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ORIGINAL RESEARCH

Sleep Apnea and Physical Movement During Sleep, But Not Sleep Duration, Are Independently Associated With Progression of Left Ventricular Diastolic Dysfunction: Prospective Hyogo Sleep Cardio-Autonomic Atherosclerosis Cohort Study

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BACKGROUND: Although co-occurrence of sleep disorder with heart failure is known, it is not clear whether that condition is a cause or consequence of heart failure. The present study was conducted as a longitudinal examination of the predictive value of sleep parameters on progression of left ventricular diastolic dysfunction.

METHODS AND RESULTS: Four-hundred fifty-two subjects were followed for a mean of 34.7 months. An outcome of diastolic dysfunction was defined as increase in early inflow velocity/early diastolic tissue velocity >14. Sleep apnea-hypopnea index, minimal oxygen saturation, sleep duration, and activity index (physical movement during sleep time, a potential parameter of poor sleep quality) were determined using apnomonitor and actigraphy findings, while heart rate variability was measured with a 24-hour active tracer device. Sixty-six of the patients developed diastolic dysfunction during the follow-up period, with a median time of 25 months. Kaplan–Meier analysis results revealed that those with sleep apnea classified as moderate (apnea-hypopnea index 15 to <30, $P<0.01$ versus none) or severe (apnea-hypopnea index ≥30, $P<0.01$ versus none), and with a high activity index (Q3 or Q4, $P<0.01$ versus Q1), but not short sleep duration ($P=0.27$) had a significantly greater risk for a diastolic dysfunction event. Results of multivariable Cox proportional hazards regression analysis indicated that moderate to severe sleep apnea after a follow-up period of 3 years (hazard ratio [HR], 9.26 [95% CI, 1.89–45.26], $P<0.01$) and high activity index (HR, 1.85 [95% CI, 1.01–3.39], $P=0.04$) were significantly and independently associated with future diastolic dysfunction. Moreover, significant association of high activity index with the outcome was not confounded by either minimal oxygen saturation or heart rate variability.

CONCLUSIONS: Sleep apnea and physical movement during sleep, but not sleep duration and autonomic nervous dysfunction, are independent important predictors for progression of left ventricular diastolic dysfunction.

Key Words: actigraphy ■ follow-up studies ■ humans ■ Kaplan–Meier estimate ■ oxygen saturation ■ prospective studies ■ sleep quality

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CLINICAL PERSPECTIVE

What Is New?

- This cohort study sheds light on the currently incompletely understood association between sleep problems and left ventricular diastolic dysfunction.
- An increased risk of progression of left ventricular diastolic dysfunction is revealed in subjects with moderate–severe sleep apnea or high nocturnal physical movements, but not with short sleep duration.
- Association of prevalent left ventricular diastolic dysfunction with sleep problems is not dependent on autonomic dysfunction and low oxygen saturation.

What Are the Clinical Implications?

- The current findings suggest that sleep apnea and nocturnal physical movement might be a potential modifiable risk factor for left ventricular diastolic dysfunction. This knowledge could improve the prediction and prevention of the disorders.

Nonstandard Abbreviation and Acronyms

AHI	apnea-hypopnea index
HRV	heart rate variability
HSCAA	Hyogo Sleep Cardio-Autonomic Atherosclerosis

Obstructive and central sleep apnea are conditions frequently observed in patients with heart failure,[1–3] while sleep disordered breathing has also been shown to co-occur with heart failure with preserved ejection fraction.[4–7] Subclinical left ventricular (LV) diastolic dysfunction often progresses to heart failure with preserved ejection fraction.[8,9] However, it is not clear whether sleep disordered breathing is a cause or consequence of heart failure. Moreover, only a limited number of studies have evaluated the association of sleep apnea with a subclinical alteration in LV diastolic function.[8,10,11] More importantly, although sleep apnea is a major cause of poor sleep quality, diverse pathophysiological conditions, such as sleep timing, short sleep duration, and physical movement during sleep, have also been shown to be associated with cardiovascular diseases[12–14] and congestive heart failure.[15] Presently, the significance of these various sleep disorders in regard to development of LV diastolic dysfunction has not been revealed.

This prospective investigation was conducted in association with the HSCAA (Hyogo Sleep Cardio-Autonomic Atherosclerosis) cohort study. The impact of sleep problems, including sleep apnea, short sleep duration, and physical movement during sleep time (a potential parameter of poor sleep quality), was examined to determine their role as predictors of progression of LV diastolic dysfunction. Furthermore, the potential involvement of intermittent hypoxia or cardiac autonomic function, determined as 24-hour and nighttime heart rate variability (HRV), was analyzed in regard to the association of sleep problems with progression of LV diastolic dysfunction.

METHODS

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Design and Participants

The HSCAA study is an ongoing cohort investigation instituted as a review of cardiometabolic risk factors, including sleep parameters, for elucidation of the clinical implications of cardiovascular and metabolic diseases.[16] Between October 1, 2010 and December 31, 2018, 976 patients with at least 1 cardiovascular risk factor, including obesity, hypertension, dyslipidemia, diabetes, and chronic kidney disease, were enrolled. Those with ischemic heart disease, moderate to severe valvular heart disease, hypertrophic cardiomyopathy, atrial fibrillation, heart failure, or cardiac diastolic dysfunction with transmitral early inflow velocity/early diastolic tissue velocity (E/e′) >14, assessed according to the recommendations of the American Society of Echocardiography and European Association of Cardiovascular Imaging[17] were excluded (n=240). One hundred ninety-six patients with missing cardiac ultrasonography baseline data were also excluded. Additionally, for the present analysis, the time of data cutoff was December 31, 2019. As a result, 88 with a follow-up period <12 months were excluded. Finally, 452 of those patients with a mean follow-up period of 34.7 months were enrolled in the present study (Figure 1). A large majority of the participants underwent apnomonitor (n=418), actigraphy (n=452), and/or HRV measurements (n=418) as examinations related to sleep apnea and minimal oxygen saturation, duration, physical movement, and cardiac autonomic function. Measurements with echocardiography were performed within 2 weeks of sleep assessment at the time of HSCAA study registration. The strength of this cohort study is that 3 measurements (apnomonitor, actigraphy, and HRV) are taken simultaneously at the time of enrollment. During the apnomonitor (1 night) and HRV measurement (48 hours), the patient wore an actigraphy device at the same time, resulting in monitoring of body movements for >48 hours. Following the measurement of cardiac

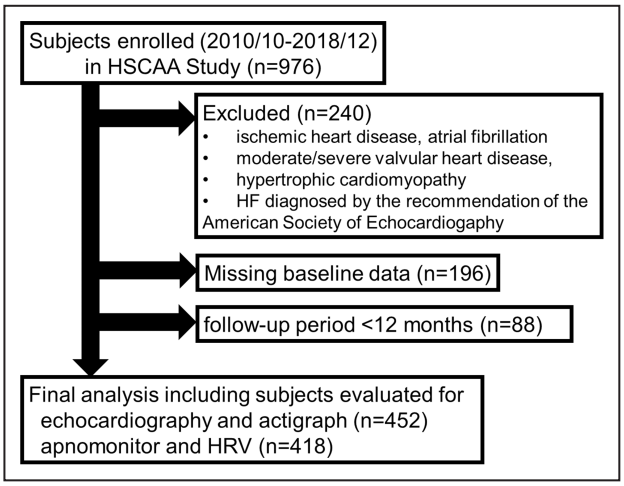

Figure 1. Flow of subject selection.
HF, heart failure; HRV, heart rate variability; and HSCAA, Hyogo Sleep Cardio-Autonomic Atherosclerosis.

function at enrollment, follow-up echocardiography was planned to be performed each year as much as possible (mandatory at 1, 3, and 5 years). The HSCAA study was approved by the institutional ethical committee of Hyogo College of Medicine (approval No. 2351) and informed written consent was obtained from each participant.

