ($p = 0.005$) in subjects with SDB (0.78 ± 0.02 cm) than in the low-RDI subjects (0.68 ± 0.02 cm). Right atrial dimensions, RV dimensions, and RV systolic function were not found to be significantly different between subjects with SDB and the low-RDI subjects. We conclude that in this community-based study of SDB and right heart echocardiographic features, RV wall thickness was increased in subjects with SDB. Whether the RV hypertrophy observed in persons with SDB is associated with increased morbidity and mortality remains unknown.

Keywords: cohort study; echocardiography; epidemiology; obesity; right ventricle; sleep-disordered breathing

Numerous cross-sectional studies have demonstrated an association between obstructive sleep apnea and coronary heart disease (1, 2), stroke (3, 4), and sudden death (5). Pulmonary hypertension and right heart failure have also been observed in patients presenting with severe obstructive sleep apnea syndrome, although the relation of more modest degrees of sleep-disordered breathing (SDB) to alterations in right heart structure and function in the general population is unknown. The paucity of data regarding right heart structure and function in SDB is likely related to several factors. SDB has been underrecognized in clinical practice, even though the prevalence of SDB in middle-aged adults is estimated to be 9% for women and 24% for men (6). In addition, the right ventricle is more challenging to assess both qualitatively and quantitatively than the left ventricle (7). The few studies that have examined the right heart in SDB have been limited by design issues and sleep laboratory referral bias (8–19). Hence, it is not surprising that prior studies have differed as to whether SDB is associated with altered right heart morphology and function.

We performed a cross-sectional study that examined a subgroup of subjects in the Framingham Heart Study who were also participants in the Sleep Heart Health Study (20). Our study was aimed at determining the right heart morphologic and functional features of SDB in a community-based sample.

METHODS

Study Sample

The design of the Framingham Heart Study (one of the sites of the Sleep Heart Health Study) has been reviewed elsewhere (21–23). The Framingham Heart Study began in 1948 as a prospective investigation of the epidemiology of cardiovascular disease. At that time, a random sample of 5,209 men and women aged 28 to 62 yr and residing in Framingham, Massachusetts were identified from the town census and recruited as the original cohort. This sample included approximately two-thirds of the age-eligible population of Framingham at that time. The original cohort included 1,644 couples, and in 1971 the children of these couples plus the children of 378 original cohort members with heart disease, and their spouses, were invited to participate in the study. The resulting Offspring cohort initially included 5,124 men and women. The Omni cohort of the Framingham Heart Study was recruited by advertisement and community outreach from December 1995 to January 1998. The Omni cohort was made up of residents of Framingham, 40–75 yr old, who identified themselves as members of a minority group (20). Our sample for this investigation was drawn from the Framingham Offspring and Omni cohorts.

The Sleep Heart Health Study, which has been described previously (20), is a multicenter study of the cardiovascular consequences of SDB that was designed to incorporate existing epidemiologic cohort studies, including the Framingham Heart Study. The institutional review board of each participating institution approved the study protocol. Either by mail or in person at the time of a visit to the study center, participants in each "parent" study were invited to participate in Sleep Heart Health Study. Between December 1995 and January 1998, the Framingham Heart Study site of the Sleep Heart Health Study recruited 473 men and 528 women, aged 45–78 yr, from the Framingham Offspring and Omni cohorts who agreed to undergo polysomnography. All Framingham Heart Study participants who reported for their periodic examination and who lived in the Framingham area were invited to participate without regard to snoring or other sleep-related symptoms. These 1,001 men and women comprised 61% of those invited to participate; the other 39% refusing to participate because of the inconvenience, concerns about loss of privacy related to a home visit, or concerns about test discomfort.

Polysomnography

Subjects underwent in-home, overnight polysomnography (20). The equipment consisted of a Compumedics (Abbotsford, Victoria, Australia) P series system, which recorded the following channels: central electroencephalogram, electrooculogram, chin electromyogram, pulse

(*Received in original form January 18, 2001 and revised form April 27, 2001*)

Supported by NIH/NHLBI contract N01-HC-38038, Sleep Heart Health Study grant U01-HL53941, and NIH/NINDS grant 5-R01-NS-17950.

