

Biventricular Myocardial Performance Is Impaired

in Proportion to Severity of Obstructive Sleep Apnea

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Obstructive sleep apnea (OSA) is an independent risk factor for cardiovascular morbidity and death. Little information is available regarding the relationship between the severity of OSA and myocardial performance in OSA patients who have normal ejection fractions. We prospectively investigated this relationship, using the tissue-Doppler myocardial performance index (TD-MPI).

We conducted overnight, full-laboratory polysomnographic examinations of 116 patients, and calculated the left and right ventricular TD-MPIs. Patients were classified into 3 groups in accordance with their apnea-hypopnea index (AHI) levels: AHI_{mild} (≥ 5 to < 15), AHI_{moderate} (≥ 15 to < 30), and AHI_{severe} (≥ 30).

Left and right ventricular TD-MPI values were higher in the AHI_{severe} group than in the AHI_{mild} and AHI_{moderate} groups (all $P < 0.05$). In addition, right ventricular TD-MPI values in the AHI_{moderate} group were higher than those in the AHI_{mild} group ($P < 0.05$). Right ventricular TD-MPI was significantly associated with AHI ($\beta = 0.468$, $P < 0.001$), left ventricular TD-MPI, and right ventricular early-to-late filling velocities (E/A ratio) in multiple linear regression analysis. On the other hand, left ventricular TD-MPI was significantly associated with right ventricular TD-MPI and left ventricular E/A ratio (both $P < 0.05$).

Our results show that OSA severity, determined by means of AHI, is independently associated with impaired right and left ventricular function as indicated by TD-MPI in patients who have OSA and normal ejection fractions. (**Tex Heart Inst J 2016;43(2):119-25**)

Obstructive sleep apnea (OSA) affects 4% to 6% of middle-aged men and 2% to 4% of middle-aged women, and its prevalence increases with age.^{1,2} This syndrome is characterized by excessive sleepiness and cognitive-behavioral, respiratory, cardiac, metabolic, and inflammatory disorders secondary to repeated episodes of upper-airway obstruction during sleep.³ Moreover, OSA is an independent risk factor for cardiovascular morbidity and death.⁴ Obstructive sleep apnea affects both ventricles and is associated with impaired ventricular function.^{5,6}

Noninvasive echocardiographic indices of systolic and diastolic ventricular function are of great clinical importance in the diagnosis and treatment of patients who have heart disease. The tissue-Doppler myocardial performance index (TD-MPI) has been proposed as a measure of overall cardiac function.⁷⁻⁹ The TD-MPI, which combines values of both systolic and diastolic ventricular function, is easily obtainable and has been clinically useful to evaluate global ventricular function noninvasively.^{10,11} In addition, TD-MPI level is an independent risk factor for left ventricular (LV) systolic asynchrony in patients who have coronary artery ectasia.¹² Although OSA has been associated with impaired ventricular function, we found no information regarding the relationship between OSA severity and LV and right ventricular (RV) myocardial function in patients who have normal ejection fractions (EFs). We therefore used the TD-MPI to investigate this.

Patients and Methods

Our study included 116 patients with symptoms of nocturnal snoring or excessive daytime sleepiness who were admitted to the sleep clinic of our hospital's Department of Pulmonology for OSA screening from January through August 2014. Detailed sleep and cardiovascular histories of the patients were recorded. All patients underwent physical examination.

Exclusion criteria were any known cardiac or lung disease, diabetes mellitus, hyperthyroidism or hypothyroidism, chronic renal or hepatic disease, or systemic hyper-

tension. We also excluded patients who had abnormal electrocardiographic (ECG) recordings, positive cardiac stress tests, or left ventricular EFs (LVEF) <0.55, and patients who were taking any medications. The Institutional Ethics Committee approved the study protocol, and each participant provided written informed consent.

After evaluating the medical histories and the results of the physical examinations, we recorded the baseline characteristics of the included patients.

