Sleep Apnea and Diabetes Predict Progression of Cardiac Diastolic Dysfunction in Pre-heart Failure Patients: a Prospective Cohort HSCAA Study

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Original investigation

Abstract

[Background] Sleep apnea, a common co-morbid condition of diabetes, has been shown to be associated with established heart failure. However, its role in association of the presence of diabetes in the progression of cardiac diastolic function in pre-heart failure phase is not known. This prospective study is to longitudinally examine the predictive value of sleep apnea and diabetes on progression of left ventricular (LV) diastolic dysfunction in patients without heart disease.

[Methods] Among 976 patients registered in HSCAA prospective cohort study, 517 without heart disease (175 type 2 diabetes, 342 non-diabetes) were followed with repeated echocardiography in every 1-3 years for a mean 34.7 months. LV diastolic dysfunction was determined by transmitral early inflow velocity/early diastolic tissue velocity (E/e´) >14. Annual change in E/e′ was calculated by using the slope of the linear regression line calculated from at least 3 echocardiographic measurements. Sleep apnea was determined by an apnomonitor device in conjunction with percutaneous oxygen saturation, and apnea hypopnea index (AHI) was calculated.

[Results] Kaplan-Meier analyses revealed that subjects with diabetes or sleep apnea had a significantly (p<0.01) greater risk for LV diastolic dysfunction, with hazards ratio of 2.21 (1.41-3.47) and 2.23 (1.40-3.55), respectively. Subjects with sleep apnea exhibited significantly higher risk for LV diastolic dysfunction in non-diabetic subjects (p<0.01), while showed tendency of higher risk in diabetic subjects (p=0.10). The annual change of E/e′ was significantly and independently associated with both diabetes (β=0.278, p<0.01) and AHI (β=0.138, p<0.01). Finally, ROC analyses revealed that addition of AHI and diabetes to classical risk factors best predicted individuals with fast progression of diastolic dysfunction (annual change of E/e′ >1.0) with an AUC of 0.81.

[Conclusions] In patients without heart disease, sleep apnea is an important predictor for progression of LV diastolic dysfunction. Its association is partly confounded, but still independent of the presence of diabetes.

Introduction

Diabetic cardiomyopathy is defined by abnormal myocardial structure and performance in the absence of coronary artery disease, hypertensive cardiomyopathy, and valvular heart disease, in individuals with diabetes mellitus [1]. In early stages, diabetic cardiomyopathy exhibits subclinical structural and functional abnormalities, including left ventricular (LV) hypertrophy and fibrosis, and these pathophysiological changes are associated with subclinical diastolic dysfunction that often progresses to heart failure (HF) with preserved ejection fraction (HFpEF) [2, 3].

In addition to hyperglycemic burden, the risk of HFpEF has been shown to sharply increase in the presence of other risk factors [4]. Obstructive sleep apnea, a frequent comorbid condition noted in diabetic patients [5], is commonly observed in association with heart failure and may be attributable to worsening of the disease [6]. Sleep problems including sleep apnea have also been shown to be closely

associated with increased incidence of HFpEF [7]. Thus, mutual interactions of diabetes and sleep apnea may contribute to progression of diabetes cardiomyopathy, particularly diastolic dysfunction. However, integrated predictors including these specific factors have yet to be investigated, which is important for demonstrating progression of left ventricular diastolic dysfunction in pre-heart failure patients.

In this prospective cohort study, we examined the impact of sleep apnea and diabetes as predictors of progression of cardiac diastolic dysfunction in pre-heart failure patients registered in the Hyogo Sleep Cardio-Autonomic Atherosclerosis (HSCAA) study.

Methods

DESIGN AND STUDY PARTICIPANTS

The HSCAA study is an ongoing single center cohort performed for a review of cardio-metabolic risk factors, including quantitatively measured sleep parameters, for elucidation of the clinical implications of cardiovascular and metabolic diseases [8]. From October 2010 to December 2018, 976 patients with at least 1 cardiovascular risk factor, including obesity, hypertension, dyslipidemia, diabetes mellitus, and chronic kidney diseases , were enrolled in that cohort study. Patients (n=240) with ischemic heart disease, moderate to severe valvular heart disease, hypertrophic cardiomyopathy, atrial fibrillation, HF, or cardiac diastolic dysfunction [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 [9] were excluded. After excluding another 131 with missing baseline data for cardiac ultrasonography and 88 with a follow-up period <12 months, 517 of those patients were enrolled in the present study (**Figure 1**). A large majority of the participants (n=462) underwent apnomonitor monitoring for a review of sleep apnea. The HSCAA study was approved by an appropriate institutional ethical committee (approval No. 2351) and informed written consent was obtained from each participant.

