Circulation Journal
Circ J 2019; 83: 604–613
doi:10.1253/circj.CJ-18-1095

ORIGINAL ARTICLE
Heart Failure

Age- and Body Size-Adjusted Left Ventricular End-Diastolic Dimension in a Japanese Hospital-Based Population

Yuta Seko, MD; Takao Kato, MD; Yusuke Morita, MD; Yuhei Yamaji, MD; Yoshizumi Haruna, MD; Toshiaki Izumi, MD; Shoichi Miyamoto, MD; Eisaku Nakane, MD; Hideyuki Hayashi, MD; Tetsuya Haruna, MD; Moriaki Inoko, MD

Background: Using the normal values for the East Asian population, we evaluated age- and body size-adjusted left ventricular end-diastolic dimension (LVEDD) and its prognostic impact in a hospital-based population in Japan.

Methods and Results: We retrospectively analyzed data obtained from 4,444 consecutive patients who had undergone both transthoracic echocardiography and electrocardiography at Kitano Hospital in 2013. Those who presented with a history of previous episodes of myocardial infarction and severe or moderate valvular disease or with low ejection fraction (<50%) were excluded from the analysis. We calculated LVEDD adjusted by age and body surface area. A total of 3,474 patients were categorized into 3 groups: 401 with large adjusted LVEDD, 2,829 with normal adjusted LVEDD, and 244 with small adjusted LVEDD. Mean patient age in the large, normal, and small adjusted LVEDD groups was 66.6±18.4, 65.6±15.7, and 62.1±15.5 years, respectively (P<0.001). After adjusting for confounding factors, the excess adjusted 3-year risk of primary outcome of large adjusted LVEDD relative to normal LVEDD was significant (HR, 1.40; 95% CI: 1.08–1.78). The risk for primary outcomes of small adjusted LVEDD relative to normal adjusted LVEDD was significantly lower (HR, 0.55; 95% CI: 0.34–0.85).

Conclusions: Adjusted large LVEDD has a deleterious impact on long-term mortality, whereas small LVEDD carried a significantly lower risk.

Key Words: Diastolic dimension; Left ventricle; Long-term mortality; Retrospective

Cardiac chamber size is altered in several heart diseases. The volume overload produced by mitral regurgitation causes compensatory left ventricular (LV) dilation, whereas pressure overload mediates LV hypertrophy with little or no increase in chamber size. Previous reports have shown LV dilatation to be a powerful predictor of adverse outcomes such as myocardial infarction (MI) or several other heart diseases independently of LV dysfunction.[1–4] Similarly, patients with dilated cardiomyopathy have a large LV chamber, which is an adaptation of LV systolic dysfunction. LV dilatation in dilated cardiomyopathy has been linked poor prognosis.[5,6] The importance of chamber size without valvular or myocardial disease, however, has not been elucidated.

LV chamber size is defined by body size, race, age, sex, and physique.[7–9] The EchoNoRMAL Study published in 2015 reported age- and body size-adjusted normal references in different races including the East Asian population.[10] Using the data in the EchoNoRMAL Study as a reference value, we analyzed the factors associated with large or small LV end-diastolic dimension (LVEDD). In addition, there have been no studies on the relationship between cardiac dimension and its prognostic impact in the Japanese population. Therefore, we also evaluated prognostic impact on cardiac events in a Japanese hospital-based population.

Methods

Subjects

We retrospectively analyzed 4,444 patients who had undergone simultaneous transthoracic echocardiography (TTE) and electrocardiography (ECG) at Kitano Hospital during 2013.[11] ECG and TTE were ordered at the discretion of the physician. A flowchart of subject selection is shown in **Figure 1**. A total of 970 patients who had previous MI (n=420) or severe or moderate valvular disease (aortic stenosis, n=133; aortic regurgitation, n=133; mitral stenosis, n=9; and mitral regurgitation, n=169) and low LV ejection fraction (LVEF; <50%, n=407) were excluded due to the

Received October 3, 2018; revised manuscript received November 25, 2018; accepted December 11, 2018; J-STAGE Advance Publication released online January 30, 2019 Time for primary review: 28 days
Cardiovascular Center, The Tazuke Kofukai Medical Research Institute, Kitano Hospital, Osaka (Y.S., Y.M., Y.Y., Y.H., T.I., S.M., E.N., H.H., T.H., M.I.); Department of Cardiovascular Medicine, Kyoto University Graduate School of Medicine, Kyoto (T.K.), Japan
Mailing address: Takao Kato, MD, Department of Cardiovascular Medicine, Kyoto University Graduate School of Medicine, 54 Shogoin Kawahara-cho, Sakyo-ku, Kyoto 606-8507, Japan. E-mail: tkato75@kuhp.kyoto-u.ac.jp
ISSN-1346-9843

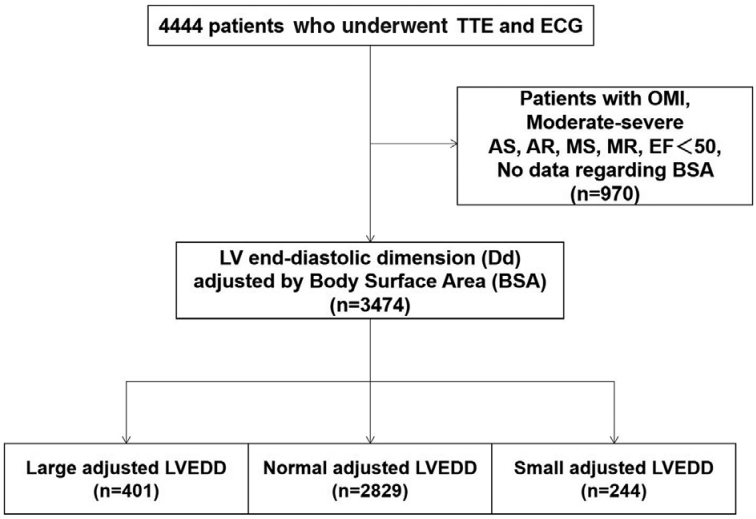


Figure 1. Subject selection according to left ventricular end-diastolic dimension (LVEDD). AR, aortic regurgitation; AS, aortic stenosis; BSA, body surface area; ECG, electrocardiography; EF, ejection fraction; LV, left ventricular; MR, mitral regurgitation; MS, mitral stenosis; OMI, old myocardial infarction; TTE, transthoracic echocardiography.