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oximeter, chest and abdominal excursion, airflow (by oronasal thermistry), single bipolar electrocardiogram, and body position. The Sleep Heart Health Study Reading Center (Cleveland, OH) scored all polysomnography recordings, using methods that have been described in detail elsewhere (24). Respiratory disturbance index (RDI) was defined as the number of apneas plus hypopneas per hour of sleep time. Apnea was defined as a reduction in airflow to <25% of baseline for >10 s, and hypopnea was defined as a decrease in airflow or thoracoabdominal excursion to <70% of baseline for >10 s, associated with a 3% fall in oxyhemoglobin saturation. A rigorous quality control program was used to optimize the quality of polysomnography studies by providing frequent feedback to technicians and excluding studies from analysis that did not meet acceptability criteria, as described elsewhere (24, 25).

Subsample

A matched cross-sectional design was used. From the pool of 1,001 Framingham Sleep Heart Health Study subjects, 90 subjects who had an RDI value higher than the 90th percentile and had recently undergone echocardiography were classified as having SDB (exposed group). The low-RDI group (unexposed group) consisted of 90 subjects, matched for age (within a 5-yr range), sex, and body mass index (BMI), who had RDI values in the lower half of the distribution (RDI < 50th percentile) and had recently undergone echocardiography. In general, the high-RDI subjects were more obese than their available matches. When a close BMI match was not available, the subject with the highest BMI within the appropriate sex and age group was chosen. The clinical covariates examined included age, sex, BMI, race, height, hypertension, smoking, diabetes, previous myocardial infarction, pulmonary function, left ventricular mass/height, left ventricular wall thickness, left ventricular end-diastolic and end-systolic dimensions, and left ventricular ejection fraction. Details regarding the methods of risk factor measurement and laboratory analysis have been described (26). Subjects with a fasting glucose ≥140 mg/dl, and/or receiving treatment for diabetes, were defined as diabetic. Subjects with a systolic blood pressure ≥140 mm Hg or a diastolic blood pressure ≥90 mm Hg on the average of two readings taken by the examining physician and/or receiving medications to treat hypertension were defined as hypertensive. Obstructive pulmonary disease was defined as a forced expiratory volume in 1 s (FEV_1) < 80% of predicted combined with a FEV_1/forced vital capacity ratio < 90% of predicted. Current smoking was defined as smoking cigarettes regularly in the year preceding the examination. Body mass index was defined as weight in kilograms divided by the height in meters squared. A panel of physicians determined the diagnosis of myocardial infarction, using previously published criteria for recognized and unrecognized myocardial infarctions (26).

Echocardiography

All Framingham Offspring and Omni participants underwent echocardiography as part of the main Framingham Heart Study protocol. Echocardiographic images were obtained in the parasternal long and short axes, apical long axes, apical four-chamber, and subcostal views with the use of a Hewlett-Packard (Palo Alto, CA) Sonos 1000 machine recorded on a Panasonic Super VHS VCR system (AG7350). Left heart measurements, based on M-mode measurements made according to the American Society of Echocardiography guidelines (27), were part of the main Framingham Heart Study database and were not measured explicitly for this study. Left heart measurements were made offline from digitally stored M-mode tracings, using digital calipers.

For this study, we used the videotaped echocardiography studies to make right heart measurements of the 180 high- and low-RDI subjects selected as described above. We reviewed the literature to develop standardized techniques for measuring the right heart by two-dimensional echocardiography (7, 28–36). To enhance the quality and consistency of measurements, two observers measured 10 studies together and developed a written manual with detailed instructions on how to measure the right heart structures. Blinded to the clinical history and RDI status of the subjects, the echocardiograms of high-RDI subjects and low-RDI subjects were reviewed in a random order to assess the following quantitative two-dimensional parameters.