ASSESSMENT OF CLASSICAL CARDIOVASCULAR RISK FACTORS

Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters (kg/m^2). Smoking status was based on self-reported cigarette smoking habit. Blood pressure and pulse rate were measured twice in a sitting position after a deep breath, with the mean values 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 [10]. Hypertension was defined as systolic BP ≥140 mmHg, diastolic BP ≥90 mmHg, or treatment for hypertension. Dyslipidemia was defined based on results showing low density lipoprotein (LDL) cholesterol (≥140 mg/dl), high density lipoprotein (HDL) 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 [11]. Examinations were repeated every 1-3 years to determine changes in LV function. To measure LV ejection fraction (LVEF), we used the modified Simpson's method for patients with LV segmental asynergy or deformation, and Teichholz's formula for patients without LV asynergy or deformation. LV 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 [9]. Early diastolic tissue velocity (e´) was measured in the septal basal region using tissue Doppler imaging and the E/e' ratio was then calculated to obtain estimated LV filling pressure. Among these parameters, E/e' >14 was evaluated as LV diastolic dysfunction as recommended [9]. Annual change in E/e' was estimated by using the slope (b) of the linear regression line calculated from at least 3 echocardiographic measurements with the following equation: E/e' = a + b x months.

ASSESSMENT OF SLEEP APNEA

To examine the presence of sleep apnea, we used an apnomonitor device (SAS-2100$^®$, Teijin, Tokyo, Japan) to determine apnea hypopnea index (AHI), as previously described [8]. Percutaneous oxygen saturation was recorded using a pulse oximeter. Apnea was defined as complete cessation of air flow lasting ≥10 seconds, hypopnea as a ≥50% reduction in air flow lasting ≥10 seconds associated with a 4% decrease in oxygen saturation, and AHI as the average number of apnea and hypopnea episodes per hour.

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. Insulin was determined by chemiluminesce   enzyme   immunoassay results and serum creatinine concentration with an enzymatic method. Estimated glomerular filtration rate (eGFR) in each subject was calculated using an equation for Japanese subjects, as follows: eGFR (ml/min/1.73 m^2) = 194×age(years)$^{-0.287}$×S-creatinine$^{-1.094}$ (if female, ×0.739).

STATISTICAL ANALYSES

To compare mean and median values among the groups, Student's t-test and a Mann-Whitney test were used. A chi-square test was used for comparisons for dichotomous variables. To analyze associations between factors, parameters with skewed distribution were natural logarithm-transformed (ln) to normalize skewed distribution. For this study, the primary outcome was LV diastolic dysfunction, which as defined as E/e' >14, as previously recommended [9]. Outcome rates for the groups were compared

using Kaplan-Meier analysis and a log-rank test. Prognostic variables for primary outcome were examined using a Cox proportional hazards regression model. Predictors for annual changes of E/e′ were examined using Pearson's correlation coefficient and logistic regression analysis. To compare each logistic model in aggregate, we constructed receiver operating characteristic (ROC) curves and determined the area under the curve (AUC). All statistical analyses were performed using the Statistical Package for Social Sciences software package (PASW Statistics version 18.0). All reported p values are 2-tailed and were considered statistically significant at <0.05.

Results

Subjects

Among 976 patients registered in the HSCAA cohort study, 517 (342 non-diabetic, 175 diabetic) were prospectively followed, including echocardiographic evaluations repeated every 1-3 years (**Figure 1**). The mean follow-up period was 34.7 ± 18.0 (standard deviation) months. **Table 1** summarizes basal clinical characteristics of the enrolled subjects who were categorized into the diabetic and non-diabetic groups. As compared with the non-diabetic subjects, the diabetic group exhibited higher age, male prevalence, higher body mass index, more current smokers, higher systolic BP, lower LDL- and HDL-cholesterol, higher fasting plasma glucose and HbA1c, and a higher number with comorbidity of dyslipidemia, more likely to use statin and renin-angiotensin system inhibitors. AHI and prevalence of a score >10 were significantly higher in the diabetic group (**Table 1**).

Predictors of events of cardiac diastolic dysfunction (E/e′>14)

As shown in **Table 1**, the majority of parameters examined for LV diastolic function (A wave, E/A, e′, E/e′) were significantly worse in the diabetic group. LVEF was identical between the groups, while LVMI tended to be higher in the diabetic than non-diabetic subjects. During the follow-up period, cardiac diastolic dysfunction (E/e′>14) events were more frequently observed in the diabetic subjects (**Table 1**) and Kaplan-Meier analysis results revealed that the event (E/e′ >14)-free survival rate was also significantly lower in that group (**Figure 2A**) with hazards ratio (HR) of 2.21 (1.41-3.47 95% confidence interval). In all subjects, those with sleep apnea (AHI >10) (p<0.01) with HR 2.23 (1.40-3.55) exhibited higher events of cardiac diastolic dysfunction as compared to subjects without that condition (**Figure 2A**). In the non-diabetic group, subjects with sleep apnea had a significantly greater number of diastolic dysfunction events (**Figure 2B**), while in the diabetic group, sleep apnea tended to be associated with higher rate of diastolic dysfunction events (**Figure 2C**).