Number of Events Required for Statistical Analyses

During the initial registration of the present cohort and follow-up examinations, we preliminarily found that 10 of 100 subjects reached the primary outcome of LV diastolic dysfunction within the 3-year follow-up period. The present study was conducted to examine 7 to 8 clinical factors, including sleep parameters and autonomic function, using multivariable Cox proportional hazards regression analysis. Vittinghoff showed that 5 to 9 events per variable are sufficient for such analysis.[18] Thus we presumed that 35 to 72 outcomes would be required. Based on the preliminary findings, it was concluded that 350 to 720 subjects with a mean follow-up period of 3 years would be needed in our Cox proportional hazards regression analysis. After excluding inappropriate subjects as described above, 66 reached the outcome during the observation period, implying that both number of subjects and outcome in this study were sufficient for statistical analyses.

Assessment of Classic Cardiovascular Risk Factors

Body mass index (BMI) was calculated as weight in kilograms divided by square of height in meters (kg/m^2). Smoking status was based on self-reported cigarette smoking habit. Blood pressure (BP) was measured twice with patients in a sitting position after a deep breath, with the mean value used for analysis. Type 2 diabetes was diagnosed based on results showing fasting plasma glucose ≥126 mg/dL, causal plasma glucose ≥200 mg/dL, or 2-hour plasma glucose ≥200 mg/dL during a 75-g oral glucose tolerance test, or previous therapy for diabetes.[19] Hypertension was defined as systolic BP ≥140 mm Hg, diastolic BP ≥90 mm Hg, or treatment for hypertension, while dyslipidemia was defined based on results showing low-density lipoprotein cholesterol (≥140 mg/dL), high-density lipoprotein cholesterol (≤40 mg/dL), elevated triglyceride level (≥150 mg/dL), or treatment for dyslipidemia.

Assessment of LV Diastolic Function

LV function was evaluated by echocardiography as previously described.[20,21] Echocardiography examinations were performed with several different devices, including an IE-33, CX50 (Philips Healthcare, MA), Artida, Aplio300 (Toshiba Medical System Co., Tochigi, Japan), and F75 (Hitachi-Aloka Medical, Tokyo, Japan), by 6 experienced sonographers and essentially repeated every 1 to 2 years to determine changes in LV function. For consistency, the sonographers checked the inter- and intra-examiner differences every 6 months as regulated by standard operating procedure. The standard operating procedure was certified by the Japan Accreditation Board (International Organization for Standardization: ISO15189). The differences between the devices are also checked on every 6 months. The echocardiographic examinations were certified by the Japan Accreditation Board in 2016, and they were renewed in August 2020. LV diastolic function was also evaluated by echocardiography. LV ejection fraction (LVEF) was calculated using Teichholz's formula in patients without LV segmental asynergy or deformation. In those with LV segmental asynergy or deformation, apical 2- and 4-chamber 2-dimensional echo views and a modified version of Simpson's method were used.[20] Left ventricular mass index (LVMI) was calculated as follows: LVMI=1.04×{(LVDd+IVST+RWT)^3–(LVDd)^3–13.6}/1000/BSA, in which RWT (relative wall thickness)=IVST+PWT/LVDd, BSA (body surface area)=height (cm)$^{0.725}$×weight (kg)$^{0.425}$×0.7184 (LVDd: left ventricular diastolic dimension, IVST: intraventricular septal thickness, PWT: posterior wall thickness). Transmitral early inflow velocity (E-wave), late diastolic filling velocity (A-wave), and E-wave deceleration time (DcT) were determined using pulsed Doppler echocardiography.[17] Early diastolic tissue velocity (e′) was measured in the septal basal region using tissue Doppler imaging, then the E/e′ ratio was calculated to obtain estimated LV filling pressure. Left arterial volume was assessed using Simpson's biplane method and left atrial volume index was calculated by dividing

left arterial volume by body surface area. Among these parameters, the primary outcome was the time to the LV diastolic dysfunction, which was defined as the time from registration into this study until the first development of E/e′ >14 diagnosed at 1, 2, 3, 4, 5, and 6 years. The E/e′ >14 was previously recommended, because the value of 14 proved to be a good cutoff and is widely used worldwide.[17] If the outcome had not occurred, the follow-up was censored at the earliest of either the case of loss-to-follow-up (n=55) or the data-locked date (December 31, 2019). Additionally, %change in E/e′ per year (100×[last follow-up E/e′–baseline E/e′]/baseline E/e′/follow-up years) was also calculated to consider the annual effect.

Assessment of Sleep Apnea and Minimal Oxygen Saturation

To examine the presence of sleep apnea, an apnomonitor device (SAS-2100, Nihon Kohden, Tokyo, Japan, supplier: Teijin, Tokyo, Japan) was used to determine the Apnea-Hypopnea Index (AHI), as previously described.[16,22] This device measured nasal breathing pressure, percutaneous oxygen saturation, and snoring during sleep. The American Academy of Sleep Medicine Manual for the Scoring of Sleep and Associated Events ver. 2.1 was adopted as the analysis criteria for respiratory events as follows[23]: apnea was defined as the amplitude ratio to normal breathing 10% or less with air flow lasting ≥10 seconds, and hypopnea as the amplitude ratio to normal breathing 70% or less with air flow lasting ≥10 seconds, associated with a 4% decrease in oxygen saturation. AHI was calculated as the average number of apnea and hypopnea episodes per hour. Bedtime and wake-up time were judged from the actigraphy results that were simultaneously measured. Percutaneous oxygen saturation was also recorded using a pulse oximeter (SAS-2100, Nihon Kohden,Tokyo, Japan, supplier: Teijin, Tokyo, Japan).[24] The sampling frequency of oxygen saturation was 2 Hz. The following cases were excluded from the measurement as artifact, when the decrease was 3% or more per second, or the sensor was disconnected. Minimum oxygen saturation was calculated as the lowest during sleep. The effects of sleep apnea (none, AHI 0 to <5; mild, AHI 5 to <15; moderate, AHI 15 to <30; severe, AHI ≥30) and minimal oxygen saturation (%) were examined. Some of the subjects (n=230) were analyzed for subjective sleep apnea using the Epworth Sleepiness Scale with a cutoff of 11.[25]