Table 1. Baseline Subject and TTE Characteristics vs. LVEDD

	Total (n=3,474)	Normal LVEDD (n=2,829)	Large LVEDD (n=401)	Small LVEDD (n=244)	P-value†	P-value Large vs. Normal†	P-value Small vs. Normal†
Age (years)	65.4±16.0	65.6±15.7	66.6±18.4	62.1±15.5	<0.001	0.0083	<0.001
Age >80 years‡	507 (14.6)	392 (13.9)	90 (22.4)	25 (10.3)	<0.001	<0.001	0.12
Male‡	1,796 (51.7)	1,527 (54.0)	146 (36.4)	123 (50.4)	<0.001	<0.001	0.29
BMI (kg/m^2)	23.1±4.2	23.1±3.9	21.1±4.0	26.5±5.0	<0.001	<0.001	<0.001
AF‡	329 (9.5)	267 (9.4)	41 (10.2)	21 (8.6)	0.79	0.73	0.73
Diabetes‡	1,007 (29.0)	798 (28.2)	115 (28.7)	94 (38.5)	0.0030	0.86	0.0058
HT‡	1,863 (53.6)	1,487 (52.6)	233 (58.1)	143 (58.6)	0.031	0.11	0.11
Dyslipidemia‡	972 (28.0)	778 (27.5)	110 (27.4)	84 (34.4)	0.067	1.0	0.077
IHD‡	849 (24.4)	693 (24.5)	96 (23.9)	60 (24.6)	0.97	1.0	1.0
CKD‡	443 (12.8)	315 (11.1)	103 (25.7)	25 (10.3)	<0.001	<0.001	0.75
LVDd (cm)	4.59±0.51	4.57±0.46	5.03±0.52	4.06±0.48	<0.001	<0.001	<0.001
Adjusted LVEDD (cm/m^2)	2.88±0.35	2.85±0.24	3.49±0.23	2.30±0.16	<0.001	<0.001	<0.001
LVDs (cm)	3.02±0.37	3.01±0.33	3.30±0.41	2.68±0.32	<0.001	<0.001	<0.001
Adjusted LVESD (cm/m^2)	1.89±0.24	1.87±0.18	2.29±0.20	1.52±0.13	<0.001	<0.001	<0.001
Normal adjusted LVESD	2,565 (73.8)	2,310 (81.6)	36 (9.0)	219 (89.8)	<0.001	<0.001	0.0011
Large adjusted LVESD	884 (25.4)	517 (18.3)	365 (91.0)	2 (0.8)	<0.001	<0.001	<0.001
Small adjusted LVESD	25 (0.7)	2 (0.1)	0 (0)	23 (9.4)	<0.001	1.0	<0.001
IVSTd (cm)	0.82±0.17	0.81±0.17	0.79±0.16	0.88±0.16	<0.001	0.053	<0.001
LVPWd (cm)	0.80±0.14	0.80±0.14	0.78±0.14	0.84±0.14	<0.001	0.11	<0.001
LVPWd High (M >1.1 cm, F >1.0 cm)‡	74 (2.1)	61 (2.2)	5 (1.3)	8 (3.3)	0.22	0.34	0.34
RWT	0.35±0.07	0.35±0.06	0.31±0.05	0.42±0.08	<0.001	<0.001	<0.001
LVMI (g/m^2)	75.1±21.4	73.7±19.4	93.9±26.5	60.3±14.1	<0.001	<0.001	<0.001
High LVMI (M >115 g/m^2, F >95 g/m^2)	304 (8.8)	185 (6.5)	119 (29.7)	0 (0)	<0.001	<0.001	0.40
LAD (cm)	3.49±0.65	3.48±0.64	3.61±0.75	3.41±0.62	0.0039	0.010	0.59
LAVI (mL/m^2)	22.7±12.3	22.1±11.1	28.6±18.4	19.0±9.8	<0.001	<0.001	<0.001
High LAVI (LAVI ≥34 mL/m^2)‡	368 (11.7)	263 (10.2)	90 (25.4)	15 (7.0)	<0.001	<0.001	0.15
EF (%)	63.3±4.1	63.4±4.0	62.8±4.8	63.6±3.8	0.23	0.29	1.00
HR (beats/min)	71.1±15.0	70.8±14.7	69.5±15.7	77.1±16.5	<0.001	0.27	<0.001

Data given as n (%) or mean±SD. †Chi-squared or Fisher's exact test for categorical variables, and Student's t-test or Wilcoxon rank sum test for continuous variables. ‡Potential risk-adjusting variables selected for Cox proportional hazard models. AF, atrial fibrillation; BMI, body mass index; BSA, body surface area; CKD, chronic kidney disease; EF, ejection fraction; HR, heart rate; HT, hypertension; IHD, ischemic heart disease; IVSTd, diastolic interventricular septal wall thickness; LAVI, left atrial volume index; LVDd, left ventricular diastolic dimension; LVDs, left ventricular systolic dimension; LVEDD, left ventricular end-diastolic dimension; LVMI, left ventricular mass index; LVPWD, diastolic left ventricular posterior wall thickness; RWT, relative wall thickness; TTE, transthoracic echocardiography.

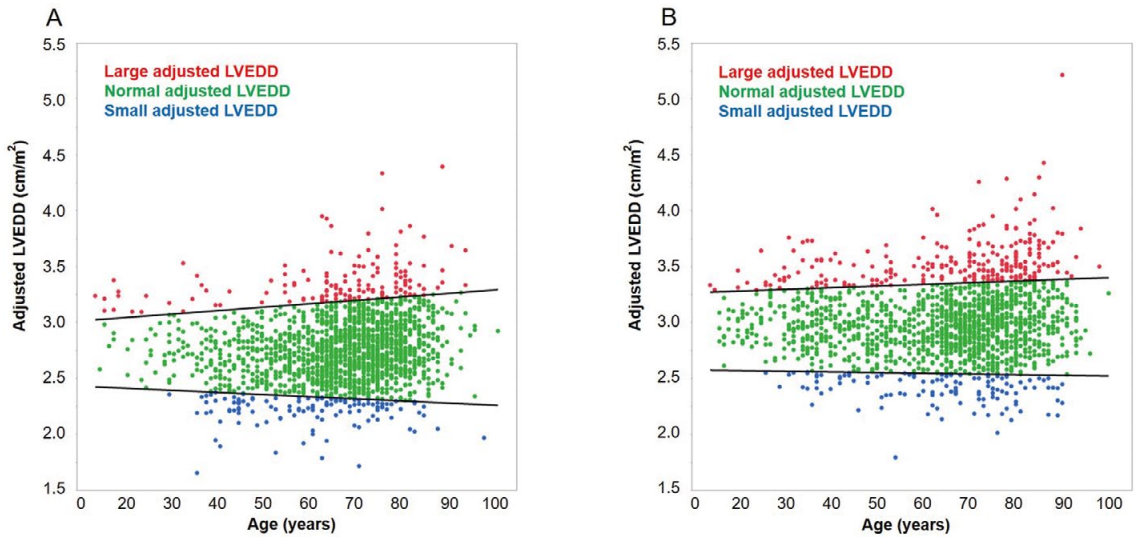


Figure 2. Adjusted left ventricular end-diastolic dimension (LVEDD) according to age for (**A**) men and (**B**) women, and patient distribution according to the reference values from the EchoNoRMAL Study.[10]

diseases' effects on cardiac dimensions, in addition to patients with no data on body surface area (BSA; n=11). Based on the TTE and ECG data, and data from the catheter suite's database, we identified the patients who had a previous MI. The final population consisted of 3,474 patients (**Figure 1**).