Predictors of annual change in E/e′

Baseline E/e′ markedly affected events of cardiac diastolic dysfunction (HR 1.36, 95%CI 1.25-1.48), thus we analyzed clinical factors associated with annual change in E/e′ based on results of multiple (≥3 times) echocardiographic measurements. In accordance with the results shown in **Figure 2**, diabetes and AHI were significantly and positively associated with annual change in E/e′ in all subjects (**Table 2A**).

Baseline E/e' was strongly and inversely associated with annual E/e' change, suggesting blunted E/e' progression in patients with already high E/e'. Multiple linear regression analyses in all subjects showed that both diabetes and AHI were significantly independent and positive predictors of annual progression of E/e' (**Table 2B**).

To further examine the impact of diabetes and AHI on prediction of diastolic dysfunction progression, we performed multiple logistic regression analyses to predict fast progression of diastolic dysfunction, which was determined by annual change in E/e' >1.0. As shown in **Figure 3**, 14.4% of all subjects exhibited an annual change in E/e' >1.0, while the percentage was 22.7% in the diabetic and 9.7% in the non-diabetic group. As seen in the upper panel of **Figure 4**, ROC analysis revealed that addition of diabetes to basal models including age, gender, BMI, hypertension, dyslipidemia and baseline E/e' resulted in a significant (p=0.04) increase in AUC from 0.73 to 0.77, whereas addition of AHI (0.75) instead of diabetes to the basal model (0.73) did not significantly change AUC. When AHI was further added to basal + diabetes, AUC was improved up to the highest value of 0.81, significantly higher than that for the basal model (p<0.01) but not reaching statistically significant than that for basal + diabetes (p=0.28).

Discussion

This is the first study to examine the impact of sleep apnea as well as diabetes on progression of cardiac diastolic dysfunction in patients without heart failure. Patients with asymptomatic HF based on cardiac ultrasonography findings together with the index of E/e' >14 were carefully excluded from analyses. We found that in addition to the presence of diabetes, sleep apnea was significantly associated with worsening of LV diastolic function. Moreover, addition of sleep apnea index to diabetes resulted in the best prediction of subjects with rapid progression of diastolic dysfunction.

Sleep apnea as predictor of progression of cardiac diastolic dysfunction

Although sleep problems including obstructive sleep apnea have been demonstrated to be closely associated with increased incidence of HFpEF [7], reports showing an association of sleep apnea with LV diastolic function, such as E/e', in patients without HF are limited. In 206 patients with AHI ≥ 5/h and without cardiac disease, hypertension, or diabetes, AHI was shown to be associated with higher E/e' [12]. Also, in 78 patients with obstructive sleep apnea without any comorbidities, disease severity tended to be associated with both LV diastolic dysfunction and abnormalities in regional systolic function with myocardial deformation changes, in spite of normal LV ejection fraction [13]. In a recent report of 1506 adults in the Hispanic Community Health Study/Study of Latinos ECHO-SOL Ancillary Study, greater AHI was associated cross-sectionally with subclinical markers of LV diastolic dysfunction (E/e') and LVMI [14].

To the best of our knowledge, no longitudinal studies that examined the predictive value of sleep apnea on progression of cardiac diastolic dysfunction are available. In our study, sleep apnea was conclusively shown to be a significant predictor of progression of LV diastolic dysfunction based on multiple results; (1) patients with AHI >10 exhibited significantly greater numbers of diastolic dysfunction events (E/e'

>14), (2) AHI value was significantly and independently associated with annual progression of E/e′, and (3) addition of AHI to classical risk factors including diabetes in ROC analyses best predicted an individual with annual worsening of E/e′ >1.0. Interestingly, AHI was not significantly associated with annual changes in LVMI in all, non-diabetic and diabetic subjects (data not shown), implicating discrete underlying mechanisms involved in the progression of LV hypertrophy and diastolic dysfunction. In addition to diabetes, we consider that sleep apnea is a promising potential predictor for progression of LV diastolic dysfunction.