Assessment of Sleep Duration and Physical Movement During Sleep Time

To examine sleep duration and quality, we used an actigraphy device (Ambulatory Monitoring, Inc., Ardsley, NY), which senses motion as acceleration, placed on the wrist of the nondominant arm, as previously described.[26–28] This device converts signals produced from an acceleration sensor into samples collected at the present frequency in hertz. “Acceleration” was judged based on the acceleration index,. which was calculated by the formula: acceleration index=2p-1, where p was the proportion of the interval required for 50% of the total activity in the interval to be completed. For example, for a 1-hour interval, if the activity total for the interval was 1000 and 500 counts occurred in the first 20 minutes of the interval, p would be 20/60 or 0.33. Doubling p and subtracting 1 scaled the index from –1 to +1. Thus, negative values represented slowing during the interval, 0 represented uniform distribution of activity during interval, and positive values represented acceleration during the interval. Moreover, the samples were totaled over a user-specified time sampling interval called a 1-minute “epoch.” Output from the actigraphy is in the form of activity “counts,” which are recorded by converting acceleration units over a given epoch. The present subjects wore the accelerometer for at least 2 consecutive days, which covered the period for measurements with apnomonitor and HRV, thus including at least 2 complete nights. To distinguish between sleep and awakening by this device, the Cole et al sleep/awakening determination algorithm was used.[29] Actigraphy results can be used to distinguish between sleep and wakefulness, and calculate total sleep time. A sleep diary was not necessarily requested of the subjects. Actigraphy results have been shown to have high levels of sensitivity and accuracy, whereas specificity is low as compared with polysomnography.[30] According to published recommendations for clinical use of actigraphy and previous reports,[31–33] activity time was calculated as the numbers of epochs with positive acceleration index values. Therefore, activity index was calculated as % epochs with positive acceleration index values during sleep. High activity index indicates more physical movement during sleep, which means poor sleep quality. A sleep time of <6 hours was defined as short sleep duration. Activity index was divided into quartiles. Some of the subjects (n=161) were analyzed for subjective sleep quality using the Pittsburgh Sleep Quality Index questionnaire, with a cutoff of 6.[34]

Assessment of Autonomic Nervous Function

To explore mechanisms underlying sleep problems associated with LV diastolic dysfunction, cardiac autonomic function was examined based on HRV together with sleep assessment. As previously reported, HRV is a noninvasive measurement of cardiac modulation based on autonomic nervous function.[16,35] In

the present study, an Active Tracer (AC-301A, Arm Electronics, Tokyo, Japan), which monitors surface ECG findings from the upper limbs via 3 channels, was used and the results obtained were analyzed using the MemCalc Chiram 3 system, version 2.0 (Suwa Trust, Tokyo, Japan). According to the recommendations for clinical use of HRV,[36] the SD of the NN (RR) interval as a time domain of HRV was calculated. Following power spectral density estimation, standard frequency-domain HRV values were calculated during sleep time as defined by simultaneous actigraphy measurements. The low-frequency domain was defined as between 0.04 and 0.15 Hz, and the high-frequency domain between 0.15 and 0.4 Hz, then the ratio of low- to high-frequency power (low-frequency domain/high-frequency domain) was determined.

Plasma Biochemical Parameters

Blood samples were obtained in the morning after an overnight fast and then quickly centrifuged to obtain plasma. Whole blood was used for hemoglobin A1c, EDTA plasma for glucose and lipids, and serum for other biochemical assays. Glucose was measured using a glucose oxidase method. Serum creatinine concentration was determined by an enzymatic method. Estimated glomerular filtration rate in each subject was calculated using an equation for Japanese subjects, as follows: estimated glomerular filtration rate (mL/min per 1.73 m^2)=194×age (years)$^{-0.287}$×S-creatinine$^{-1.094}$ (if female, ×0.739).

Statistical Analysis

To compare mean values among the groups, Student *t* test was used. A χ^2 test was used for comparisons of dichotomous variables. Times to E/e′ >14 were compared among the groups using Kaplan–Meier and Cox proportional hazards regression analyses. Numbers at risk at each point for Kaplan–Meier analyses include subjects except those with the outcome before the point, loss-to-follow-up beyond the first year, or the data locked date had been passed. The proportional hazards assumption was checked by Schoenfeld's test, which assesses the correlation between time and scaled residuals. If this assumption was violated for a variable, its interaction term with a step function for the follow-up time was added. The associations between %Change in E/e′ per year with sleep parameters were analyzed using multiple linear regression models. All statistical analyses were performed with EZR, version 1.52 (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R, version 4.02 (The R Foundation for Statistical Computing, Vienna, Austria).[37] All reported *P* values are 2-tailed and were considered to be statistically significant when <0.05.

RESULTS

Basal Clinical Characteristics in Subjects With or Without Future LV Diastolic Dysfunction

Among the 976 patients registered in the HSCAA cohort study, 452 were prospectively followed, including echocardiographic evaluations (Figure 1). The mean follow-up period was 34.7±18.0 (SD) months. Table 1 summarizes the basal clinical characteristics of the enrolled subjects, and presents comparisons among subjects with and without moderate to severe sleep apnea (AHI ≥15), short sleep duration (<6 hours), and high activity index (Q3, Q4). In total subjects, mean age was 58.9±12.7 years, with the prevalence of male sex at 49.5%, and presence of hypertension, dyslipidemia, and diabetes at 64.8%, 35.6%, and 57.7%, respectively. Among subjects with hypertension, 38 were not being treated. Subjects with moderate to severe sleep apnea (n=109, 26.0%) exhibited higher age and BMI, higher levels of systolic and diastolic BP, triacylglycerol, fasting plasma glucose, and HbA1c, lower levels of high-density lipoprotein cholesterol and estimated glomerular filtration rate, and higher prevalence of male, hypertension, dyslipidemia, and diabetes. Baseline E/e′ and LVMI, but not LVEF, were significantly worse in those with moderate to severe sleep apnea. %Change in E/e′ per year tended to be higher in moderate to severe sleep apnea. Additionally, future diastolic dysfunction (E/e′ >14) was more frequently observed in those with moderate to severe sleep apnea than in those without (28.4% versus 10.6%, *P*<0.01). Those with high activity index (Q3–4) exhibited higher age, higher levels of low-density lipoprotein cholesterol, fasting plasma glucose, and hemoglobin A1c, lower levels of high-density lipoprotein cholesterol, and higher prevalence of male, current smoker, hypertension, and diabetes. Although baseline E/e′ and %change in E/e′ per year were comparable between the groups, future diastolic dysfunction was more frequently observed in those with high activity index than those without (21.1% versus 7.9%, *P*<0.01). Those with short sleep duration exhibited higher BMI and triacylglycerol, whereas all echocardiographic parameters were comparable. Although %change in E/e′ per year was significantly higher in short duration, prevalence of future diastolic dysfunction was not significantly different between those with short and normal sleep duration. SD of the NN (RR) interval, a HRV parameter, was significantly lower in the groups with moderate to severe sleep apnea and high activity index as compared with the counterparts. SD of the NN (RR) interval was not significantly different between subjects with and without short sleep duration.