The research protocol was approved by the Institutional Review Board of Kitano Hospital (approval number: P16-02-005). Informed consent was waived because this was a retrospective study. We disclosed the details of the present study to the public as an opt-out method and the notice clearly informed patients of their right to refuse enrollment. The study protocol conformed to the ethics guidelines of the 1975 Declaration of Helsinki, as reflected in a priori approval by the institution's human research committee. Patient records and information were anonymized and de-identified before analysis.

Data Collection

Using the TTE database, we extracted data regarding LV wall thickness, LV diastolic dimension (LVDd), LV systolic dimension (LVDs), left atrium diameter, left atrial volume index (LAVI), LVEF, and BSA. From the ECG database, we extracted cardiac rhythm data and recorded it as it was documented. Therefore, we could not determine whether atrial fibrillation (AF) was paroxysmal or persistent. The LV mass index (LVMI) and relative wall thickness (RWT) were calculated using the formula recommended by the American Society of Echocardiography (ASE) as follows: $LVMI=\{0.8\times1.04[(LVDd+LVPWTd+IVSTd)^3-(LVDd)^3]+0.6\}/BSA$, where LVDd is the LV diastolic diameter, IVSTd is the diastolic interventricular septal wall thickness, and LVPWTd is the diastolic LV posterior wall thickness, and $RWT=(2\times LVPWTd)/(LVDd)$.[12]

Large, normal, and small adjusted LVEDD were defined according to the formula proposed by the EchoNoRMAL Study.[10] The following equations were used to define the upper and lower reference values of LV diastolic dimension divided by BSA for men: 2.98+0.0031×(age) and 2.45−0.0019×(age), and for women: 3.25+0.0015×(age) and 2.58−0.00059×(age). All 3,474 patients were categorized into 3 groups as shown in **Figure 1**. High LVPWTd was defined as >11 mm in men or >10 mm in women.[12] Two-dimensional TTE data were analyzed at baseline. LVEF was measured using the Teichholz method or the modified Simpson rule methods. As supplementary analyses, we calculated the adjusted LV end-systolic dimension (LVESD) according to the following formula:[10] the upper and lower reference values of LVESD divided by BSA for men: 2.16−0.0033×(age) and 1.55−0.0044×(age), and for women: 2.17−0.00056×(age) and 1.56−0.0018×(age).

We extracted patient information from the electronic medical records at the present institution, including age, sex, and type of disease (i.e., ischemic heart disease, *International Statistical Classification of Diseases and Related Health Problems*, Tenth Edition [ICD-10] codes I20, I21, I22, I23, I24, and I25; hypertension [HT], ICD-10 codes I10, I11, I12, I13, I14, and I15; dyslipidemia, ICD-10 code E78; diabetes mellitus [DM], ICD-10 codes E10, E11, E12, E13, and E14; and chronic kidney disease [CKD], ICD-10 code N18). The follow-up data from serial clinic visits were also collected retrospectively during June 2017 from the electronic medical records.

Outcome Measures

The primary outcome measure was a composite of all-cause death and major adverse cardiac events (MACE) defined as acute heart failure, acute MI, unstable angina pectoris, cerebral infarction, cerebral hemorrhage, aorta and peripheral vascular disease including the treatment of aortic aneurysm. The secondary outcome measure was all-cause death and MACE.

Statistical Analysis

Categorical variables are presented as n (%). They were compared using the chi-squared test or Fisher's exact