Sleep Test and Apnea-Hypopnea Index

All sleep data were recorded with use of E-Series equipment (Compumedics Limited; Abbotsford, Australia), including electroencephalography, electrooculography, submental electromyography, oxygen saturation (by means of pulse oximetry), respiratory movements (by means of inductance plethysmography), nasal and oral airflow (with use of thermistors), and nasal pressure (with use of nasal cannulas and pressure sensors). Sleep stages and sleep-disordered breathing were then scored in accordance with standard criteria.¹³ Apnea was defined as total obstruction of airflow for >10 s, and hypopnea was defined as a reduction in ventilation of ≥50% that results in a decrease in arterial saturation of ≥4% due to partial airway obstruction. The average number of apnea and hypopnea episodes per hour of sleep was defined as the apnea-hypopnea index (AHI). Patients with AHI values ≥5 were diagnosed to have OSA.

Echocardiography

Standard 2-dimensional, M-mode, and tissue-Doppler echocardiographic examinations were performed with use of the Vivid 7[®] cardiac ultrasonography system (GE Medical Systems; Horten, Norway) and a 2.5–3.5-MHz transducer. Simultaneous ECG recordings were obtained. One echocardiographer (blinded to the patients' clinical and laboratory data) interpreted each echocardiographic examination independently. All patients were examined while at rest in the left lateral decubitus position. M-mode echocardiograms were recorded from the parasternal window, to determine left and right atrial and ventricular dimensions. Left atrial diameter, LV end-systolic diameter, LV end-diastolic diameter, and LVEF were determined in apical 2- and 4-chamber views with use of the Simpson biplane formula, in accordance with the suggestions of the American Society of Echocardiography.¹⁴ Tracings of endocardial borders in end-diastole and end-systole were made in the technically best cardiac cycle, and the mean of 3 measurements was used.

After acquisition adjustments were made, LV and RV tissue-Doppler echocardiographic evaluations were performed from the apical 4-chamber position by placing the pulsed-wave Doppler beam on the part of the mitral annulus that is close to the LV lateral wall and inter-

ventricular septum (for the LV), and on the part of the tricuspid annulus that is close to the RV lateral wall (for the RV). During recording, special attention was given to placing the Doppler beam in the myocardium, not the endocardium or epicardium. Measurements were made for 3 consecutive heartbeats in all positions, and their average was taken. Doppler measurements were made at a recording rate of 100 mm/s. The isovolumetric relaxation time (IVRT), isovolumetric contraction time (IVCT), and ejection time (ET) of both ventricles were measured in all patients. The left and right TD-MPIs were defined as the sum of the IVRT and IVCT divided by ET (Fig. 1). All echocardiograms were recorded and interpreted online on hard disks for offline analysis by another observer who was blinded to the patients' data. Mean intraobserver variability (3.9% ± 2.4%) and interobserver variability (4.2% ± 3.2%) were evaluated in data from 12 randomly selected patients and were calculated as the absolute difference divided by the average of the 2 observations.

Statistical Analysis

All analyses were conducted with use of SPSS for Windows version 17.0 (IBM Corporation; Armonk, NY). Data were expressed as mean ± SD. Categorical variables between the groups were compared with use of the χ^2 test. Analysis of variance was used on continuous variables among the AHI groups. Analysis of normality was performed with use of the Kolmogorov-Smirnov test. Associations between other variables in RV TD-MPI and LV TD-MPI were evaluated by means of the Pearson correlation coefficient. Multiple linear regression analysis was performed to identify the independent associations of RV TD-MPI and LV TD-MPI by including the values that were correlated with RV

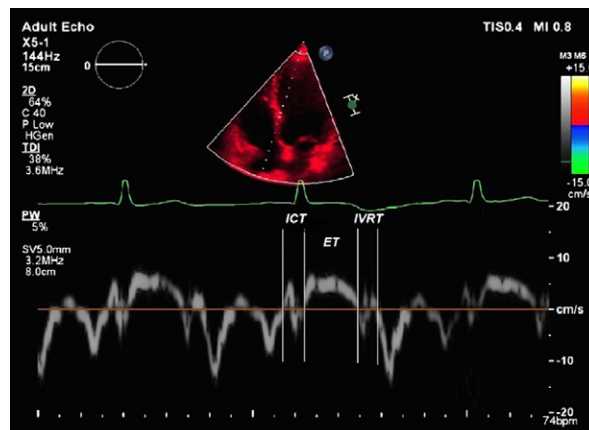


Fig. 1 Example of a tissue-Doppler echocardiogram used to calculate the tissue-Doppler myocardial performance index, which is defined as the sum of isovolumetric relaxation time (IVRT) and isovolumetric contraction time (ICT), divided by ejection time (ET).