Diabetes and cardiac diastolic dysfunction

LV diastolic dysfunction is an important cause of HFpEF in individuals with diabetes and epidemiologic studies have demonstrated the presence of diastolic dysfunction in type 2 diabetes patients [15, 16]. In our recent study, diabetic patients exhibited higher E/e′ as compared to those with either normal or impaired glucose tolerance [11]. Among the available parameters of LV diastolic function, E/e' determined with a non-invasive approach has long been used to assess LV filling pressure in various patient populations [17]. In type 2 diabetes patients, E/e' has been shown to provide independent and incremental prognostic information for predicting cardiovascular morbidity and mortality [18]. Thus, elevated E/e' can be a useful parameter of early diastolic impairment in diabetic patients, potentially foretelling diabetic cardiomyopathy. Longitudinal studies of diabetic patients are needed to better understand and predict this subtle slow onset of diabetic cardiomyopathy, though such evaluations of changes in continuous parameters of LV diastolic function over time in patients without clinically diagnosed HF are scant. Previously, the presence of diabetes was shown to be associated with changes in several cardiac parameters over an 8-year period, including LVEF by -2.98%, LV mass index by +5.86 g, and E/e' by +1.64 [19]. In that study, LV systolic function and LV mass deteriorated similarly along with E/e′ during the 8-year follow-up period. In the present study, frequent measurements of cardiac function showed that diabetic subjects exhibited significantly greater annual changes in E/e′ than non-diabetic subjects, whereas LVEF did not show obvious changes. Also, baseline LVMI was not significantly different between the diabetes and non-diabetes groups. On the other hand, annual changes in LVMI were significantly greater in our diabetic subjects, although these changes were not as marked as the changes in E/e′ (data not shown). Moreover, baseline LVMI was not significantly associated with annual change in E/e′ in all subjects (r=0.20, P=0.73), suggesting that LV hypertrophy may not be essential for the progression of E/e′. Future kinetics analyses to compare the progression of E/e′ and LVMI in diabetic patients are warranted to clarify the pathological sequence of diabetic cardiomyopathy.

Potential mediators of the association between diabetes and cardiac diastolic dysfunction have yet to be well clarified. A previous study showed that even in a population with normal glucose tolerance, a parameter of diastolic dysfunction was inversely associated with HbA1c [20]. Although variations of HbA1c may be serve as predictors of changes in E/e′ [21], in the present cohort, HbA1c was not a major predictor of annual change in E/e′. In a prior cross-sectional study, glycemic variability, determined by continuous glucose monitoring, was also shown to be associated with left ventricular diastolic function in type 2 diabetes mellitus subjects [22]. Population-based cohort study found that the presence of

hyperinsulinemia at the baseline predicted worsening of LV diastolic dysfunction [23]. In the present study, plasma insulin was not associated with annual change in E/e' in all subjects (r=0040, p=0.53), or after dividing them into diabetic (r=0.184, p=0.11) and non-diabetic (r=0.001, p=0.99) groups. As previously shown by our groups [24, 25], visceral fat adiposity, or an adipocytokine such as leptin may be attributed to diastolic dysfunction in diabetes. Pericardial fat accumulation may also contribute to cardiac diastolic dysfunction in diabetes [26]. Another potential mediator includes presence of diabetic microangiopathy, E/e' shown to be worsened in groups classified based on albuminuria severity [27]. However, in our cohort, the presence of diabetic microangiopathy regardless of type (retinopathy, neuropathy, nephropathy) was not significantly associated with annual changes in E/e' (data not shown). Anti-diabetic agents such as the sodium glucose cotransporter type 2 (SGLT2) inhibitors may potentially affect the progression of LV diastolic dysfunction [28], which were recently shown to reduce worsening heart failure or death from cardiovascular causes in patients with heart failure [29]. Less than 5% of the present cohort was treated with SGLT2 inhibitors during registration period. Future surveys regarding anti-diabetic reagents given during follow-up may unveil their potential associations with progression of LV diastolic dysfunction.

Study Limitations

This study has several limitations. First, the results of the sub-group analyses of diabetes and non-diabetes must be interpreted carefully, due to the number of subjects, potentially resulting in statistical type 1 and 2 errors. Second, not all items used as diagnostic criteria for cardiac diastolic dysfunction could be evaluated, particularly atrial volume. In several studies, E/e' has been found to lack accuracy for reflecting LV filling pressure in patients with preserved ejection fraction. Nevertheless, we consider that our results provide important initial information to unveil the pathophysiological mechanisms related to HFpEF and diabetic cardiomyopathy.

Conclusions

In patients without heart disease, sleep apnea is an important predictor for progression of LV diastolic dysfunction. Its association is partly confounded, but still independent of the presence of diabetes.