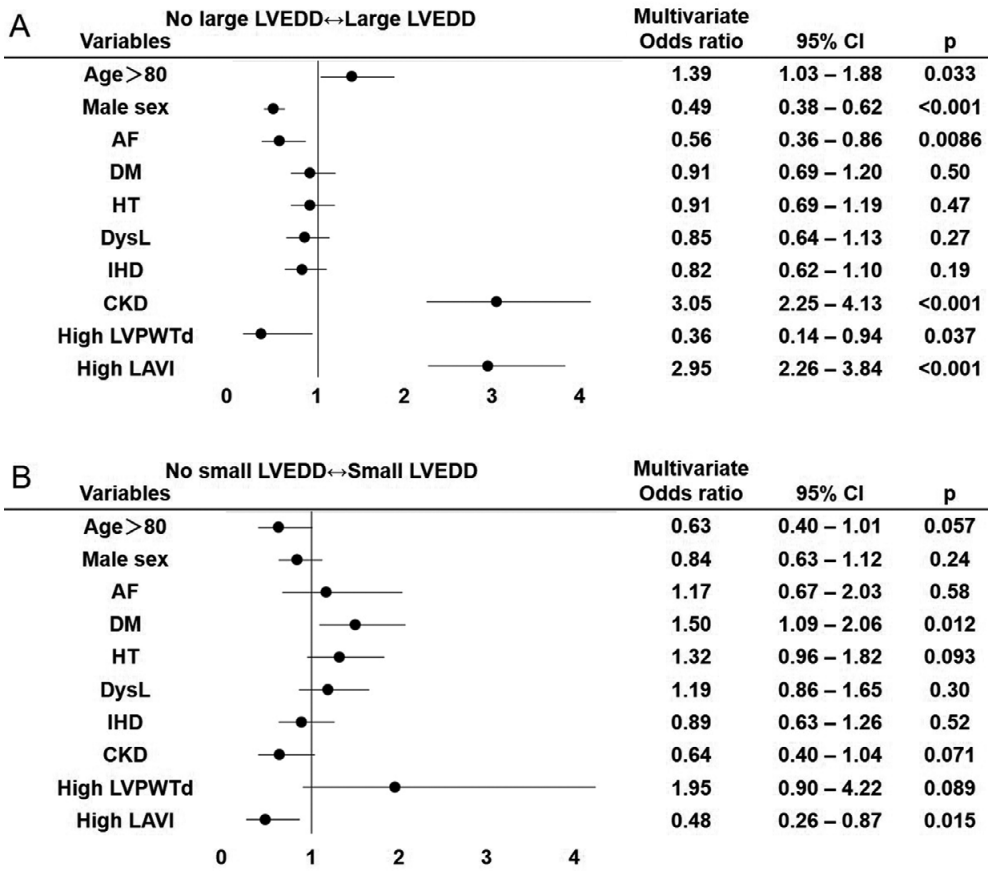


Figure 3. Multivariable logistic regression analysis. Factors associated with (**A**) large adjusted left ventricular end-diastolic dimension (LVEDD) and (**B**) small adjusted LVEDD. AF, atrial fibrillation; CKD, chronic kidney disease; DM, diabetes mellitus; DysL, dyslipidemia; HT, hypertension; IHD, ischemic heart disease; LAVI, left atrial volume index; LVPWTd, diastolic left ventricular posterior wall thickness.

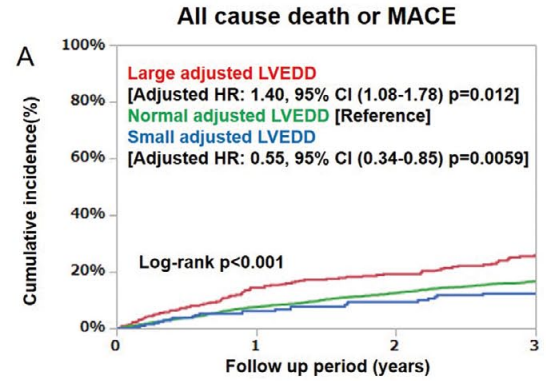
test. Continuous variables are expressed as mean±SD or median (IQR). Based on their distributions, the continuous variables were compared using Student's t-test or Wilcoxon rank-sum test. To determine the differences between 3 groups, we performed the Dunn post-hoc test in each group.

To analyze the factors associated with large and small adjusted LVEDD, we used a multivariable logistic regression model involving the following potentially independent clinically relevant variables: age >80 years, sex, echocardiographic parameters (high LVPWd defined as >11 mm in men and 10 mm in women, and high LAVI defined as 34 mL/m^2), and comorbidities (**Table 1**). We did not include LVMI or RWT because these parameters were derived from the calculation formula including LVDd.

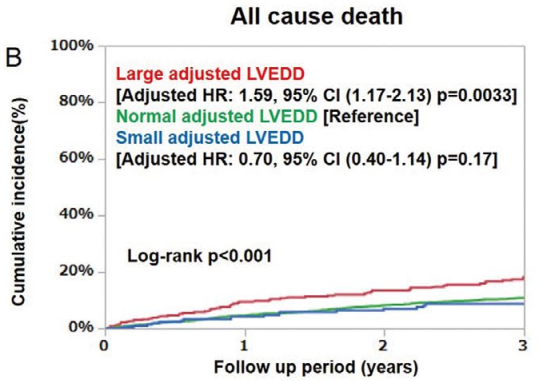
Next, we compared the 3-year clinical outcomes between the large, normal, and small adjusted LVEDD groups. Cumulative incidences of clinical events were estimated using the Kaplan-Meier method, and the intergroup differences were assessed using the log-rank test. Multivariable Cox proportional hazards models were used to estimate the risk of primary and secondary outcomes associated with a large or small adjusted LVEDD relative to a normal adjusted LVEDD. The results are expressed as hazard ratios (HR) and 95% CI. We selected 10 clinically relevant risk-adjusted variables (**Table 1**) for the primary and secondary outcomes for use in the main analysis. Proportional hazard assumptions for the large, normal, and small adjusted LVEDD groups were assessed using plots of log (time) vs. log [−log (survival)] stratified by variable and were verified as acceptable. We also evaluated the interactions between each subgroup and the clinical effects of a large and small adjusted LVEDD relative to normal adjusted LVEDD for clinical outcomes.

For the supplemental analysis comparing the risk prediction of LVEDD and LVESD, we analyzed the cumulative incidences and HR regarding the adjusted LVESD. We compared the net re-classification improvement (NRI) and integrated discrimination improvement (IDI) between adjusted LVEDD and adjusted LVESD regarding the improvement in prognosis accuracy.[13]

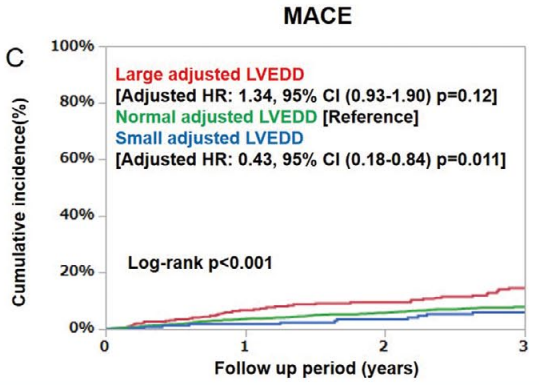
All statistical analysis was conducted by physicians (Y.S., T.K., Y.M.) using JMP version 13 (SAS Institute, Chicago, IL, USA) and R 3.4.1 (R Foundation for Statistical Computing, Austria). NRI and IDI are 2 new metrics for the formal assessment of new risk factors, to supplement the improvement in the area under the curve (AUC), and were evaluated using the R package of survIDINRI (version 1.1.1). All reported P-values are 2-tailed, and



	Interval (years)	0	1	2	3
Large adjusted LVEDD	N of patients with at least 1 event		50	65	83
	N of patients at risk	401	278	232	195
	Cumulative incidence		14.3%	19.2%	25.8%
Normal adjusted LVEDD	N of patients with at least 1 event		180	288	368
	N of patients at risk	2829	2102	1811	1550
	Cumulative incidence		7.5%	12.4%	16.5%
Small adjusted LVEDD	N of patients with at least 1 event		13	19	24
	N of patients at risk	244	187	160	143
	Cumulative incidence		6.1%	9.3%	12.3%



	Interval (years)	0	1	2	3
Large adjusted LVEDD	N of patients with at least 1 event		33	45	58
	N of patients at risk	401	294	249	215
	Cumulative incidence		9.4%	13.3%	18.1%
Normal adjusted LVEDD	N of patients with at least 1 event		111	188	241
	N of patients at risk	2829	2167	1901	1653
	Cumulative incidence		4.6%	8.2%	10.9%
Small adjusted LVEDD	N of patients with at least 1 event		9	14	17
	N of patients at risk	244	191	164	149
	Cumulative incidence		4.3%	6.9%	8.7%