Table 1. Comparisons of Clinical Characteristics Among Sleep Parameters

Variables	Total	Apnea (n=418)		Duration (n=452)		Activity index (n=452)	
		None-mild	Moderate–severe	Normal	Short	Q1–2	Q3–4
n (%)	452	309	109	341	111	226	226
Age, y	58.9±12.7	58.1±12.4	62.1±12.6†	58.5±12.7	60.0±12.7	56.2±13.5	61.6±11.3†
Male, n (%)	224 (49.5)	139 (44.9)	72 (66.0) †	163 (47.8)	61 (54.9)	74 (32.7)	150 (66.3)†
Body mass index, kg/m^2	24.4±4.8	23.4±4.0	27.0±5.2†	24.1±4.6	25.2±5.3*	24.1±5.0	24.7±4.5
Current smoker, n (%)	108 (23.8)	79 (25.5)	27 (24.7)	84 (24.6)	24 (21.6)	42 (18.5)	66 (29.2)*
Systolic BP, mm Hg	124.8±15.4	122.4±14.4	131.5±16.1†	124.2±15.8	126.7±13.9	123.4±16.7	126.2±14.0
Diastolic BP, mm Hg	75.3±9.3	74.4±9.2	77.4±9.2†	75.0±9.5	76.1±8.8	74.5±10.0	76.0±8.5
Heart rate, beats/min	68.6±9.5	68.1±9.3	69.9±9.9	68.1±9.1	69.9±10.3	67.6±8.6	69.2±9.9
LDL-cholesterol, mg/dL	113.1±35.4	111.8±36.3	116.9±33.0	111.3±34.7	118.1±37.1	119.4±36.3	106.5±33.4†
HDL-cholesterol, mg/dL	55.3±17.3	56.6±17.6	50.8±15.0†	55.7±17.3	54.0±17.2	57.7±17.1	53.3±17.3*
Triacylglycerol, mg/dL	133.9±96.7	123.6±68.2	165.9±149.5†	128.5±73.6	151.5±147.6*	124.1±66.6	142.4±115.9
eGFR, mL/min per 1.73 m^2	83.8±23.9	85.6±22.9	78.6±26.1*	84.9±22.1	80.0±28.7	84.5±21.8	83.1±25.6
FPG, mg/dL	109.4±32.5	106.3±32.3	118.5±32.0†	109.6±33.7	108.6±28.2	102.9±25.8	114.9±36.4†
HbA1c, %	6.0±1.3	5.9±1.3	6.5±1.3†	6.0±1.3	6.1±1.2	5.7±1.0	6.3±1.5†
Hypertension, n (%)	293 (64.8)	181 (58.6)	87 (79.8)†	221 (64.8)	72 (64.9)	136 (60.2)	157 (69.5)*
Dyslipidemia, n (%)	261 (57.7)	168 (54.4)	82 (75.2)†	195 (57.2)	66 (59.5)	125 (55.3)	136 (60.2)
Diabetes mellitus, n (%)	161 (35.6)	96 (31.1)	60 (55.0)†	115 (33.7)	46 (41.4)	63 (27.9)	98 (43.4)†
LV function							
LVMI	97.8±21.4	95.0±19.8	105.7±24.6†	97.1±20.5	99.8±23.7	93.9±19.4	101.9±22.5†
LVEF, %	68.9±7.4	68.7±8.0	69.9±4.0	68.2±8.5	69.8±5.7	69.6±7.1	68.4±7.7
E, cm/s	61.3±15.2	62.2±15.8	58.3±13.4*	61.4±14.9	61.0±16.4	63.9±15.2	58.6±14.8†
A, cm/s	69.0±15.7	66.9±15.6	75.2±15.0†	68.6±15.4	70.2±16.6	67.6±16.2	70.5±15.1
E/A	0.9±0.3	0.9±0.3	0.7±0.2†	0.9±0.3	0.8±0.2	1.0±0.4	0.8±0.2†
DcT	210.2±46.3	206.7±43.6	219.1±50.7*	209.6±44.5	211.8±51.6	205.6±46.0	214.9±46.3*
e′	6.8±1.9	7.1±1.9	6.0±1.5†	6.8±1.9	6.8±1.9	7.2±1.9	6.4±1.7†
E/e′	9.2±2.2	8.9±2.2	10.0±2.1†	9.2±2.2	9.2±2.2	9.0±2.2	9.4±2.2
LAVI	27.9±7.7	27.8±7.8	28.0±7.7	28.1±7.6	26.9±8.3	27.7±7.4	28.5±8.2
Heart rate variability							
SDNN	122.0±36.9	124.2±38.0	111.5±31.3†	122.6±37.5	120.1±35.0	127.1±40.1	117.1±32.9†
HF	192.6±311.2	193.2±346.4	146.3±171.4	197.7±320.6	175.8±279.2	234.8±398.6	151.6±183.3†
LF/HF	6.1±29.4	6.0±31.7	4.4±2.2	5.7±30.2	7.2±27.0	3.6±2.1	8.4±41.2

(*Continued*)

Table 1. Continued

Variables	Total	Apnea (n=418)		Duration (n=452)		Activity index (n=452)	
		None-mild	Moderate–severe	Normal	Short	Q1–2	Q3–4
Sleep parameters							
AHI	10.8±11.6	5.3±4.0	26.3±12.1†	9.9±10.9	13.5±13.0†	8.4±10.6	13.0±12.0†
Minimal oxygen saturation, %	84.6±7.8	87.1±5.6	77.2±9.0†	84.9±7.6	83.9±8.5	86.4±6.4	83.1±8.6†
Sleep duration, h	7.5±2.4	7.6±2.2	6.9±2.4†	8.4±1.9	4.6±0.9†	8.0±2.5	7.0±2.0†
Activity index	33.8±16.4	32.7±15.2	40.0±18.6†	32.0±15.1	39.4±18.7†	21.3±7.9	46.3±12.7†
Future LV diastolic dysfunction, n (%)	66 (14.6)	33 (10.6)	31 (28.4) †	47 (13.7)	19 (17.1)	18 (7.9)	48 (21.1)†
%change of E/e′ per y	6.6±21.5	5.5±21.1	9.4±23.6	5.5±20.3	10.3±24.3*	5.9±18.9	7.4±23.7

Data are presented as the mean±SD for continuous variables, and n (%) for dichotomous variables. *P* values are shown for comparisons of the means of 2 groups (unrepeated *t* test) or percentages (χ^2 test). A, late diastolic filling velocity; AHI, Apnea-Hypopnea Index; BP, blood pressure; DcT, deceleration time; E/e′early inflow velocity/early diastolic tissue velocity; E, early inflow velocity; e′, early diastolic tissue velocity; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; HF, high-frequency domain; LAVI, left atrial volume index; LDL, low-density lipoprotein; LF/HF, low-frequency domain/high-frequency domain; LV, left ventricle; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; and SDNN, standard deviation of the NN (RR) interval.
*P<0.05, †P<0.01 (Apnea: vs none to mild; Duration: vs normal; Activity index: vs Q1–2).

Table 2 presents comparisons between subjects with (E/e′ >14, n=66) and without (≤14, n=386) future LV diastolic dysfunction. As compared with the outcome-free subjects, those with future diastolic dysfunction exhibited higher age, higher levels of systolic BP, fasting plasma glucose, and hemoglobin A1c, and higher prevalence of hypertension, dyslipidemia, and diabetes. In subjects with hypertension, the prevalence of subjects under treatment tended to be higher in subjects with future LV diastolic dysfunction than in those without (*P*=0.07), suggesting sustained hypertensive load may contribute to the LV diastolic dysfunction. Baseline LV diastolic parameters (A, E/A, e′, E/e′), but not E or DcT, were significantly worse in the future diastolic dysfunction group, while basal LVMI, LVEF, and left atrial volume index all tended to be higher in the future event group. Among the sleep parameters examined, AHI and activity index values, prevalence of moderate or severe sleep apnea, and high activity index (Q3 or Q4), but not short sleep duration, were significantly higher in the future diastolic dysfunction group. Epworth Sleepiness Scale and Pittsburgh Sleep Quality Index questionnaire results were not significantly different between the groups (Table S1). Basal HRV parameters were not significantly different between the groups, while minimal oxygen saturation was significantly lower in the future diastolic dysfunction group (Table 2). One-hundred five patients, 23.2% of all subjects, completed the assessments at 1, 3, and 5 years. In addition, there were no significant differences among characteristics, such as age, male sex, BMI, the prevalence of hypertension, dyslipidemia, and diabetes between the subjects who completed the assessments at 1, 3, and 5 years and the rest of the subjects (data not shown). The mean and range of measured E/e′ of each follow-up assessment were as follows: 9.7±2.8 (at 1 year), 9.9±2.8 (2 years), 9.9±2.7 (3 years), 10.3±3.0 (4 years), and 10.0±2.8 (5 years).