TABLE I. Comparison of Baseline, Laboratory, Polysomnographic, and Echocardiographic Characteristics

Variable	AHI Group			P Value	P Value		
	Mild (≥5 to <15) (n=26)	Moderate (≥15 to <30) (n=41)	Severe (≥30) (n=49)		Mild vs Severe	Mild vs Moderate	Moderate vs Severe
Baseline							
Age (yr)	44.1 ± 10.2	44.2 ± 10	46.4 ± 11.2	0.519	0.355	0.875	0.392
Male sex	16 (61.5)	30 (73.2)	33 (67.3)	0.602	0.376	0.471	0.667
BMI (kg/m ²)	28.5 ± 4.9	29.7 ± 3.3	31 ± 2.7	0.01	0.003	0.123	0.08
SBP (mmHg)	113 ± 10.5	118.5 ± 10.1	122.3 ± 10.4	0.001	<0.001	0.026	0.079
DBP (mmHg)	73.7 ± 6	75.5 ± 5.9	76.1 ± 6.3	0.259	0.145	0.341	0.595
Heart rate (beats/min)	76.1 ± 8.1	75.8 ± 10	76.3 ± 9.3	0.532	0.512	0.578	0.493
Current smoking	12 (46.2)	19 (46.3)	23 (46.9)	0.839	0.821	0.911	0.689
Past smoking	3 (11.5)	11 (26.8)	9 (18.4)	0.526	0.556	0.331	0.51
Laboratory							
Glucose (mg/dL)	93.4 ± 8.7	91.1 ± 9.8	92.1 ± 8	0.596	0.511	0.364	0.568
Total cholesterol (mg/dL)	186.5 ± 25.3	188.7 ± 21.7	193 ± 34.8	0.607	0.478	0.672	0.562
Triglycerides (mg/dL)	189.8 ± 62	192.4 ± 52.5	178.5 ± 70	0.54	0.385	0.629	0.359
HDL-C (mg/dL)	42.7 ± 8.6	40.9 ± 7.4	39.6 ± 11.7	0.414	0.175	0.53	0.425
LDL-C (mg/dL)	120.9 ± 29.9	121.7 ± 20.8	130.5 ± 29.8	0.201	0.089	0.458	0.115
Creatinine (mg/dL)	0.8 ± 0.12	0.78 ± 0.18	0.86 ± 0.25	0.116	0.131	0.405	0.044
hs-CRP (mg/dL)	0.32 ± 0.28	0.41 ± 0.32	0.48 ± 0.32	0.158	0.05	0.146	0.214
Hemoglobin (g/dL)	14.2 ± 1.8	14.3 ± 1.6	14.7 ± 1.2	0.29	0.162	0.781	0.211
WBC (×10 ³ /μL)	7.6 ± 1.9	7.9 ± 1.8	8.2 ± 1.9	0.31	0.18	0.597	0.372
Echocardiographic							
LAD (mm)	33.7 ± 4.6	33.1 ± 3.4	34.3 ± 4.5	0.398	0.449	0.719	0.204
LVEDD (mm)	47.9 ± 3.2	46.2 ± 6.1	46.8 ± 6.7	0.53	0.541	0.343	0.654
IVST (mm)	10.5 ± 1.6	10.2 ± 1.2	10.7 ± 1.7	0.218	0.562	0.383	0.096
PWT (mm)	10.1 ± 1.8	10.6 ± 5.3	10.7 ± 1.8	0.817	0.493	0.536	0.962
SPAP (mmHg)	26.9 ± 5.4	35.6 ± 4.9	43.5 ± 6.1	<0.001	<0.001	<0.001	<0.001
LVEF	0.66 ± 0.04	0.66 ± 0.05	0.67 ± 0.05	0.487	0.564	0.611	0.215
LV IVRT (ms)	79.5 ± 14	82.4 ± 16.2	85.9 ± 16.4	0.228	0.112	0.548	0.274
LV IVCT (ms)	49.3 ± 12.9	52.8 ± 15.3	54.1 ± 14.7	0.394	0.151	0.266	0.748
LV ET (ms)	288.3 ± 21.2	281.5 ± 21.5	273.5 ± 24.7	0.026	0.009	0.236	0.106
LV TD-MPI	0.45 ± 0.08	0.48 ± 0.09	0.5 ± 0.12	0.018	0.006	0.172	0.115
LV E/A ratio	1.14 ± 0.5	1.02 ± 0.4	0.86 ± 0.4	0.01	0.004	0.199	0.05
RV IVRT (ms)	73 ± 10	74.3 ± 13.3	86.9 ± 24.3	0.001	0.002	0.729	0.002
RV IVCT (ms)	63.8 ± 19	73.5 ± 14.7	74.8 ± 21.3	0.045	0.017	0.041	0.738
RV ET (ms)	272.6 ± 26.6	255.3 ± 23.8	248 ± 28.7	0.001	<0.001	0.011	0.207
RV TD-MPI	0.49 ± 0.07	0.58 ± 0.09	0.67 ± 0.11	<0.001	<0.001	<0.001	<0.001
RV E/A ratio	1.09 ± 0.2	0.89 ± 0.2	0.76 ± 0.1	<0.001	<0.001	<0.001	<0.001
Polysomnographic							
Apnea index	10.9 ± 25	7.2 ± 7.5	36.2 ± 28.1	<0.001	<0.001	0.55	<0.001
ODI	16.1 ± 27.4	13.4 ± 10.4	48.2 ± 31.3	<0.001	<0.001	0.759	<0.001
AHI	8.3 ± 2.9	23.1 ± 3.5	51.9 ± 17.3	<0.001	<0.001	<0.001	<0.001
DS (%) at Sao ₂ <90%	3.9 ± 1.5	7.9 ± 2.6	15.8 ± 3.7	<0.001	<0.001	<0.001	<0.001
Average Sao ₂ (%)	93.6 ± 3.2	90.6 ± 3	83 ± 3.5	<0.001	<0.001	<0.001	<0.001
MSNAO (%)	85.1 ± 3.3	83.4 ± 3	75.8 ± 5.7	<0.001	<0.001	0.137	<0.001