	Interval (years)	0	1	2	3
Large adjusted LVEDD	N of patients with at least 1 event		22	30	42
	N of patients at risk	401	278	232	195
	Cumulative incidence		6.6%	9.4%	14.4%
Normal adjusted LVEDD	N of patients with at least 1 event		83	128	166
	N of patients at risk	2829	2102	1811	1550
	Cumulative incidence		3.5%	5.7%	7.8%
Small adjusted LVEDD	N of patients with at least 1 event		4	7	11
	N of patients at risk	244	187	160	143
	Cumulative incidence		1.9%	3.6%	6.1%

Figure 4. Cumulative incidence of (**A**) the primary outcome measure (all-cause death or major adverse cardiac events [MACE]) and (**B**,**C**) secondary outcome measures (**B**, all-cause death; **C**, MACE) for adjusted left ventricular end-diastolic dimension (LVEDD). MACE were defined as acute heart failure, acute myocardial infarction, unstable angina pectoris, cerebral infarction, cerebral hemorrhage, aortic dissection, and treatment of aortic aneurysm.

Table 2. Clinical Outcome vs. Adjusted LVEDD

	Normal adjusted LVEDD	Large adjusted LVEDD	Small adjusted LVEDD	Variables	Unadjusted		Adjusted	
	No. patients with event/no. patients at risk (cumulative 3-year incidence [%])				HR (95% CI)	P-value	HR (95% CI)	P-value
Composite of all-cause death and MACE	453/2,829 (16.5)	96/401 (25.8)	25/244 (12.3)	Normal adjusted LVEDD	Ref.		Ref.	
				Large adjusted LVEDD	1.58 (1.26–1.96)	<0.001	1.40 (1.08–1.78)	0.012
				Small adjusted LVEDD	0.62 (0.40–0.91)	0.012	0.55 (0.34–0.85)	0.0059
All-cause death	299/2,829 (10.9)	70/401 (18.1)	19/244 (8.7)	Normal adjusted LVEDD	Ref.		Ref.	
				Large adjusted LVEDD	1.72 (1.32–2.22)	<0.001	1.59 (1.17–2.13)	0.0033
				Small adjusted LVEDD	0.72 (0.44–1.12)	0.15	0.70 (0.40–1.14)	0.17
MACE	213/2,829 (7.8)	47/401 (14.4)	11/244 (6.1)	Normal adjusted LVEDD	Ref.		Ref.	
				Large adjusted LVEDD	1.65 (1.19–2.24)	<0.001	1.34 (0.93–1.90)	0.12
				Small adjusted LVEDD	0.58 (0.30–1.01)	0.054	0.43 (0.18–0.84)	0.011

LVEDD, left ventricular end-diastolic dimension; MACE, major adverse cardiac event.

P<0.05 was considered statistically significant.

Results

Baseline Clinical and Echocardiographic Characteristics

A total of 401 patients had large, 2,829 patients had normal, and 244 patients had small adjusted LVEDD (**Figure 1**). The patient distribution according to sex (male, **Figure 2A**; female, **Figure 2B**) was determined using the reference values from the EchoNoRMAL Study.[10] The baseline characteristics of the whole patient group are listed in **Table 1**. There were significant differences in sex, history of DM, HT, and CKD, LV dimensions, wall thickness, and LA dimension between the 3 groups (**Table 1**). Compared with the normal group, the patients with a large LVEDD were more likely to be older and female, and were more likely to have CKD, lower body mass index (BMI), higher LVMI, lower RWT, and higher LAVI. The patients with small LVEDD were younger than the normal group, and were more likely to have higher BMI, DM, higher LVMI, lower RWT, higher LAVI, and a lower heart rate.

Factors Associated With Adjusted LVEDD Size

According to the multivariable logistic regression analysis, age >80 years, CKD, and high LAVI were independently associated with large adjusted LVEDD, while male sex and AF had a negative association (**Figure 3A**). DM was an independent factor associated with small adjusted LVEDD, while high LAVI had a negative association (**Figure 3B**).

Large and Small vs. Normal Adjusted LVEDD: Clinical Outcome

The median follow-up duration after the index echocardiography was 1,274 days (IQR, 410–1,470 days), with a follow-up rate of 80.9% at 1 year, 74.9% at 2 years, and 67.4% at 3 years. The cumulative 3-year incidence of the primary and of the secondary outcome measures was significantly higher in the large adjusted LVEDD group than for the normal group. The cumulative 3-year incidence of the primary and of the secondary outcome measures was significantly lower in the small adjusted LVEDD group than for the normal group (composite of all-cause death and MACE, **Figure 4A**; all-cause death, **Figure 4B**; MACE, **Figure 4C**). After adjustment for confounders, the excess risk of primary outcomes and all-cause death in the large adjusted LVEDD group relative to that in normal adjusted LVEDD group remained significant (**Table 2**). The excess risk of primary outcome in the small adjusted LVEDD group relative to that in the normal adjusted LVEDD group remained significant (**Table 2**).

Subgroup Analysis

There were no significant interactions between the subgroup factors and the effect of large or small LVEDD relative to normal LVEDD for primary outcomes, except for sex (**Table 3**). When stratified by sex, the risk for the primary outcome measures was significantly higher in the large adjusted LVEDD group and lower in the small adjusted LVEDD group than for the normal group in men (**Table 3**). In women, however, the risk for the primary outcome measures in the large and small adjusted LVEDD group relative to that in the normal adjusted LVEDD group was not significant (**Table 3**).

Adjusted LVESD: Group Comparisons

Baseline clinical and echocardiographic characteristics and the trend of outcomes between the LVESD groups were generally consistent with those in the adjusted LVESD groups (**Supplementary Figures 1**,**2**; **Supplementary Table 1**; composite of all-cause death and MACE, **Supplementary Figure 3A**; all cause death, **Supplementary Figure 3B**; MACE, **Supplementary Figure 3C**). The excess risk of primary and secondary outcomes in the large adjusted LVESD group relative to that in the normal adjusted LVESD group

remained significant (**Supplementary Table 2**). According to NRI and IDI analysis, the improvement in prognosis accuracy did not differ significantly between adjusted LVESD and adjusted LVEDD (**Table 4**).