1. Right atrial end-systolic size (superior–inferior, medial–lateral) in the apical four-chamber view
2. Right ventricular (RV) end-diastolic dimensions (minor and long axes) in the apical four-chamber view
3. RV systolic function: The RV fractional area change (starting at the tricuspid valve annulus, tracing of the interface of the RV cavity free wall endocardium was done in diastole and systole) in the apical four-chamber view
4. RV end-diastolic free wall thickness in the subcostal view

To optimize precision, the computerized linear measurement cross-hairs were used for all measurements. Measurements were made on three cardiac cycles, if possible, and averaged.

Statistical Analysis

Statistical analyses were performed using SAS (37) on a SUN Ultrasparc (SUN Microsystems, Mountain View, CA) workstation. Associations between RDI status and RV structure variables were examined by linear regression (38) with adjustment for the matching variables: age, sex, and body mass index. A p value ≤ 0.05 was considered statistically significant. Stepwise multivariable linear regression (38) was used to assess whether the clinical covariates (race, height, hypertension, smoking, diabetes, and previous myocardial infarction) contributed significantly to the estimation of right heart measures, accounting for age, sex, body mass index, and RDI status. For right heart measures found to be significantly associated with RDI status, these same clinical covariates were added individually to determine whether any had a substantial effect on the primary association. An additional secondary analysis used stepwise multivariable linear regression analyses to examine whether FEV_1 percent predicted (%pred) or left-heart echocardiographic covariates (left ventricular mass/height, left ventricular wall thickness, left ventricular end diastolic and end systolic dimensions, and left ventricular ejection fraction) confounded or modified the apparent relation between right ventricular wall thickness and SDB.

Paired analyses were also performed and demonstrated qualitatively similar results. Notably, there was a large proportion of "missing pairs" (22%) for the RV wall thickness measurement that resulted in a decreased sample size. We report the results of the unpaired analyses in Table 2.

Reproducibility analyses were based on 20 echocardiograms randomly chosen. Intraobserver analyses compared the first reading (U.C.G.) immediately after the training period and rereadings about 2 mo later. Interobserver (U.C.G. and L.A.M.) reproducibility was based on a comparison between the final reading by U.C.G. and a single reading by L.A.M. Intraobserver and interobserver variability were assessed with Pearson correlation coefficients for all right atrial and RV measurements.

Because the frames were not preselected, reproducibility assessments also reflect the variability inherent in image selection. The intraobserver correlation coefficients were as follows: right atrium (r = 0.77, superior–inferior axis; r = 0.56, medial–lateral axis), RV (r = 0.70, end diastolic minor axis; r = 0.76, end diastolic long axis). Correlation coefficients for the fractional area change and RV wall thickness were r = 0.53 and r = 0.82, respectively.

The correlation coefficients for interobserver reproducibility were as follows: right atrium (r = 0.77, superior–inferior axis; r = 0.78, medial–lateral axis), RV (r = 0.86, end-diastolic minor axis; r = 0.89, end-diastolic long axis). The correlation coefficients for fractional area change and RV wall thickness were r = 0.83 and r = 0.67, respectively.

RESULTS

The mean RDI score for the 90 high-RDI subjects (>90th percentile, RDI > 21) was 42 ± 15 (range, 21–104) compared with a mean RDI score of 5 ± 3 (range, 0.3–12.9) for the 90 low-RDI subjects (50th percentile or less, RDI < 13) who were matched on age, sex, and BMI (Table 1). The median RDI score was 36 for the high-RDI subjects with an interquartile (25th–75th percentile) range of 31 to 46, and was 5 for the low-RDI subjects with an interquartile range of 3–6 (Table 1). Overall, the sample was 74% white and 74% male. The mean