AHI = apnea-hypopnea index; BMI = body mass index; DBP = diastolic blood pressure; DS = duration of sleep; E/A = early-to-late filling velocity; ET = ejection time; HDL-C = high-density-lipoprotein cholesterol; hs-CRP = high-sensitivity C-reactive protein; IVCT = isovolumetric contraction time; IVRT = isovolumetric relaxation time; IVST = interventricular septal thickness; LAD = left atrial diameter; LDL-C = low-density-lipoprotein cholesterol; LV = left ventricular; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; MSNAO = minimal saturation of nocturnal arterial oxygen; ODI = oxygen desaturation index; PWT = posterior-wall thickness; RV = right ventricle; Sao₂ = arterial oxygen saturation; SBP = systolic blood pressure; SPAP = systolic pulmonary artery pressure; TD-MPI = tissue-Doppler myocardial performance index; WBC = white blood cell count

Data are presented as mean ± SD or as number and percentage. *P* < 0.05 was considered statistically significant.

TD-MPI and LV TD-MPI in bivariate analysis. Standardized β regression coefficients and their significance from multiple linear regression analysis were reported. A P value <0.05 was considered statistically significant.

Results

Patients were classified into 3 groups in accordance with AHI level: ≥ 5 to <15 was AHI_{mild} (26 patients; mean age, 44.1 ± 10.2 yr), ≥ 15 to <30 was AHI_{moderate} (41 patients; mean age, 44.2 ± 10 yr), and ≥ 30 was AHI_{severe} (49 patients; mean age, 46.4 ± 11.2 yr).