Discussion

The main findings of this study are as follows: (1) higher age, CKD, and high LAVI were independently associated with large adjusted LVEDD, while male sex and AF

Table 3. Clinical Outcome vs. Adjusted LVEDD and Subject Characteristics

	Normal adjusted LVEDD	Large adjusted LVEDD	Small adjusted LVEDD	Variables	Unadjusted		Adjusted		P-value for interaction
	No. patients with event/no. patients at risk (cumulative 3-year incidence [%])				HR (95% CI)	P-value	HR (95% CI)	P-value	
Age									0.64
>80 years	122/392 (33.5)	33/90 (46.1)	4/25 (20.0)	Normal adjusted LVEDD	Ref.		Ref.		
				Large adjusted LVEDD	1.32 (0.89–1.92)	0.17	1.27 (0.79–1.97)	0.31	
				Small adjusted LVEDD	0.46 (0.14–1.10)	0.084	0.45 (0.11–1.20)	0.12	
≤80 years	331/2,437 (13.8)	63/311 (20.3)	21/219 (11.4)	Normal adjusted LVEDD	Ref.		Ref.		
				Large adjusted LVEDD	1.54 (0.98–1.91)	0.0030	1.46 (1.07–1.96)	0.017	
				Small adjusted LVEDD	0.69 (0.43–1.05)	0.086	0.60 (0.35–0.96)	0.032	
Sex									0.0097
Male	290/1,527 (19.4)	52/146 (37.8)	8/123 (7.2)	Normal adjusted LVEDD	Ref.		Ref.		
				Large adjusted LVEDD	2.18 (1.60–2.90)	<0.001	1.80 (1.41–2.60)	0.0010	
				Small adjusted LVEDD	0.33 (0.15–0.61)	<0.001	0.30 (0.12–0.61)	<0.001	
Female	163/1,302 (12.9)	44/255 (18.6)	17/121 (17.4)	Normal adjusted LVEDD	Ref.		Ref.		
				Large adjusted LVEDD	1.38 (0.98–1.91)	0.065	1.03 (0.69–1.50)	0.88	
				Small adjusted LVEDD	1.10 (0.64–1.76)	0.71	0.87 (0.47–1.48)	0.63	
CKD									0.87
Yes	92/315 (24.2)	39/103 (37.9)	3/25 (12.8)	Normal adjusted LVEDD	Ref.		Ref.		
				Large adjusted LVEDD	1.56 (1.06–2.26)	0.024	1.54 (0.98–2.36)	0.063	
				Small adjusted LVEDD	0.37 (0.09–0.97)	0.043	0.54 (0.13–1.48)	0.26	
No	361/2,514 (15.4)	57/298 (21.2)	22/219 (12.2)	Normal adjusted LVEDD	Ref.		Ref.		
				Large adjusted LVEDD	1.38 (1.03–1.81)	<0.001	1.32 (0.95–1.78)	0.092	
				Small adjusted LVEDD	0.68 (0.43–1.02)	0.066	0.55 (0.32–0.88)	0.012	
AF									0.90
Yes	71/267 (28.0)	18/41 (45.5)	4/21 (21.0)	Normal adjusted LVEDD	Ref.		Ref.		
				Large adjusted LVEDD	1.74 (1.01–2.86)	0.047	1.34 (0.70–2.41)	0.36	
				Small adjusted LVEDD	0.61 (0.19–1.48)	0.31	0.59 (0.14–1.68)	0.36	
No	382/2,562 (15.3)	78/360 (23.4)	21/223 (11.5)	Normal adjusted LVEDD	Ref.		Ref.		
				Large adjusted LVEDD	1.54 (1.20–1.95)	<0.001	1.35 (1.02–1.78)	0.038	
				Small adjusted LVEDD	0.62 (0.39–0.94)	0.022	0.55 (0.32–0.87)	0.0098	

(**Table 3** continued the next page.)

	Normal adjusted LVEDD	Large adjusted LVEDD	Small adjusted LVEDD	Variables	Unadjusted		Adjusted		P-value for interaction
	No. patients with event/no. patients at risk (cumulative 3-year incidence [%])				HR (95% CI)	P-value	HR (95% CI)	P-value	
HT									0.42
Yes	334/1,487 (20.6)	81/233 (34.3)	18/143 (13.6)	Normal adjusted LVEDD	Ref.		Ref.		
				Large adjusted LVEDD	1.73 (1.35–2.19)	<0.001	1.46 (1.10–1.93)	0.010	
				Small adjusted LVEDD	0.54 (0.32–0.84)	0.0054	0.52 (0.29–0.86)	0.0084	
No	119/1,342 (10.7)	15/168 (10.9)	7/101 (10.0)	Normal adjusted LVEDD	Ref.		Ref.		
				Large adjusted LVEDD	1.01 (0.57–1.67)	0.97	1.21 (0.66–2.06)	0.52	
				Small adjusted LVEDD	0.79 (0.33–1.56)	0.52	0.65 (0.23–1.43)	0.31	
LAVI									0.23
High	72/263 (24.6)	33/90 (36.5)	4/15 (30.8)	Normal adjusted LVEDD	Ref.		Ref.		
				Large adjusted LVEDD	1.54 (1.01–2.31)	0.045	1.33 (0.84–2.07)	0.22	
				Small adjusted LVEDD	1.24 (0.38–2.99)	0.69	1.17 (0.35–2.88)	0.77	
Normal	334/2,321 (14.8)	48/265 (19.4)	15/199 (8.9)	Normal adjusted LVEDD	Ref.		Ref.		
				Large adjusted LVEDD	1.29 (0.95–1.73)	0.11	1.38 (1.00–1.86)	0.048	
				Small adjusted LVEDD	0.49 (0.28–0.80)	0.0027	0.48 (0.27–0.78)	0.018	
LVMI									0.60
High	45/185 (22.2)	32/119 (32.5)	N/A	Normal adjusted LVEDD	Ref.		Ref.		
				Large adjusted LVEDD	1.22 (0.77–1.91)	0.39	1.65 (0.92–2.99)	0.093	
				Small adjusted LVEDD	N/A		N/A		
Normal	408/2,644 (16.1)	64/282 (23.1)	25/244 (12.3)	Normal adjusted LVEDD	Ref.		Ref.		
				Large adjusted LVEDD	1.53 (1.16–1.97)	0.0028	1.34 (0.99–1.78)	0.059	
				Small adjusted LVEDD	0.64 (0.42–0.94)	0.022	0.57 (0.34–0.88)	0.0097	
Adjusted LVESD									0.59
High	125/517 (24.3)	92/365 (26.8)	1/2 (35.4)	Normal adjusted LVEDD	Ref.		Ref.		
				Large adjusted LVEDD	1.09 (0.83–1.42)	0.55	1.32 (0.95–1.81)	0.097	
				Small adjusted LVEDD	1.90 (0.11–8.51)	0.56	1.21 (0.07–5.67)	0.85	
Normal, Small	328/2,312 (14.7)	4/36 (14.1)	24/242 (11.9)	Normal adjusted LVEDD	Ref.		Ref.		
				Large adjusted LVEDD	0.88 (0.27–2.07)	0.80	1.14 (0.35–2.70)	0.80	
				Small adjusted LVEDD	0.68 (0.43–1.00)	0.051	0.57 (0.35–0.92)	0.021	