TABLE 1. CLINICAL CHARACTERISTICS OF STUDY SUBJECTS*

Characteristic	High-RDI Subjects (*n* = 90)	Low-RDI Subjects (*n* = 90)
Sex, % male	74	74
Mean age, yr	60 ± 9	61 ± 9
Body mass index, kg/m^2	32 ± 5	28 ± 4
Race, % white	78	71
Mean RDI score	42.0 ± 15.3	4.6 ± 2.6
Range of RDI scores	21.4–104.4	0.3–12.9
Median RDI score	36.5	4.6
Interquartile range, 25%–75%	31.4–46.3	2.6–6.3
Mean % sleep time with O_2 saturation < 90%	12.6 ± 15.8	1.40 ± 4.90
Mean % sleep time with O_2 saturation < 85%	3.26 ± 9.76	0.29 ± 1.82
Habitual snoring, %	58.9	25.6
Self-reported breathing pauses during sleep, %	17.8	2.2
Mean score, Epworth Sleepiness Scale	7.77 ± 4.01	6.89 ± 4.38
Hypertension, %	54	43
Smoking, %	8	11
Diabetes, %	16	11
Obstructive pulmonary disease, % (n = 173)	13	16
Previous myocardial infarction, %	2	2

Definition of abbreviation: RDI = respiratory distress index.

* High-RDI subjects had scores in the >90th percentile; low-RDI subjects had RDI scores <50th percentile. Means ± SD are shown for continuous variables, % for categorical variables. See text for definitions.

ages of the high-RDI subjects and low-RDI subjects were 60 ± 9 and 61 ± 9 yr, respectively. The mean body mass index was higher for subjects with high-RDI scores than for low-RDI subjects (32 ± 5 vs. 28 ± 4; p = 0.001). As expected, the high-RDI subjects had a higher prevalence of self-reported habitual snoring and breathing pauses during sleep, a higher mean Epworth Sleepiness Scale score, and a higher percentage of sleep time with low oxygen saturation than the low-RDI subjects. The prevalence of hypertension, diabetes, smoking, and prior myocardial infarction was similar in both groups. Spirometry data obtained within the previous 5 yr were available for 173 of the 180 participants (96%). Thirteen percent of the high-RDI subjects and 16% of the low-RDI subjects had obstructive pulmonary disease as previously defined.

Echocardiographic studies are often technically limited in obese subjects (39). Because our sample of subjects with high-RDI scores was matched on BMI, the majority of our sample was obese. Approximately 30% were missing M-mode echocardiographic data on the left ventricle and between 1 and 2% (right atrial and RV internal dimensions) and 13% (RV wall thickness) were missing two-dimensional echocardiographic data on the right heart.

The base models included age, sex, BMI, and RDI status (Table 2). RV wall thickness was significantly greater in high-RDI subjects compared with the low-RDI subjects (0.78 ± 0.02 vs. 0.68 ± 0.02 cm, p = 0.005). Right atrial dimensions, RV internal dimensions, RV systolic function, and all LV measurements were not significantly different between high-RDI subjects and low-RDI subjects. Stepwise multiple linear regression was used to assess whether the clinical covariates (race, height, hypertension, smoking, diabetes, and previous myocardial infarction) contributed significantly to the estimation of the right heart measures. None was selected to remain in the models. For RV wall thickness, these same covariates were entered individually into the base models to determine whether any altered the association with RDI status. None of these covariates had a substantial effect on the primary association between RV wall thickness and RDI status.

The percent predicted FEV_1 and left heart echocardiographic covariates (left ventricular mass/height, left ventricular wall thickness, left ventricular end-diastolic and end-systolic dimensions, and left ventricular ejection fraction) were also analyzed as potential correlates of RV wall thickness, using stepwise multivariable linear regression. None of these covariates was selected to remain in the models. Furthermore, when entered individually into the base model, none of these covariates had a substantial effect on the relation between RDI and RV wall thickness. Thus, the base models were retained as the final models (Table 2).

Twenty-two percent of subjects could not be included in the paired analysis, because of the lack of a technically measurable RV wall thickness in at least one member of the pair. However, despite the smaller number of subjects, the association between high-RDI and RV wall thickness remained significant in the paired analysis (p = 0.04). To use all available data, we reported the results of the unpaired analysis in Table 2. Graphic and correlation analyses revealed no evidence that RV wall thickness or other RV measurements varied with increasing RDI within the high-RDI group.

The percentage of sleep time with oxygen saturation less than 90% was highly correlated with RDI (r = 0.69, p = 0.0001), as was the percentage of sleep time spent with oxygen saturation less than 85% (r = 0.71, p = 0.0001). In multivariate models adjusting for age, sex, and BMI, there was a non-significant increase in RV wall thickness with increasing sleep time at low oxygen saturation. An increase of 10% in the percentage of sleep time at less than 85% saturation was associated with an increase in RV wall thickness of 0.04 cm (p = 0.08).