Baseline and Laboratory Findings

Table I shows the baseline characteristics and laboratory findings. Body mass index (BMI) values were significantly higher in the AHI_{severe} group than in the AHI_{mild} group ($P < 0.05$). The systolic blood pressures in the AHI_{severe} and AHI_{moderate} groups were significantly higher than those in the AHI_{mild} group (both $P < 0.05$). The creatinine levels in the AHI_{moderate} group and the levels of high-sensitivity C-reactive protein in the AHI_{mild} group were significantly lower than those in the AHI_{severe} group (both $P < 0.05$).

Echocardiographic Findings

Table I shows the echocardiographic comparisons. Among findings of statistical significance, the LV TD-ET values were lower and the LV TD-MPI values were higher in the AHI_{severe} group than in the AHI_{mild} group (both $P < 0.05$). The LV late-to-early filling (E/A) ratio was lower in the AHI_{severe} group than in the other groups (both $P < 0.05$).

The RV TD-IVRT values in the AHI_{severe} group were significantly higher than those in the other groups (both $P < 0.05$). The RV TD-IVCT values were lower and the RV ET values were higher in the AHI_{mild} group than in the other groups (all $P < 0.05$).

The highest RV TD-MPI and lowest E/A values were observed in the AHI_{severe} group ($P < 0.05$ vs the other groups). The RV TD-MPI values in the AHI_{moderate} group were higher than those in the AHI_{mild} group ($P < 0.05$).

Bivariate and Multivariate Relationships between RV TD-MPI and Variables

Table II shows the bivariate associations of RV TD-MPI with age ($r=0.23$, $P=0.013$), BMI ($r=0.265$, $P=0.004$), AHI ($r=0.61$, $P < 0.001$), LV TD-MPI ($r=0.467$, $P < 0.001$), RV E/A ratio ($r= -0.486$, $P < 0.001$) and systolic blood pressure ($r=0.194$, $P=0.037$). Figure 2 shows the relationship between AHI and RV TD-MPI. Upon multivariate linear regression analysis, RV TD-MPI was independently associated with AHI ($\beta=0.468$, $P < 0.001$), LV TD-MPI ($\beta=0.289$, $P < 0.001$), and RV E/A ratio ($\beta= -0.23$, $P=0.007$).

TABLE II. Bivariate and Multivariate Relationships between RV TD-MPI and Variables

Variable	Pearson Correlation Coefficient	P Value	Standardized Regression Coefficient*	P Value
Age	0.23	0.013	0.093	0.183
Body mass index	0.265	0.004	0.034	0.679
AHI	0.61	<0.001	0.468	<0.001
LV TD-MPI	0.467	<0.001	0.289	<0.001
RV E/A ratio	-0.486	<0.001	-0.23	0.007
SBP	0.194	0.037	-0.046	0.559
SPAP	0.787	<0.001	0.871	<0.001
DS at Sao ₂ $<90\%$	0.558	<0.001	-0.013	0.904
Average Sao ₂	-0.491	<0.001	0.12	0.231
MSNAO (Sao ₂)	-0.545	<0.001	-0.148	0.099

AHI = apnea-hypopnea index; DS = duration of sleep; E/A = early-to-late filling velocity; LV = left ventricular; MSNAO = minimal saturation of nocturnal arterial oxygen; RV = right ventricular; Sao₂ = arterial oxygen saturation; SBP = systolic blood pressure; SPAP = systolic pulmonary artery pressure; TD-MPI = tissue-Doppler myocardial performance index

*Multiple linear regression analysis

$P < 0.05$ was considered statistically significant.