LVESD, left ventricular end-systolic dimension. Other abbreviations as in Tables 1,2.

showed a negative association; DM was an independent factor associated with small adjusted LVEDD, while high LAVI had a negative association; and (2) large adjusted LVEDD had a deleterious impact on outcome, while small LVEDD had a favorable impact.

Large adjusted LVEDD was associated with CKD and high LAVI in this study. CKD patients have been reported to have a large LV volume.[14–16] One mechanism of LV dilatation is anemia and chronic fluid overload in CKD.[15] Patients with high LAVI also have a large LV volume,[17] and the atria will enlarge in response to pressure and volume overload.[18] Another consideration is that LV dilatation

Table 4. Improvement in Prognostic Accuracy: Adjusted LVESD vs. Adjusted LVEDD

	Adjusted LVESD vs. adjusted LVEDD
IDI (95% CI)	1.1 (−1.8 to 4.2)
P-value	0.60
NRI (95% CI)	24.3 (−63.1 to 27.2)
P-value	0.91

IDI, integrated discrimination improvement; NRI, net re-classification improvement. Other abbreviations as in Tables 1,3.

is a compensatory mechanism for LV systolic dysfunction. In fact, LV dilatation was related to the risk of worse outcome in patients with MI, dilated cardiomyopathy, and valvular disease.[1–6,19] In the present study, we excluded these patients with reduced EF (EF <50), old MI, and moderate and severe valvular disease (aortic stenosis, aortic regurgitation, mitral stenosis, and mitral regurgitation). The present study suggests that an adjusted large LVEDD is still an independent factor associated with worse outcomes even after adjusting for confounders and excluding patients with reduced EF and valvular heart disease.

Small adjusted LVEDD was associated with DM and not having a high LAVI in this study. Non-high LAVI is indicative of a non-stiff LV. In addition, younger age tended to be associated with small LVEDD with a favorable outcome. In contrast, DM patients have a lower LV end-diastolic volume (LVEDV) and are more likely to have concentric remodeling[20,21] with cardiac steatosis and diastolic stiffness. HT causes pressure overload and subsequent LV hypertrophy[22–24] and diastolic dysfunction,[25] which is also the suggested reason as to why HT tended to be linked to small LVEDD. Thus, although associated with favorable outcome, the underlying reasons for small LVEDD differed on a patient-by-patient basis.

The standard value for LVEDD differs according to age, sex, and race.[7–10] The age coefficient also differed between men and women: it was large for men compared with that in women. The values of the age coefficient were derived from a systematic review;[10] thus, the precise mechanism for the observed difference was not provided. The noted difference is likely to be influenced by differences in the ventricular response. Female sex, however, carries an increased risk of myocardial hypertrophy with small chamber size caused by hormone disturbance after menopause, as reflected by the wide distribution in women according to age (**Figure 2B**).[26,27] The wide distribution is a possible reason for the significant sex-related differences in outcome with adjusted LVEDD size. Another possible reason for the sex-related differences in outcomes is that, because of the low incidence of adverse events in women, non-cardiac mortality comprised a substantial proportion of all-cause death; therefore, there was less power to differentiate the prognostic impact of the size of LVEDD in women than in men.

Despite of the importance of chamber size, only one study has reported on the normal Japanese reference values,[8] in which the references were given, in 5-year age increments for men and women, derived from 700 Japanese subjects with various comorbidities but without cardiac disease, without adjustment for body size. In addition, there is a paucity of echocardiographic data on long-term prognosis in Japan. Using the large clinical database, this is the first report in Japan to show the impact of adjusted LVEDD on outcome in a hospital-based population with 3-year follow-up. In this study, we selected adjusted LVEDD as an indicator of ventricular dilatation. LVEDD is a simple indicator and is routinely measured on TTE; LVEDV or LV end-systolic volume (LVESV) derived using the modified Simpson's method are not always measured on screening. We also showed that the large adjusted LVESD had a worse outcome. On Kaplan–Meier curve analysis, adjusted LVEDD had a better prediction ability than adjusted LVESD, although NRI and IDI indicated an equivalent ability in the present study, probably due to the very limited number of small LVESD subjects. Although the LV systolic function and morphology are complex and tightly related to each other, the effects of large adjusted LVEDD have prompted physicians to investigate the underlying cause of the dimensional change as well as to manage the patients to prevent adverse outcomes. In addition, further large population-based studies in Japan are needed to validate the age-, BSA-, and sex-adjusted normal values on echocardiography, because the normal values used in this study were for an East Asian population not including Japanese subjects,[10] instead of the normal values in the JAMP study.[8]

Study Limitations

This study had several limitations. First, ECG and TTE were ordered at the discretion of the treating physician, with no standardized indications. Second, patient data were extracted from the electronic medical records, which resulted in a low follow-up rate, especially at 3 years. In addition, information regarding the symptoms was not included. Thus, we had no data on the proportion of heart failure with preserved EF. Third, we adopted normal reference values in an East Asian population not including Japanese ethnicity.[10] We used this study because it set a usual value and formula. In fact, a similar trend was seen in the JAMP study.[8] Fourth, we did not adopt LVEDV and LVESV because this measurement using the modified Simpson's method was not always performed. Fifth, this was a single-center study performed in Japan; thus, possible selection bias cannot be excluded despite the large sample size. Finally, there remain unmeasured confounders affecting the long-term prognosis. Nevertheless, we conducted extensive statistical adjustment for the measured confounders.

Conclusions

Patients with large adjusted LVEDD are at a higher long-term risk of clinical events, while small LVEDD had a favorable impact.

Disclosures

The authors declare no conflicts of interest.

Author Contributions

Y.S. and T.K. conceived the design, performed statistical analysis, and wrote the manuscript. Y.M. carried out statistical analysis. Y.Y., Y.H., T.I., S.M., E.N., H.H., T.H. and M.I. collected the data and made critical revisions. All authors read and approved the final manuscript.