Time-to-E/e′ >14 Analyses

The median period before occurrence of LV diastolic dysfunction (n=66) was 25 months. The number of participants undergoing outcome assessment at each time point were as follows: baseline and 1 year: n=452, 2 years: n=345, 3 years: n=271, 4 years: n=174, and 5 years: n=105. As shown in Figure 2, Kaplan–Meier analysis findings indicated that subjects with moderate (log-rank test, *P*<0.01) or severe (*P*<0.01) sleep apnea, and high activity index (Q3, *P*=0.01; Q4, *P*<0.01) exhibited a significantly greater risk for decline in diastolic dysfunction as compared with the control group. Those with moderate to severe sleep apnea also showed a significantly greater risk for diastolic dysfunction (*P*<0.01), as compared with those with no (*P*<0.01) or no to mild sleep apnea (*P*<0.01).

Table 2. Comparisons of Clinical Characteristics Between Future Outcome-Free and Cardiac Diastolic Dysfunction (E/e′ >14)

Variables	Total (n=452)	E/e′≤14 (n=386)	E/e′>14 (n=66)	*P* value
Age, y	58.9±12.7	57.9±12.8	64.7±10.2	<0.01
Male, n (%)	224 (49.5)	192 (49.7)	32 (48.4)	0.95
Body mass index, kg/m^2	24.4±4.8	24.2±4.7	25.1±5.3	0.17
Current smoker, n (%)	108 (23.8)	92 (23.8)	16 (24.2)	1.00
Systolic BP, mm Hg	124.8±15.4	124.1±15.1	129.0±16.5	0.01
Diastolic BP, mm Hg	75.3±9.3	75.2±9.3	75.8±9.6	0.62
Heart rate, beats/min	68.6±9.5	72.5±10.0	72.3±11.2	0.89
LDL-cholesterol, mg/dL	113.1±35.4	112.0±35.7	123.7±31.5	0.14
HDL-cholesterol, mg/dL	55.3±17.3	55.1±17.3	56.7±17.1	0.50
Triacylglycerol, mg/dL	133.9±96.7	133.7±100.3	135.3±74.3	0.90
eGFR, mL/min per 1.73 m^2	83.8±23.9	83.8±24.0	83.4±23.5	0.88
Fasting plasma glucose, mg/dL	109.4±32.5	106.3±29.7	126.1±41.3	<0.01
HbA1c, %	6.0±1.3	5.9±1.2	6.7±1.6	<0.01
Hypertension, n (%)	293 (64.8)	242 (62.6)	51 (77.2)	0.03
Under treatment, n (%)	255 (56.4)	213 (55.1)	42 (63.6)	0.07
Dyslipidemia, n (%)	261 (57.7)	213 (55.1)	48 (72.7)	0.01
Diabetes, n (%)	161 (35.6)	125 (32.3)	36 (54.5)	<0.01
Baseline echocardiographic parameters				
LVMI	97.8±21.4	97.0±21.1	102.2±22.5	0.07
LVEF, %	68.9±7.4	68.4±7.6	74.0±2.6	0.08
E, cm/s	61.3±15.2	60.8±15.0	64.4±16.2	0.08
A, cm/s	69.0±15.7	67.4±15.4	78.3±14.4	<0.01
E/A	0.9±0.3	0.9±0.3	0.8±0.2	0.01
DcT	210.2±46.3	208.6±45.3	219.3±51.4	0.08
e′	6.8±1.9	7.0±1.9	5.9±1.3	<0.01
E/e′	9.2±2.2	8.9±2.0	10.9±2.0	<0.01
LAVI	27.9±7.7	27.5±7.5	30.2±8.9	0.07
Heart rate variability (n=418)				
SDNN	122.0±36.9	123.1±37.6	115.8±32.1	0.15
Q1, n (%)	104 (24.8)	86 (24.0)	18 (30.0)	0.45
HF	192.6±311.2	189.4±228.8	211.1±598.7	0.61
Q1, n (%)	104 (24.8)	84 (23.4)	20 (33.3)	0.18
LF/HF	6.1±29.4	6.4±31.9	4.0±2.1	0.55
Q4, n (%)	104 (24.8)	89 (24.8)	15 (25.0)	1.00
Sleep parameters				
AHI (n=418)	10.8±11.6	9.9±11.0	15.8±13.2	<0.01
Severity of sleep apnea				<0.01
No, n (%)	167 (40.0)	152 (43.0)	15 (23.4)	
Mild, n (%)	142 (34.0)	124 (35.0)	18 (28.1)	
Moderate, n (%)	78 (18.6)	55 (15.5)	23 (36.0)	
Severe, n (%)	31 (7.4)	23 (6.5)	8 (12.5)	
Minimal oxygen saturation, %	84.6±7.8	85.1±7.7	82.1±8.2	<0.01
Sleep duration, h	7.5±2.4	7.5±2.3	7.3±2.7	0.52
Short sleep duration, n (%)	111 (24.5)	92 (23.8)	19 (28.8)	0.47
Activity index	33.8±16.4	32.7±15.8	40.5±18.1	<0.01
Quartiles of activity index				<0.01
Q1, n (%)	113 (25.0)	105 (27.2)	8 (12.1)	

(*Continued*)

Table 2. Continued

Variables	Total (n=452)	E/e′≤14 (n=386)	E/e′>14 (n=66)	*P* value
Q2, n (%)	113 (25.0)	103 (26.6)	10 (15.1)	
Q3, n (%)	113 (25.0)	93 (24.1)	20 (30.3)	
Q4, n (%)	113 (25.0)	85 (22.1)	28 (42.5)	

Data are presented as the mean±SD for continuous variables, and n (%) for dichotomous variables. *P* values are shown for comparisons of the means of 2 groups (unrepeated *t* test) or percentages (χ^2 test). A, late diastolic filling velocity; AHI, Apnea-Hypopnea Index; BP, blood pressure; DcT, deceleration time; E, early inflow velocity; e′, early diastolic tissue velocity; E/A, early inflow velocity/late diastolic filling velocity; E/e′, early inflow velocity/early diastolic tissue velocity; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; HF, high-frequency domain; LAVI, left atrial volume index; LDL, low-density lipoprotein; LF/HF, low-frequency domain/high-frequency domain; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; and SDNN, standard deviation of the NN (RR) interval.

Similarly, subjects with a Q3 to 4 activity index result had a significantly higher risk when compared with those rated as Q1 ($P<0.01$) or Q1 to 2 ($P<0.01$). Those with short sleep duration did not show significant risk for this outcome.

To further evaluate the impact of sleep parameters and HRV for future diastolic dysfunction, univariable and multivariable Cox proportional hazard regression analyses were performed (Table 3). In these analyses, the interaction term of moderate to severe sleep apnea with a step function for the follow-up time (1 if the follow-up time for a subject exceeds 3 years and 0 otherwise) were added, because the coefficient for moderate to severe sleep apnea increased with time after 3 years, resulting in the violation of proportional hazards assumption. Consequently, interaction between moderate to severe sleep apnea and follow-up time >3 years, minimal oxygen saturation, and higher activity index (Q3–4), but not HRV were significantly associated with future diastolic dysfunction in univariable analysis. As for multivariable analyses, moderate to severe sleep apnea after 3 years (hazard ratio [HR], 10.26 [95% CI: 2.09–50.39], $P<0.01$), and higher activity index (Q3–4) (HR, 2.08 [95% CI, 1.15–3.73], $P=0.01$) showed a significant association with future diastolic dysfunction, as defined by E/e′ >14; whereas when continuous outcome was used for analyses, moderate to severe sleep apnea and short sleep duration were borderline significantly associated with %change of E/e′ per year in multiple linear regression analyses adjusted for covariates (Table S2). However, short sleep duration and HRV parameters were not significantly associated with diastolic dysfunction with either the univariable or multivariable Cox proportional hazards analysis. For the associations between sleep apnea or activity index with other future LV diastolic parameters (E/A >1, DcT >240, LVMI >110 for men, LVMI >100 for women),[38,39] moderate to severe sleep apnea and high activity index (Q3–4) were not significantly associated with all other LV diastolic parameters (Table S3). Epworth Sleepiness Scale and Pittsburgh Sleep Quality Index questionnaire results were also not significantly associated with future diastolic dysfunction (Table S4).