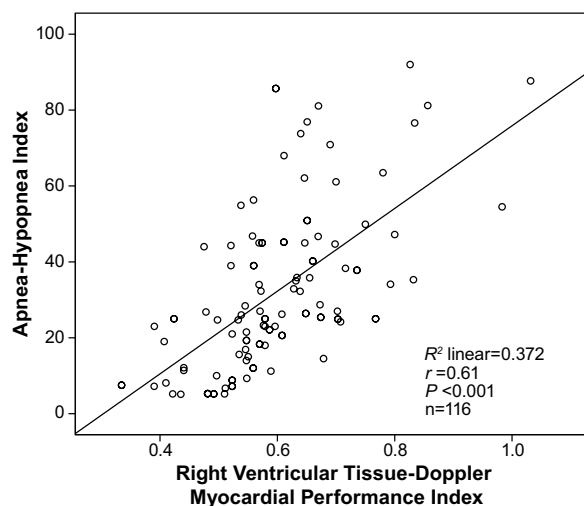


Fig. 2 Scatter plot shows a positive correlation between the apnea-hypopnea index and the right ventricular tissue-Doppler myocardial performance index in patients with obstructive sleep apnea.

$P < 0.05$ was considered statistically significant.

Bivariate and Multivariate Relationships between LV TD-MPI and Variables

Table III shows the bivariate associations of LV TD-MPI with age ($r=0.207$, $P=0.026$), BMI ($r=0.207$,

$P=0.026$), AHI ($r=0.349$, $P<0.001$), RV TD-MPI ($r=0.467$, $P<0.001$), and LV E/A ratio ($r=-0.179$, $P=0.113$). Figure 3 shows the relationship between AHI and LV TD-MPI. Upon multivariate linear regression analysis, LV TD-MPI was associated with RV TD-MPI ($\beta=0.258$, $P=0.005$), LV E/A ratio ($\beta=-0.234$,

$P=0.03$), and duration of sleep at arterial oxygen saturation $<90\%$ ($\beta=-0.421$, $P=0.007$).

Discussion

Our results showed that OSA severity, determined by means of AHI, was independently associated with impairment of RV and LV functions as indicated by TD-MPI in patients who had OSA and normal EFs. An important finding of our study is that an increase in AHI affects RV global function more than it affects LV global function.

Previously, an inconsistent relationship between RV function and AHI was shown¹⁵; however, we found a strong correlation between AHI and RV TD-MPI, and in a larger population of patients who had isolated OSA. Previous investigators showed a correlation between OSA, LV mass, and LV global functions.¹⁶ Others found a relationship between OSA, LV mass, and LV diastolic functions.¹⁷ Obstructive sleep apnea might cause pulmonary hypertension and right-sided heart failure.¹⁸ Hammerstingl and colleagues¹⁹ said that the relationship of OSA to right-sided heart function was debatable. In their study, RV longitudinal strain values indicated that RV systolic functions decrease with disease severity; however, the authors observed no correlation between RV-MPI and AHI in their study and control groups.¹⁹ In a previous report, a correlation between AHI and biventricular TD-MPI was identified, similar to our findings.²⁰ Obstructive sleep apnea (AHI >5) was inversely correlated with RV function when compared to that in control subjects.^{21,22} Therefore, in the current study, our main purpose was to show the relationship between biventricular TD-MPI and OSA severity as indicated by increases in AHI, rather than by the presence of OSA. To make our findings more reliable, we excluded patients who were taking medications or who had disorders that could have affected MPI values. To our knowledge, no previous investigators had evaluated the relationship between OSA severity and biventricular TD-MPI.

When we categorized our patients in accordance with AHI level (mild, moderate, and severe), the TD-MPI values of both ventricles varied significantly among the groups. We found that both LV and RV TD-MPI indicated global cardiac functional impairment that was proportional to the severity of OSA, even when patients had normal EFs. After we adjusted for BMI and age and repeated the correlation analysis, we observed that, although the relationship between AHI and LV TD-MPI was lost, the one between AHI and RV TD-MPI persisted. The LV TD-MPI correlated only with the RV TD-MPI and LV E/A ratio. Therefore, above all else, RV functions are impaired in patients who have OSA.