DISCUSSION

To investigate the effect of sleep-disordered breathing on right heart morphology and systolic function, we selected subjects whose RDI scores were in the upper 10% of our community-based sample (RDI ⩾ 21, mean RDI = 42) and a low-RDI group from the lower half of the distribution (RDI ⩽ 13, mean RDI = 5). There was a significant difference in RV wall thickness between the two groups, which was not affected by obesity (8, 40–44), hypertension (9, 10), or pulmonary func-

TABLE 2. ADJUSTED* ECHOCARDIOGRAPHIC MEASUREMENTS OF HEART MORPHOLOGY AND VENTRICULAR SYSTOLIC FUNCTION

	Number of Subjects with Measurable Feature	High-RDI Subjects	Low-RDI Subjects	p Value
Right atrial diameter				
Short axis (medial–lateral), cm	178	3.95 ± 0.07	4.02 ± 0.07	0.49
Long axis (superior–inferior), cm	178	4.76 ± 0.06	4.86 ± 0.06	0.23
RV internal dimensions				
Minor axis, end diastole, cm	177	2.86 ± 0.06	2.88 ± 0.06	0.81
Long axis, end diastole, cm	178	7.38 ± 0.07	7.41 ± 0.07	0.76
Systolic area, cm^2	178	8.38 ± 0.21	8.70 ± 0.20	0.28
Diastolic area, cm^2	177	18.15 ± 0.35	18.38 ± 0.35	0.66
RV fractional area change, %	176	0.54 ± 0.01	0.53 ± 0.01	0.31
RV wall thickness, cm	157	0.78 ± 0.02	0.68 ± 0.02	0.005
LV internal dimensions				
Diastolic internal diameter, cm	127	4.99 ± 0.06	4.99 ± 0.05	0.92
Systolic internal diameter, cm	125	3.18 ± 0.06	3.18 ± 0.05	0.99
LV ejection fraction, %	125	69.4 ± 0.92	69.3 ± 0.82	0.92
LV posterior wall thickness, cm	133	1.00 ± 0.02	1.01 ± 0.01	0.67
LV mass/body surface area, g/m^2	127	96.7 ± 2.6	96.5 ± 2.3	0.97

Definition of abbreviations: LV = left ventricular; RV = right ventricular.
* Means and Standard errors are adjusted for age, sex, and body mass index.

tion (11, 13, 16–18, 45, 46). There were no significant differences in the right atrial or RV minor and long axis dimensions or RV systolic function between the two groups.

The relation of SDB to right heart structure and function is controversial. Three prior studies have used two-dimensional echocardiography to examine the prevalence of RV hypertrophy in SDB in small samples of patients (n = 50 or 51) referred for suspected sleep apnea (8–10). The prevalence of RV hypertrophy in these studies ranged from 0 to 71% (8–10). It has been argued that concomitant chronic pulmonary disorders are required for sleep apnea to cause right heart failure (11, 13, 16–18, 45, 46). However, Sanner and colleagues (14) demonstrated that sleep apnea was independently associated with depressed RV ejection fraction by radionuclide ventriculography after adjusting for lung function, age, body mass index, sex, blood gas analysis, pulmonary artery pressure, and left ventricular ejection fraction. Hanly and colleagues (9) found no difference in right or left ventricular dimensions between nonapneic snorers and subjects with obstructive sleep apnea.

The reasons for the disparate conclusions of the prior studies examining RV hypertrophy, RV systolic function, and RV enlargement are not certain. The prior studies were relatively small and limited to subjects referred for evaluation of suspected sleep apnea or for surgery for sleep apnea (8–12, 14, 18, 19), precluding comparison with asymptomatic control subjects and introducing possible referral bias in terms of the severity of SDB. Some studies did not explicitly employ blinded interpretation of echocardiograms (10) or radionuclide ventriculography (14). Reproducibility was limited or not addressed in the three studies examining RV hypertrophy (8–10) and in three of the studies examining RV function (12, 14, 18). Studies were limited analytically by the lack of control for potential confounders through multivariable analysis (9–12, 19). Another limitation of prior studies was the use of dichotomous determinations of RV hypertrophy (8, 10), dysfunction (11, 12, 14), or enlargement (19).