Analyses of Confounding Effects Among Sleep Parameters

Finally, we examined whether the significant association of high activity index with progression of LV diastolic dysfunction was dependent on sleep apnea, minimal oxygen saturation, or cardiac autonomic function using multivariable Cox proportional hazards analyses (Table 3). The association of high activity index with future diastolic dysfunction remained significant even when including interaction term between moderate to severe sleep apnea and follow-up time >3 years. That is, both moderate to severe sleep apnea after 3 years (HR, 9.26 [95% CI, 1.89–45.26], $P<0.01$), and activity index (HR, 1.85 [95% CI, 1.01–3.39], $P=0.04$) were significantly and independently associated with the outcome (combination 1). In contrast, multiple linear regression analyses were virtually unaffected by an addition of minimal oxygen saturation or HRV (combination 2 and 3). Moreover, univariable and multivariable Cox proportional hazards analyses demonstrated that moderate to severe sleep apnea exhibited a significantly larger effect in follow-up time >3 years compared with <3 years in subjects with a high activity index (Table S5).

DISCUSSION

This is the first known study to prospectively examine the impact of various aspects of sleep disorders on progression of LV diastolic dysfunction in patients without heart failure. The greatest strength of this cohort study is that 3 measurements (apnomonitor, actigraphy, and HRV) are taken simultaneously at the time of enrollment, which made it possible to examine their mutual relationship with future LV diastolic dysfunction. We found that poor sleep quality represented as moderate to severe sleep apnea and high physical movement during sleep time, but not short sleep duration, are important predictors for progression of LV diastolic dysfunction. Notably, the association of physical movement during sleep with future diastolic dysfunction remained significant in the multivariable analyses used after adjusting for sleep apnea. Thus,

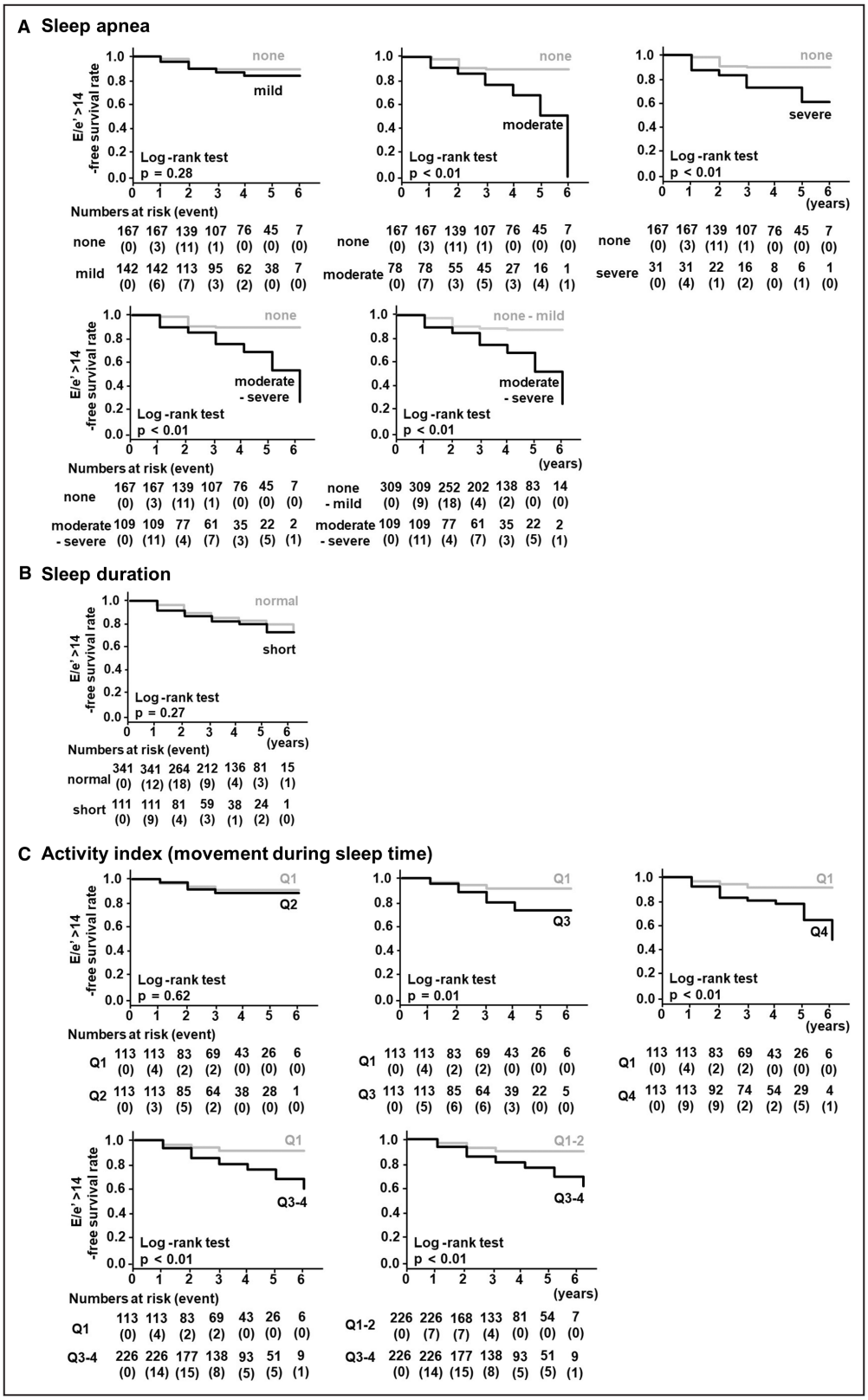

Figure 2. Kaplan–Meier analysis of effects of sleep problems on LV diastolic dysfunction (defined by E/e′ >14) in all subjects.

A, Effects of sleep apnea. None: AHI <5; mild: AHI 5 to <15; moderate: AHI 15 to <30; severe: AHI ≥30. **B**, Effects of short sleep duration (<6 vs ≥6 hours). **C**, Effects of high activity index. AHI indicates Apnea-Hypopnea Index; E/e′, early inflow velocity/early diastolic tissue velocity; LV, left ventricular; and Q, activity index quartile (Q4 the highest).