Abbreviations

AHI: apnea hypopnea index

AUC: area under the curve

A-wave: late diastolic filling velocity

BMI: Body mass index

DcT: E-wave deceleration time

eGFR: Estimated glomerular filtration rate

E-wave: Transmitral early inflow velocity

e´: Early diastolic tissue velocity

HDL high density lipoprotein

HF: heart failure

HFpEF: heart failure with preserved ejection fraction

HSCAA: Hyogo Sleep Cardio-Autonomic Atherosclerosis

LDL: low density lipoprotein

LV: left ventricular

LVEF: LV ejection fraction

LVMI: LV mass index

ROC: receiver operating characteristic

Declarations

Ethics approval and consent to participate: The HSCAA study was approved by an appropriate institutional ethical committee (approval No. 2351) and informed written consent was obtained from each participant.

Consent for publication: not applicable

Available of data and materials: The data that support the findings of this study are available from Hyogo College of Medicine. Data are available from the authors upon reasonable request and with permission of the Hyogo College of Medicine.

Competing interests: non to declare for all authors

Authors' contributions. M.K. and H.K. contributed to conception and design, Y.K., A.M., M.K., T.D., M.K.-H., K.K.-H., A.M., K.K., Y.K., and T.S. contributed to analysis and interpretation of data, Y.K., M.K., and H.K. contributed to drafting of the article, and A.G, M.A. and M.I. provided critical revisions for important intellectual content.

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Tables

Table 1. Clinical characteristics and their comparisons between diabetic and non-diabetic subjects

Variables	Total (n=517)	Non-diabetes (n=342)	Diabetes (n=175)	P
Age, years	58.9 ± 0.5	57.2 ± 0.7	62.2 ± 0.8	<0.01
Gender, male, n (%)	248 (48.0%)	143 (41.8%)	105 (60.0%)	<0.01
Body mass index, kg/m^2	24.4 ± 0.2	23.8 ± 0.2	25.3 ± 0.3	<0.01
Current smoking, n (%)	119 (23.0%)	65 (19.0%)	54 (30.8%)	<0.01
Systolic BP, mmHg	125.3 ± 0.7	124.0 ± 0.8	127.7 ± 1.2	0.01
Diastolic BP, mmHg	75.6 ± 0.4	75.6 ± 0.5	75.5 ± 0.6	0.93
Heart rate, beats/min	68.6 ± 0.5	68.0 ± 0.7	69.6 ± 0.9	0.21
LDL-cholesterol, mmol/L	2.97 ± 0.06	3.12 ± 0.07	2.70 ± 0.09	<0.01
HDL-cholesterol, mmol/L	1.43 ± 0.02	1.49 ± 0.03	1.33 ± 0.03	<0.01
Triacylglycerol, mmol/L	1.52 ± 0.05	1.43 ± 0.06	1.65 ± 0.11	0.07
Blood urea nitrogen, mmol/L	5.1 ± 0.1	5.0 ± 0.1	5.4 ± 0.1	0.06
Creatinine, μmol/L	63 ± 0.9	62 ± 0.9	65 ± 1.8	0.30
eGFR, ml/min/1.73m^2	83.9 ± 1.1	83.9 ± 1.4	83.8 ± 1.9	0.96
Fasting plasma glucose (mmol/L)	6.1 ± 0.1	5.2 ± 0.0	7.4 ± 0.2	<0.01
HbA1c, %	6.0 ± 0.0	5.2 ± 0.0	7.3 ± 0.1	<0.01
Insulin (pmol/L)	40 ± 1 (n=488)	41 ± 2 (n=342)	38 ± 2 (n=146)	0.31
Comorbidities				
Hypertension, n (%)	301 (64.3%)	187 (54.6%)	114 (65.1%)	0.06
Dyslipidemia, n (%)	279 (53.9%)	165 (48.2%)	114 (65.1%)	<0.01
Anti-hypertensive drugs				
Calcium-channel blockers, n(%)	237 (45.8%)	163 (47.6%)	74 (42.2%)	0.26
ACE inhibitor or ARB, n (%)	132 (25.5%)	63 (18.4%)	69 (39.4%)	<0.01
α or β blocker, n (%)	66 (12.7%)	48 (14.0%)	18 (10.3%)	0.26
Diuretic agent, n (%)	26 (5.0%)	17 (4.9%)	9 (5.1%)	0.98
Statin	138 (26.7%)	64 (18.7%)	74 (42.3%)	<0.01