Our sample was derived from the community, rather than through referrals from a sleep laboratory or surgical clinic to treat sleep apnea (8–12, 14, 18, 19). The selection of cases and matched low-RDI subjects from a prospectively evaluated community-based sample minimized the referral bias likely to occur in laboratory-based studies and improved our ability to adjust for potential confounding factors. Laboratory-based studies typically utilize an arbitrary dichotomous definition of obstructive sleep apnea syndrome based on the RDI; however, the operational definition of respiratory events varies widely among sleep laboratories (47) and these differences have a large effect on the level of RDI (48). A strength of the present study is that we compared subjects in the upper tail of the distribution of RDI scores (>90th percentile) with those in the lower half of the distribution. In addition, we examined right heart morphology and systolic function as continuous variables because dichotomous definitions of RV hypertrophy (8, 10), RV dysfunction (11, 12, 14), and RV enlargement (19) used in the other studies do not take into account differences that might be expected on the basis of sex or body size. Other strengths of the present study include that it was well controlled, used systematic blinded ascertainment of clinical covariates, multivariable analyses, and blinded interpretation of echocardiography. Finally, our study is one of the few studies to examine the relations of SDB to RV (9, 19) or right atrial dimensions (49).

A limitation of our study is the measurement variability inherent in quantitation of right heart structure and function, variability that may lead to random misclassification and a potential bias toward the null. This challenge increases with obesity (39). Our intraobserver reproducibility for right heart measurements, based on 20 repeat readings by the same reader, was only fair, with correlation coefficients for the two readings ranging from 0.53 to 0.82 for the various measurements. Our interobserver reproducibility, assessed later in the study, was somewhat better, with correlation coefficients ranging from 0.67 to 0.83. Transthoracic echocardiography has limitations that preclude making measurements in some persons in whom the structure being studied cannot be well visualized. In our study, it was technically feasible to measure RV wall thickness in 87% of subjects (78% of the pairs). For the other right heart measures, fewer than 3% of subjects had missing data. This compares favorably, however, with a prior study of RV morphology in SDB (39, 40).

We matched high- and low-RDI subjects as tightly as possible on BMI, but the 90 high-RDI subjects nevertheless had a significantly higher BMI than the low RDI subjects (32 ± 5 vs.

28 ± 4, p = 0.001). The fact that we were unable to find, among our 1,001 subjects with polysomnography and echocardiography data, 90 low-RDI subjects with BMI equal to that of the high-RDI group is not surprising, because of the strong association of obstructive sleep apnea syndrome with obesity (41, 50, 51). Because we were unable to tightly match on BMI, we adjusted for this covariate in our linear regression models. Our finding of increased RV wall thickness in subjects with high-RDI persisted after adjustment for BMI.

Our study indicates that sleep-disordered breathing is associated with increased RV wall thickness in a general population. The mean RV wall thickness of persons with high and low RDIs differed by 0.1 cm, which is one-fourth of the 0.4-cm difference in RV wall thickness that has been reported between healthy persons and patients with clinically evident right ventricular hypertrophy (29). The fact that this association with altered heart structure was observed for a level of RDI found in 10% of our sample suggests the possibility of a relatively large public health consequence of this degree of SDB. The full scope of the public health importance of SDB remains to be determined. It has been demonstrated that left ventricular hypertrophy is an independent predictor of adverse cardiovascular outcomes (52). Whether RV hypertrophy has similar prognostic value needs further study.

Acknowledgment: The authors acknowledge a generous corporate donation for an echocardiographic equipment upgrade to a Sonos 1000 by the Hewlett-Packard Foundation. We also thank Compumedics for modifying equipment for use by SHHS. We are indebted to Michael Crommie, PhD, for a critical review of the manuscript.

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