Table 3. Univariable and Multivariable Cox Proportional Hazards Analyses of Effects of Autonomic Function and Sleep Parameters on Future Cardiac Diastolic Dysfunction (E/e′ >14)

Variables	Univariable		Multivariable	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Heart rate variability				
SDNN (Q1) (vs Q2–4)	0.85 (0.49–1.47)	0.56	1.05 (0.59–1.86)	0.85
HF (Q1) (vs Q2–4)	0.70 (0.41–1.20)	0.20	0.89 (0.51–1.56)	0.69
LF/HF (Q4) (vs Q1–3)	1.07 (0.60–1.89)	0.80	1.20 (0.65–2.19)	0.55
Sleep parameters				
Moderate to severe sleep apnea (vs none to mild) for 0–3 y	2.24 (1.30–3.88)	<0.01	1.59 (0.84–2.99)	0.14
Moderate to severe sleep apnea (vs none to mild) for >3 y	19.57 (4.21–90.94)	<0.01	10.26 (2.09–50.39)	<0.01
Minimal oxygen saturation (per 5)	0.85 (0.75–0.97)	0.01	1.00 (0.85–1.18)	0.97
Short sleep duration (vs normal)	1.34 (0.79–2.30)	0.27	1.18 (0.68–2.05)	0.54
Activity index Q3–4 (vs Q1–2)	2.57 (1.50–4.43)	<0.01	2.08 (1.15–3.73)	0.01
Combination 1				
Moderate to severe sleep apnea (vs none to mild) for 0–3 y	…	…	1.47 (0.78–2.75)	0.22
Moderate to severe sleep apnea (vs none to mild) for >3 y	…	…	9.26 (1.89–45.26)	<0.01
Activity index Q3–4 (vs Q1–2)	…	…	1.85 (1.01–3.39)	0.04
Combination 2				
Minimal oxygen saturation (per 5)	…	…	1.01 (0.86–1.18)	0.88
Activity index, Q3–4 (vs Q1–2)	…	…	1.89 (1.02–3.50)	0.04
Combination 3				
SDNN, Q1 (vs Q2–4)	…	…	1.06 (0.59–1.89)	0.83
Activity index, Q3–4 (vs Q1–2)	…	…	2.13 (1.15–3.94)	0.01

The covariates in each multivariable Cox proportional hazards analysis included age, male sex, BMI, smoking history, presence of hypertension, dyslipidemia, and diabetes, and baseline E/e′. HRs for moderate to severe sleep apnea are presented separately for each time interval because of a violation of the proportional hazard assumption. BMI indicates body mass index; E/e′, early inflow velocity/early diastolic tissue velocity; HF, high-frequency domain; HR, hazard ratio; LF/HF, low-frequency domain/high-frequency domain; Q1-Q4, quartiles of activity index; and SDNN, standard deviation of the NN (RR) interval.

even though both sleep parameters could be deeply associated with poor sleep quality, physical movement during sleep is not completely equal to the presence of sleep apnea. Moreover, minimal oxygen saturation and autonomic nervous dysfunction do not appear to be the principal underlying mechanism for the effect of poor sleep quality.

Although sleep problems including obstructive sleep apnea have been demonstrated to be closely associated with increased incidence of heart failure with preserved ejection fraction,[5] there are a limited number of reports showing an association of sleep apnea with LV diastolic function, such as E/e′, in patients without heart failure. In a study of 206 patients with AHI ≥5/h and without cardiac disease, hypertension, or diabetes, AHI was found to be associated with higher E/e′.[40] Also, in 78 patients with obstructive sleep apnea without any comorbidities, disease severity showed a tendency to be associated with both LV diastolic dysfunction and abnormalities in regional systolic function because of myocardial deformation changes, in spite of normal LV ejection fraction.[26] In a recent report of 1506 adults enrolled in the Hispanic Community Health Study/Study of Latinos: ECHO-SOL Ancillary Study, greater AHI was demonstrated to have a cross-sectional association with subclinical markers of LV diastolic dysfunction (E/e′) and LVMI.[9] The present study is in line with those reports, while longitudinal analysis results further showed the impact of moderate to severe sleep apnea on future events related to LV diastolic dysfunction (E/e′ >14). In particular, this significant relationship was observed after 3 years. In other words, the effects of sleep apnea for LV diastolic function require a longer time. However, this was an observational study, and for various reasons, the number of participants undergoing outcome assessment decreased by about a quarter in 5 years. Although the effect of moderate to severe sleep apnea for LV diastolic function became significant after 3 years, it cannot be completely ruled out that this reduction in the number of participants may have biased the results. Therefore, it is necessary to validate the results with a design that allows longer observation periods in the future.

Sleep disorders are not solely represented by sleep apnea, because diverse pathophysiological conditions such as short sleep duration and impaired sleep quality represented as physical movement during sleep have been shown to be associated with cardiovascular disease[12–14] and congestive heart failure.[15] No known studies have examined the relationship between quantitatively measured sleep quality and LV diastolic function, except for cases of sleep disordered breathing. Additionally, no longitudinal study has been performed to investigate the impact of sleep problems on progression of LV diastolic dysfunction. The present study is the first to examine these important points, with actigraphy used to measure various sleep parameters together with measurement of AHI, longitudinal monitoring of LV diastolic function performed with echocardiography, and measurements of minimal oxygen saturation and cardiac autonomic function done to identify a potential underlying mechanism with an impact on sleep problems. For these analyses, potential confounding factors, including age, sex, hypertension, and diabetes, were taken into account with regard to the impact of accurate assessment of sleep problems on progression of LV diastolic dysfunction.

The present results showed that physical movement during sleep but not short sleep duration was significantly associated with LV diastolic dysfunction. A previous population cross-sectional study failed to find any association between sleep condition, measured by the Pittsburg Sleep Quality Index questionnaire, and LV diastolic dysfunction.[41] However, that discrepant result may have been because of study design (longitudinal versus cross-sectional) and different methods for measuring sleep (objective versus subjective). In the present study, some of the subjects were analyzed for subjective sleep apnea and sleep quality using the Epworth Sleepiness Scale (n=230) and Pittsburg Sleep Quality Index questionnaire (n=161), though no significant association of findings obtained with those methods and diastolic dysfunction was observed (Tables S1 and S4), which is in line with a prior report.[41] The differences in results between subjective and objective sleep evaluations suggest that subclinical sleep apnea or other sleep problems may have an impact on progression of LV diastolic function even in the absence of subjective symptoms. Detection of unaware sleep apnea or physical movement during sleep would be useful for revealing patients at high risk for future LV diastolic dysfunction in clinical settings. Moreover, the presence of moderate to severe sleep apnea was borderline significantly associated in multiple linear regression analyses adjusted for covariates. These results suggested that sleep apnea may have an effect on the annual change of E/e′.

Since activity index represents physical movement during sleep,[30] it may be a potential parameter of sleep quality.[42] However, at present it is not clear what this measurement of activity during the sleep period using actigraphy actually represents. In the present cohort, a significant but weak correlation (r=0.246, P<0.01) was observed between AHI and activity index. In contrast, the association of high activity index with outcome remained significant even after adjustment for moderate to severe sleep apnea and minimal oxygen saturation (Table 3). Moreover, Cox proportional analyses showed that in the subgroup with a high activity index, the presence of moderate to severe sleep apnea exhibited a significant additive impact on progression of diastolic dysfunction (Table S5). Thus, physical movement during sleep is not equal to the presence of sleep apnea and other sleep problems may be involved, such as periodic limb movements[43] and REM sleep disorders.[44] Importantly, sleep apnea and physical movement during sleep time are independent predictors for progression of LV diastolic dysfunction.

Autonomic nervous imbalance has also been speculated to have potential to mediate the effect of sleep on diastolic dysfunction. In our recent study, higher levels of autonomic functions were significantly associated with the parameter of better cardiac diastolic function (E/A), with that association independent of diabetes, BMI, visceral adiposity, and insulin resistance index.[21] Thus, reduced autonomic function may be a potential predictor for decreased cardiac diastolic function in patients with metabolic disorders and physical movement during sleep. Although future studies are necessary, the present results indicate that the impact of physical movement during sleep on LV diastolic dysfunction is not explained solely by HRV, a marker of autonomic dysfunction.