Anti-diabetic drugs				
DPP-4 inhibitor	-	-	57 (32.6%)	-
GLP-1 analogue	-	-	2 (1.1%)	-
Sulfonylurea	-	-	44 (25.1%)	-
Thizolidine	-	-	11 (6.2%)	-
Metformine	-	-	52 (29.7%)	-
SGLT2 inhibitor	-	-	2 (1.1%)	-
Insulin	-	-	29 (16.5%)	-
Diabetes duration (years)	-	-	7.0 ± 0.5	-
Diabetic microvascular complications				
Neuropathy, n (%)	-	-	62 (35.4%)	-
Retinopathy, n (%)	-	-	10 (5.7%)	-
Nephropathy, n (%)	-	-	37 (21.1%)	-
Sleep apnea				
apnea-hypopnea index (AHI)	7.0 (2.9-15.2) (n=462)	5.7 (2.0-12.5) (n=297)	9.6 (4.0-18.2) (n=165)	<0.01
AHI>10, n (%)	174 (37.7%)	96 (32.3%)	78 (47.3%)	<0.01
Baseline Echocardiographic parameters				
LVMI	97.5 ± 0.9	96.3 ± 1.1	100.0 ± 1.5	0.06
LVEF, %	68.7 ± 0.3	69.0 ± 0.3	68.2 ± 0.5	0.21
E, cm/s	61.4 ± 0.6	62.2 ± 0.8	59.8 ± 1.1	0.10
A, cm/s	69.1 ± 0.7	66.7 ± 0.8	73.9 ± 1.1	<0.01
E/A	0.93 ± 0.0	0.99 ± 0.0	0.81 ± 0.0	<0.01
DcT	209.8 ± 2.0	207.0 ± 2.5	215.4 ± 3.6	0.05
E/e'	9.2 ± 0.1	9.0 ± 2.2	9.7 ± 0.1	<0.01
e'	6.8 ± 0.0	7.1 ± 0.1	6.3 ± 0.1	<0.01
Follow-up				
E/e'>14 event, n (%)	77 (14.9%)	36 (10.5%)	41 (23.4%)	<0.01
Annual change of E/e'	0.23 ± 0.04 (n=306)	0.14 ± 0.05 (n=196)	0.38 ± 0.08 (n=110)	0.01

Data are presented as the mean ± standard error or median (25th-75th percentile) for continuous variables, and n (%) for dichotomous variables. P values are shown comparisons of means of 2 groups (unrepeated t-test) and median (Mann-whitney test), or percentages (Chi-square test). BP, blood pressure; LDL, low density lipoprotein; HDL, high density lipoprotein; eGFR, estimated glomerular filtration rate; ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blocker; DPP, dipeptidyl peptidase; GLP, glucagon-like peptide; SGLT, sodium glucose transporter; AHI, apnea hypopnea index

Table 2. Simple linear regression analyses of the factors associated with annual progression in E/e'	
(A) Simple regression analyses	
Variables	All
	n=306
Age	0.097
Gender (male=1, female=0)	0.047
Body mass index	0.003
Current smoking, (yes=1, no=0)	0.024
Diabetes mellitus (yes=1, no=0)	0.147 *
Hypertension	0.101
Dyslipidemia	0.038
Systolic blood pressure	0.035
Diastolic blood pressure	-0.068
Heart rate	0.057
low density lipoprotein-cholesterol	0.099
high density lipoprotein-cholesterol	-0.065
Triacylglycerol	0.092
Blood urea nitrogen	0.117
Creatinine	0.015
estimated glomerular filtration rate	-0.016
Fasting plasma glucose	0.050
HbA1c	0.101
Insulin	0.040
	(n=286)
Baseline E/e'	-0.264 **
ln apnea-hypopnea index	0.128 *
Anti-hypertensive drugs	
Calcium-channel blockers	0.023
Inhibitors of renin-angiotensin system	0.129 *

α or β blocker	0.050	
Diuretics	0.090	

(B) Multiple regression analyses

	All	
	n=306	
Diabetes (yes=1, no=0)	0.278	**
ln apnea-hypopnea index	0.138	**
R^2	0.140	**