References

1. Vasan RS, Larson MG, Benjamin EJ, Evans JC, Levy D. Left

ventricular dilatation and the risk of congestive heart failure in people without myocardial infarction. *N Engl J Med* 1997; **336:** 1350–1355.
2. Lauer MS, Evans JC, Levy D. Prognostic implications of subclinical left ventricular dilatation and systolic dysfunction in men free of overt cardiovascular disease (the Framingham Heart Study). *Am J Cardiol* 1992; **70:** 1180–1204.
3. Gadsbøll N, Torp-Pedersen C, Høilund-Carlsen PF. In-hospital heart failure, first-year ventricular dilatation and 10-year survival after acute myocardial infarction. *Eur J Heart Fail* 2001; **3:** 91–96.
4. Yeboah J, Bluemke DA, Hundley WG, Rodriguez CJ, Lima JA, Herrington DM. Left ventricular dilation and incident congestive heart failure in asymptomatic adults without cardiovascular disease: Multi-ethnic study of atherosclerosis (MESA). *J Card Fail* 2014; **20:** 905–911.
5. Kitaoka H, Matsumura Y, Yamasaki N, Kondo F, Furuno T, Doi Y. Long-term prognosis of patients with mildly dilated cardiomyopathy. *Circ J* 2002; **66:** 557–560.
6. Hofmann T, Meinertz T, Kasper W, Geibel A, Zehender M, Hohnloser S, et al. Mode of death in idiopathic dilated cardiomyopathy: A multivariate analysis of prognostic determinants. *Am Heart J* 1988; **116:** 1455–1463.
7. Lancellotti P, Badano LP, Lang RM, Akhaladze N, Athanassopoulos GD, Barone D, et al. Normal Reference Ranges for Echocardiography: Rationale, study design, and methodology (NORRE Study). *Eur Heart J Cardiovasc Imaging* 2013; **14:** 303–308.
8. Daimon M, Watanabe H, Abe Y, Hirata K, Hozumi T, Ishii K, et al. Normal values of echocardiographic parameters in relation to age in a healthy Japanese population: The JAMP study. *Circ J* 2008; **72:** 1859–1866.
9. Shah BN. Normal reference range values in adult echocardiography: Further evidence that race matters. *Indian Heart J* 2016; **68:** 758–759.
10. Echocardiographic Normal Ranges Meta-Analysis of the Left Heart Collaboration. Ethnic-specific normative reference values for echocardiographic LA and LV size, LV mass, and systolic function: The EchoNoRMAL Study. *JACC Cardiovasc Imaging* 2015; **8:** 656–665.
11. Seko Y, Kato T, Haruna T, Izumi T, Miyamoto S, Nakane E, et al. Association between atrial fibrillation, atrial enlargement, and left ventricular geometric remodeling. *Sci Rep* 2018; **8:** 6366.
12. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: An update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr* 2015; **28:** 1–39.e14.
13. Uno H, Tian L, Cai T, Kohane IS, Wei LJ. A unified inference procedure for a class of measures to assess improvement in risk prediction systems with survival data. *Stat Med* 2013; **32:** 2430–2442.
14. Foley RN, Parfrey PS, Harnett JD, Kent GM, Martin CJ, Murray DC, et al. Clinical and echocardiographic disease in patients starting end-stage renal disease therapy. *Kidney Int* 1995; **47:** 186–192.
15. Foley RN, Parfrey PS, Harnett JD, Kent GM, Murray DC, Barré PE, et al. The prognostic importance of left ventricular geometry in uremic cardiomyopathy. *J Am Soc Nephrol* 1995; **5:** 2024–2031.
16. Liu YW, Su CT, Song EJ, Tsai WC, Li YH, Tsai LM, et al. The role of echocardiographic study in patients with chronic kidney disease. *J Formos Med Assoc* 2015; **114:** 797–805.
17. Moller JE, Hillis GS, Oh JK, Seward JB, Reeder GS, Wright RS, et al. Left atrial volume: A powerful predictor of survival after acute myocardial infarction. *Circulation* 2003; **107:** 2207–2212.
18. Abhayaratna WP, Seward JB, Appleton CP, Douglas PS, Oh JK, Tajik AJ, et al. Left atrial size: Physiologic determinants and clinical applications. *J Am Coll Cardiol* 2006; **47:** 2357–2363.
19. Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, et al. 2017 ESC/EACTS guidelines for the management of valvular heart disease. *Eur Heart J* 2017; **38:** 2739–2791.
20. Levelt E, Mahmod M, Piechnik SK, Ariga R, Francis JM, Rodgers CT, et al. Relationship between left ventricular structural and metabolic remodeling in type 2 diabetes. *Diabetes* 2016; **65:** 44–52.
21. van Heerebeek L, Hamdani N, Handoko ML, Falcao-Pires I, Musters RJ, Kupreishvili K, et al. Diastolic stiffness of the failing diabetic heart: Importance of fibrosis, advanced glycation end products, and myocyte resting tension. *Circulation* 2008; **117:** 43–51.
22. Donaldson C, Palmer BM, Zile M, Maughan DW, Ikonomidis JS, Granzier H, et al. Myosin cross-bridge dynamics in patients with hypertension and concentric left ventricular remodeling. *Circ Heart Fail* 2012; **5:** 803–811.
23. Verdecchia P, Angeli F, Mazzotta G, Bartolini C, Garofoli M, Aita A, et al. Impact of chamber dilatation on the prognostic value of left ventricular geometry in hypertension. *J Am Heart Assoc* 2017; **6:** e005948.
24. Wachtell K, Rokkedal J, Bella JN, Aalto T, Dahlöf B, Smith G, et al. Effect of electrocardiographic left ventricular hypertrophy on left ventricular systolic function in systemic hypertension (The LIFE Study): Losartan intervention for endpoint. *Am J Cardiol* 2001; **87:** 54–60.
25. Nadruz W, Shah AM, Solomon SD. Diastolic dysfunction and hypertension. *Med Clin North Am* 2017; **101:** 7–17.
26. Fazal L, Azibani F, Vodovar N, Cohen Solal A, Delcayre C, Samuel JL. Effects of biological sex on the pathophysiology of the heart. *Br J Pharmacol* 2014; **171:** 555–566.
27. Luczak ED, Leinwand LA. Sex-based cardiac physiology. *Annu Rev Physiol* 2009; **71:** 1–18.

Supplementary Files

Please find supplementary file(s);
http://dx.doi.org/10.1253/circj.CJ-18-1095