Previous investigators have disagreed with regard to the relationship between OSA and RV function.²³⁻²⁵ We

TABLE III. Bivariate and Multivariate Relationships between LV TD-MPI and Variables

Variable	Pearson Correlation Coefficient	P Value	Standardized Regression Coefficient*	P Value
Age	0.207	0.026	-0.008	0.934
Body mass index	0.207	0.026	-0.084	0.36
AHI	0.349	<0.001	0.043	0.705
RV TD-MPI	0.467	<0.001	0.258	0.005
LV E/A ratio	-0.355	<0.001	-0.234	0.03
SPAP	0.4	<0.001	0.155	0.425
DS at $SaO_2 <90\%$	0.179	0.054	-0.421	0.007
Average SaO_2	-0.272	0.003	-0.059	0.675
MSNAO (SaO_2)	-0.188	0.043	0.152	0.243

AHI = apnea-hypopnea index; DS = duration of sleep; E/A = early-to-late filling velocity; LV = left ventricular; MSNAO = minimal saturation of nocturnal arterial oxygen; RV = right ventricular; SaO_2 = arterial oxygen saturation; SPAP = systolic pulmonary artery pressure; TD-MPI = tissue-Doppler myocardial performance index

*Multiple linear regression analysis

$P<0.05$ was considered statistically significant.

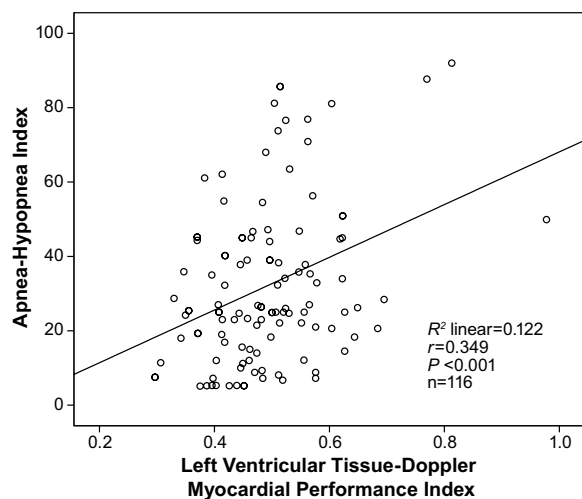


Fig. 3 Scatter plot shows a positive correlation between the apnea-hypopnea index and the left ventricular tissue-Doppler myocardial performance index in patients with obstructive sleep apnea.

$P<0.05$ was considered statistically significant.

excluded patients who had additional disorders or who were taking medications, and we directly evaluated the effects of AHI on biventricular functions. According to our results, AHI severity strongly affects RV function. Mechanisms that might cause RV dysfunction in OSA patients include repetitive nocturnal arterial oxygen desaturation and hypercapnia, large intrathoracic negative-pressure periods, and increases in pulmonary artery pressure.^{26,27} In animal models, intermittent hypoxia resulted in pulmonary artery remodeling and RV hypertrophy.²⁸ Moreover, in OSA patients, hypoxic or hypercapnic periods and oxidative stress lead to pulmonary vasoconstriction and endothelial dysfunction, which causes pulmonary remodeling.²⁹ Airway occlusion in OSA results in the generation of negative intrathoracic pressure, which causes increased venous return, volume overload, and RV distention during apnea episodes.³⁰ Primarily as a result of close anatomic association, the ventricles influence each other as a result of direct-injury extension, afterload changes, or ventricular interdependence. Accordingly, we speculate that, in OSA, RV dysfunction might lead to LV dysfunction.

Study Limitations

Coronary angiography was not performed in our patients; however, the diagnosis of coronary artery disease was excluded by means of clinical characteristics, medical histories, ECG results, and results of treadmill exercise tests. It would have been more instructive had we recorded data about ventricular interaction as an indicator of ventricular dysfunction. During some patients' echocardiographic examinations, we observed evidence of ventricular interaction such as ventricular septal shift or paradoxical movement; however, we did not record this, because it was not included in our study design.

Conclusion

In patients who have OSA, we found that RV and LV functions are impaired as AHI level increases; however, we attribute this impairment chiefly to RV dysfunction.

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