(A) Pearson's correlation coefficients are shown. *p<0.05, **p<0.01.
(B) Standard regression coefficients are shown. All analyses include age, gender, BMI, hypertension, dyslipidemia and baseline E/e' as covariates. *p<0.05, **p<0.01.
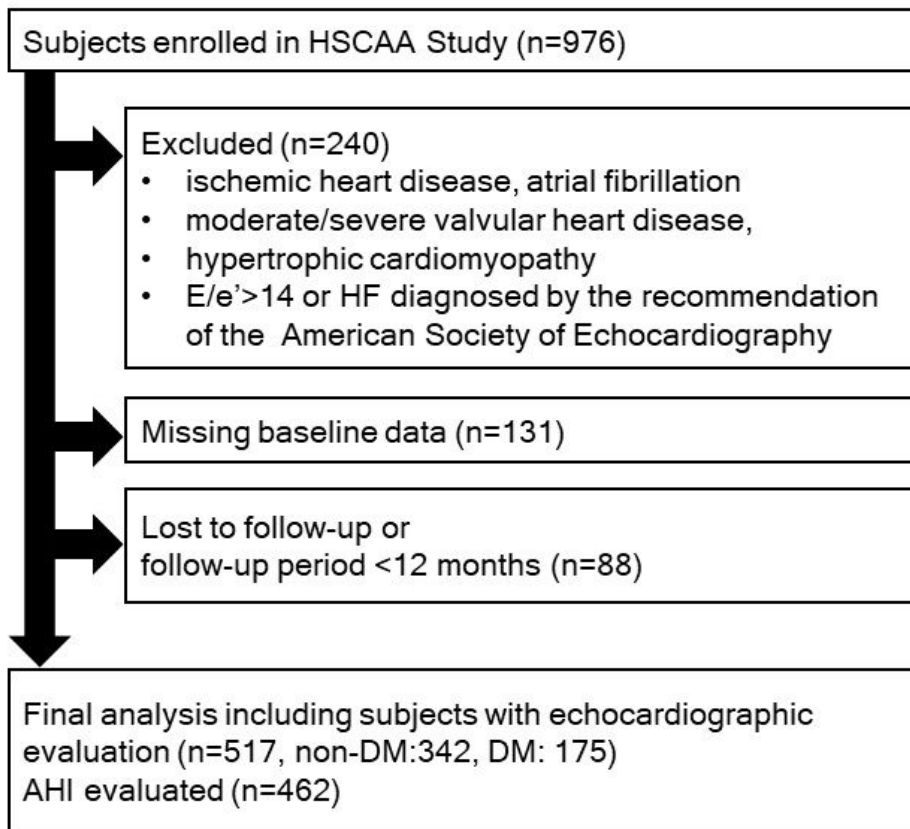
Figures

Subjects enrolled in HSCAA Study (n=976)

Excluded (n=240)
- ischemic heart disease, atrial fibrillation
- moderate/severe valvular heart disease,
- hypertrophic cardiomyopathy
- E/e'>14 or HF diagnosed by the recommendation of the American Society of Echocardiography

Missing baseline data (n=131)

Lost to follow-up or
follow-up period <12 months (n=88)

Final analysis including subjects with echocardiographic evaluation (n=517, non-DM:342, DM: 175)
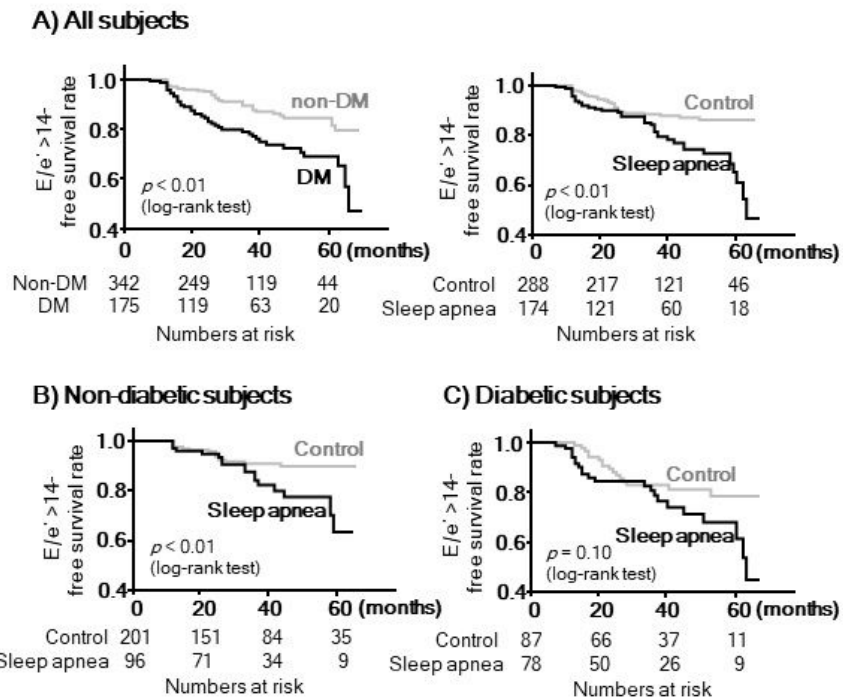AHI evaluated (n=462)

Figure 1

Figure 1

Study participants.

Figure 2

Kaplan Meier analysis of effects of diabetes and sleep apnea on cardiac diastolic dysfunction as defined by E/e' >14 in all (A), non-diabetic (B), and diabetic subjects (C). Sleep apnea was defined based on apnea-hypopnea index >10.