This study has several limitations. First and foremost, we only used E/e′ >14 as a criterion for diastolic dysfunction. Since we enrolled patients without heart failure and excluding the majority of heart diseases including those with E/e′ >14, the stronger end point, heart failure hospitalization could not be set as the primary outcome. To evaluate diastolic dysfunction, recent guidelines recommended using a combination of parameters including E/e′, e′, tricuspid regurgitant velocity, and left atrial volume index.[17] Since tricuspid regurgitant velocity cannot be measured in some cases, and left atrial volume index is an index to see the long-term load, we chose to use E/e′ for the outcome in this prospective cohort study. In the present study, we failed to see significant associations of other potential LV diastolic parameters including E/A, DcT, and LVMI with sleep parameters. Only when DcT >240 was used as a criterion for future LV diastolic dysfunction, the high activity index tended to be associated with future LV diastolic dysfunction. E/A and LVMI are rather known to be indicators associated with cardiac organic changes, and may be more suitable for medium- to long-term than short-term markers.

Second, echocardiography measurements were the main end point and the point of interest of this study, though that method can produce varying results depending on various factors, such as examiner ability, preload, subject age, and others, which may have effects on reproducibility. Indeed, 6 different examiners performed the echocardiographic analyses; thus we could not completely negate the impact of potential interexaminer variations or differences in preload regarding these measurements. Care is needed in regard to interpreting the results. For LVEF, despite the potential for yielding inaccurate results, our institution regularly uses 2 different methods to calculate 1 mean value (linear Teichholz method for patients without LV segmental asynergy and modified Simpson's method for those with asynergy). Although LVEF values were not the major outcome examined in this study, caution is needed when interpreting those analytic results.

Third, the collection rate for the sleep problems questionnaire from the subjects was not good. Even though the results were similar to previous reports, caution is required when interpreting differences between subjective and objective sleep parameters, particularly regarding the impact of asymptomatic sleep problems.

Fourth, the impact of hypertension or BP as a risk factor for diastolic dysfunction may not have been accurately assessed in this study. Although BP was measured twice with the subject in a sitting position, a 1-time measurement is prone to be misleading because of white coat hypertension and other factors.

Fifth, even though the number of subjects was adequate to examine associations among factors, the cohort only contains a single Japanese population; thus the results may not be generalized, particularly with regard to ethnicity.

Finally, there may have been misdiagnosed patients in the no sleep apnea group, since AHI values measured by a Type 4 polysomnography monitor tend to be lower than those by a Type 2 device. Moreover, we could not distinguish between central and obstructive sleep apnea by the apnomonitor device used in this study. Although the present study does not include subjects with apparent heart failure and it is unlikely that substantial numbers of patients with central apnea would be included, impacts of including patients with central apnea cannot be completely denied. Nevertheless, we consider that the present findings provide important initial information to unveil pathophysiological mechanisms related to sleep problems for progression of LV diastolic dysfunction.

CONCLUSIONS

Sleep apnea and physical movement during sleep, but not short sleep duration, are independent predictors for progression of LV diastolic dysfunction.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Tables S1–S5

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SUPPLEMENTAL MATERIAL

Table S1. Comparisons of Epworth Sleepiness Scale and Pittsburg Sleep Quality Index questionnaire results between future outcome-free and cardiac diastolic dysfunction (E/e' >14) subjects

Variables	Total	E/e' ≤14	E/e' >14	p
Epworth Sleepiness Scale, n	230	195	35	
≥11, n (%)	14 (6.0)	12 (6.1)	2 (5.7)	1.00
Pittsburg Sleep Quality Index, n	161	136	25	
≥6, n (%)	70 (43.4)	61 (44.8)	9 (36)	0.54

Data are presented as n (%) for dichotomous variables. P values are shown for comparisons of percentages (Chi-square test).

Table S2. Multiple linear regression analyses of sleep parameters for %change of E/e' per year.

Variables	β (SE)	p
Sleep apnea (moderate to severe =1, none to mild =0)	4.64 (2.60)	0.07
Minimal oxygen saturation (per 5)	-0.30 (0.77)	0.69
Sleep duration (short =1, normal =0)	3.79 (2.23)	0.08
Activity index (Q3 to 4 =1, Q1 to 2 =0)	1.54 (2.07)	0.45

*The covariates in each multiple linear regression analysis included age, male sex, BMI, smoking history, presence of hypertension, dyslipidemia and diabetes mellitus, and baseline E/e'.

SE: standard error

Table S3. Multivariable Cox proportional hazards analyses of AHI and activity index for cardiac diastolic function parameters [E/A >1, DcT >240, LVMI (male >110, female >100)]

	E/A >1		DcT >240		Male: LVMI >110 Female: LVMI >100	
Variables	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
Moderate to severe sleep apnea (vs. none to mild)	1.23 (0.66-2.30)	0.50	1.03 (0.64-1.65)	0.88	1.35 (0.68-2.69)	0.38
Activity index, Q3-4 (vs. Q1-2)	0.97 (0.55-1.70)	0.92	1.44 (0.95-2.19)	0.08	1.27 (0.65-2.47)	0.48

The covariates in each multivariable Cox proportional hazards analyses included age, male sex, BMI, smoking history, the presence of hypertension, dyslipidemia and diabetes mellitus, and baseline E/e'.

HR: hazard ratio, CI: confidence interval

Table S4. Univariable and multivariable Cox proportional hazards analyses of Epworth Sleepiness Scale and Pittsburg Sleep Quality Index questionnaire for cardiac diastolic dysfunction (E/e' >14)

	Univariable		Multivariable*	
Variables	HR (95% CI)	p	HR (95% CI)	p
Epworth Sleepiness Scale (per 1)	0.93 (0.82-1.04)	0.24	0.92 (0.81-1.05)	0.24
≥11 (yes=1, no=0)	0.88 (0.21-3.70)	0.87	1.07 (0.18-6.35)	0.93
Pittsburg Sleep Quality Index (per 1)	1.01 (0.90-1.14)	0.75	1.02 (0.92-1.14)	0.61
≥6 (yes=1, no=0)	0.67 (0.29-1.52)	0.34	0.92 (0.38-2.26)	0.86

*The covariates in each multivariable Cox proportional hazards analyses included age, male sex, BMI, smoking history, presence of hypertension, dyslipidemia and diabetes mellitus, and baseline E/e'.

HR: hazard ratio, CI: confidence interval

Table S5. Univariable and multivariable Cox proportional hazards analyses of moderate to severe sleep apnea for cardiac diastolic dysfunction (E/e' >14) in subjects with high activity index (Q3-4)

	Univariable		Multivariable*	
Variables	HR (95% CI)	p	HR (95% CI)	p
Moderate to severe sleep apnea (vs. none to mild) for 0-3 years	1.18 (0.60-2.33)	0.62	1.04 (0.49-2.19)	0.91
Moderate to severe sleep apnea (vs. none to mild) for > 3 years	11.77 (2.47-55.98)	<0.01	7.29 (1.56-37.10)	0.01

*The covariates in multivariable Cox proportional hazards analyses included age, male sex, BMI, smoking history, presence of hypertension, dyslipidemia and diabetes mellitus, and baseline E/e'.

HR: hazard ratio, CI: confidence interval