Figure 3
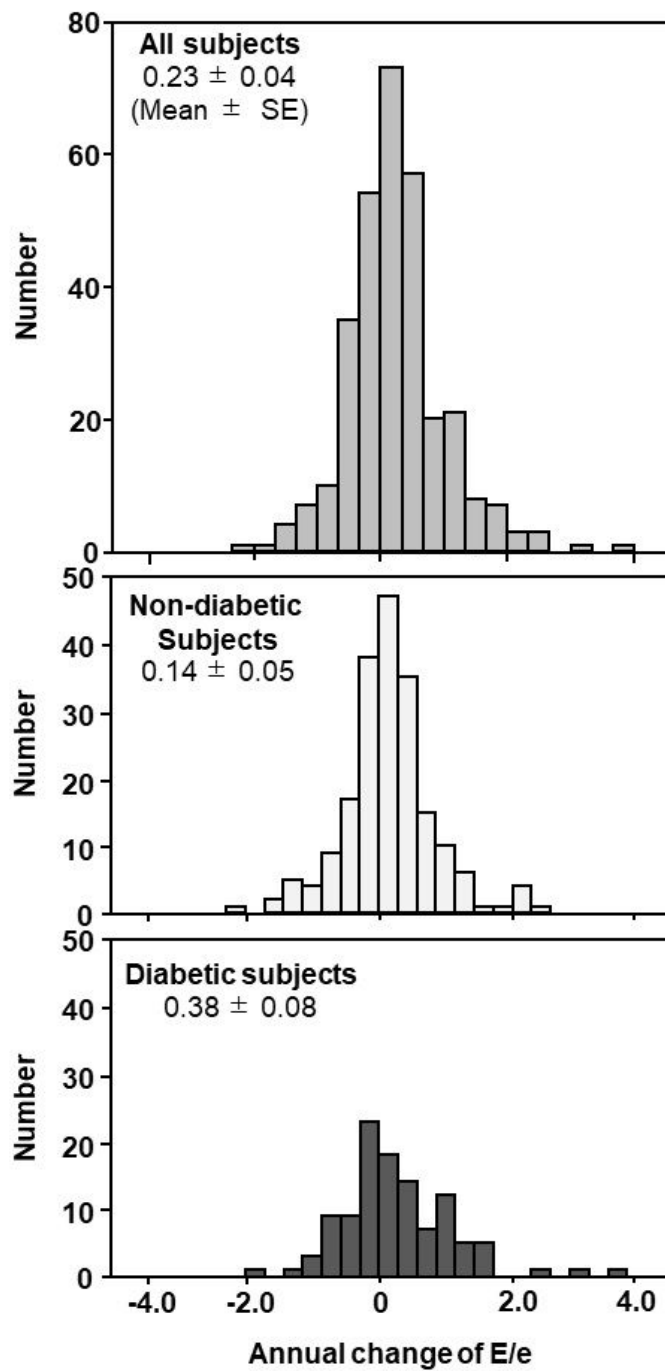
Figure 3

Distribution of subjects (all, non-diabetic, and diabetic subjects) according to annual changes in E/e'.
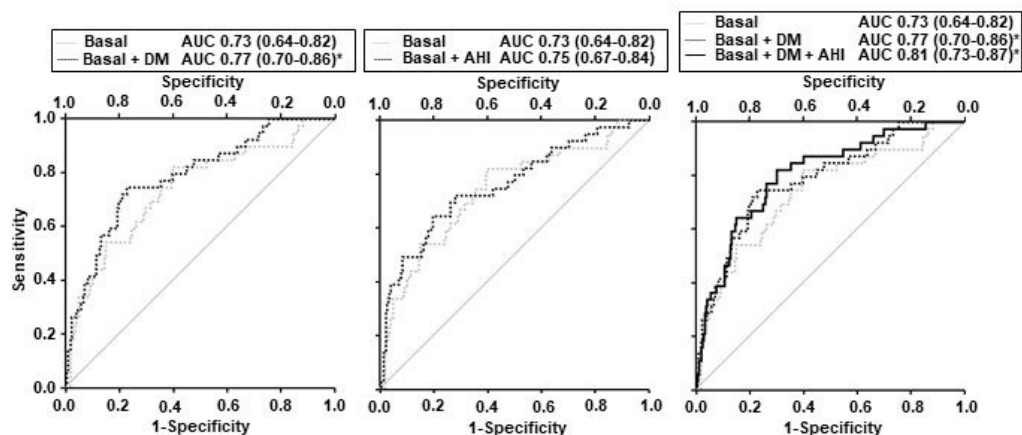
Figure 4

Figure 4

Receiver operating characteristics curves and area under the curve for predicting subjects with annual change of E/e' >1.0. The figures show results of analysis of the impact of addition of diabetes, AHI, and diabetes + AHI to the basal models (age, gender, BMI, hypertension, dyslipidemia, baseline E/e'). * p<0.05 vs basal model.