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An effect of left ventricular hypertrophy on mild-to-moderate left ventricular diastolic dysfunction

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Abstract *Objectives:* Left ventricular diastolic dysfunction (LVDD) is associated with a variety of medical conditions. Left ventricular hypertrophy (LVH) is one of the most common abnormalities that induce LVDD. However, it is unclear whether LVH is a predictor of future LVDD deterioration that leads to diastolic heart failure in patients who already have mild-to-moderate LVDD. In this study, we investigated the effect of LVH on LV diastolic function in mild-to-moderate LVDD patients.
Methods: Of the patients with mild-to-moderate LVDD (Grade I and II) with preserved left ventricular ejection fraction (EF), 225 with LVH (LVH group) and 225 without LVH (non-LVH group) were consecutively selected. LVDD was defined by the abnormal patterns of Doppler mitral inflow and tissue Doppler. Left ventricular filling pressure (FP) was estimated by the following formula: $1.9 + 1.24 \times$ [early mitral inflow velocity (E)/early mitral annular velocity (e')]. The Tei index was implemented to assess global (both systolic and diastolic) left ventricular function. Echocardiographic parameters for LVDD, such as isovolumic relaxation time (IVRT), were compared between the two groups.
Results: FP and Tei index were significantly higher in the LVH group compared to the non-LVH group [15.68 mmHg vs. 14.07 mmHg, $P < 0.0001$, and 0.58 vs. 0.53, $P < 0.003$, respectively]. IVRT was significantly longer in the LVH group than in the non-LVH group [103.93 ± 23.93 vs.

95.94 ± 20.16, $P < 0.0001$].

Conclusions: In mild-to-moderate LVDD patients, both FP and the Tei index were significantly higher when LVH was present. This may suggest LVH as a possible predictor for the future development of severe LVDD and diastolic heart failure.

1. Introduction

Diastolic heart failure, also known as heart failure with preserved EF, is a clinical syndrome that accounts for approximately half of all heart failure patients.[1,2] Diastolic heart failure is diagnosed when there are clinical symptoms of heart failure, the presence of normal or near normal left ventricular systolic function and evidence of left ventricle diastolic dysfunction (LVDD).[2,3] LVDD is known to have strong associations with advanced age, female gender, obesity, hypertension, diabetes mellitus, and left ventricular hypertrophy (LVH).[4–7] However, it is still unclear whether all cases of LVDD are characteristically the same among different aetiologies. Because the prevalence of heart failure is increasing by approximately 1% annually,[1,8] understanding the pathophysiology of LVDD is important for identifying the high-risk group.

LVH is known to be the most common pathological condition that induces LVDD, and it is associated with worsened cardiovascular prognosis.[6,8,9] However, to date, there has been no direct comparison of the LVDD characteristics between patients with LVH and those without. We hypothesized that mild-to-moderate LVDD with LVH carries a higher risk of developing severe LVDD and diastolic heart failure than LVDD without LVH. In this context, we studied two LVDD groups, a mild-to-moderate LVDD with LVH group (the LVH group) and a mild-to-moderate LVDD without LVH group (the non-LVH group), to determine the echocardiographic differences between the groups. We compared the patient demographics and the echocardiographic characteristics, including left ventricular filling pressure (FP) and the Tei index (also known as myocardial performance index) between the two groups.

2. Methods

2.1. Data collection

The study was reviewed and approved by the Internal Review Board. A total of 450 patients with an echocardiographic diagnosis of LVDD (225 patients with LVH and 225 patients without LVH) were consecutively selected from our echocardiography database.

2.2. Patient demographic profiles

Demographic profiles, laboratory values, medications, and medical histories were obtained from the electronic health records. Hypertension is defined as a history of hypertension requiring the current use of anti-hypertensive medications. The blood pressure values in the study were obtained from the echocardiogram. Coronary artery disease (CAD) was defined as a history of a stress test that was positive for ischemia, the presence of coronary flow-limiting stenosis by coronary angiogram, and/or a history of coronary revascularization. Chronic obstructive pulmonary disease (COPD) was a clinical diagnosis with/without pulmonary function testing. Diabetes mellitus was defined according to the American Diabetes Association guidelines.[10] Valvular heart disease was defined as the presence of moderate to severe mitral, aortic, or tricuspid valvular disease, or a history of valve repair/replacement.[11]

2.3. Exclusion criteria

Patients with atrial fibrillation, tachycardia, or myocardial infarction within the last six months, hypertrophic cardiomyopathy, and valvular heart diseases were excluded because the conventional echocardiographic parameters are known to have weak to no correlation with FP.[12–14] Patients with EF less than 50% were excluded to eliminate the effect of LV systolic dysfunction on FP.

2.4. 2D and Doppler echocardiography

All echocardiograms were performed by certified technicians, and the results were stored digitally in the echocardiogram database. EF was measured by the quantitative 2-dimensional biplane volumetric Simpson method from the 4- and the 2-chamber views[15] by the following equation: 100 X (end diastolic volume − end systolic volume)/end diastolic volume. The parameters for left ventricle mass, left atrial volume and left ventricle internal diameter in diastole obtained from the chamber quantification was indexed for the body surface area. To assess the diastolic parameters, the mitral inflow and the mitral annular motion velocity were measured by the Doppler studies. The following were also assessed: peak early diastolic velocity (E); the deceleration time from the peak of the early diastolic wave to baseline (DT); the peak atrial systolic velocity (A); the E/A ratio; the isovolumic contraction time (IVCT) from the mitral valve closure to the aortic valve opening; the ejection time (ET) from the aortic valve opening to closure; and the isovolumic relaxation time (IVRT) from the aortic valve closure to the mitral valve opening. The mitral annular motion velocity was recorded at the medial mitral annulus site in the apical 4-chamber view by the pulsed tissue Doppler echocardiography (the tissue Doppler). The peak early diastolic motion velocity (e'), the peak motion velocity during atrial systole (a'), and

the ratio of the peak early diastolic transmitral flow velocity E to e' (E/e') were also measured.

2.5. Definition of LVDD and LVH

Conventionally, abnormal relaxation is considered the mildest form of diastolic dysfunction (grade I).[16] In this study, the presence of mitral E/A <0.75 or DT > 240 ms was considered evidence of abnormal relaxation. In a more severe stage of diastolic dysfunction with pseudonormal LV filling (grade II), the transmitral flow characteristics are similar to those in patients with normal diastolic function. However, patients with this abnormality generally have elevated FP. In this study, both pseudonormal and normal LV filling were defined by the presence of mitral E/A of 0.75 to 1.50 and DT of 151 to 240 ms, but distinguished by tissue Doppler. Restrictive diastolic filling (grade III, reversibly restrictive; grade IV, irreversibly restrictive) is associated with markedly elevated LV filling pressures and is the most severe form of diastolic dysfunction.[17] The presence of mitral E/A >1.5 or DT ≤ 140 ms was considered evidence of restrictive diastolic filling. Only Grade I and II LVDD were included in this study. The American Society of Echocardiography-recommended formula was used to estimate LV mass from the LV linear dimensions by 2D echo, which is based on modelling the LV as a prolate ellipse of revolution and indexed to the body surface area. LVH was defined by the left ventricular mass index (g/m^2) higher than 88 g/m^2 in females and 102 g/m^2 in males, as proposed by the American Society of Echocardiography.[15]

2.6. Tei index

The Tei index (also known as myocardial performance index), initially described by Tei C, et al,[18] is a Doppler-derived time interval index that combines both systolic and diastolic cardiac performance. The Tei index appears to have close correlation with the widely accepted systolic and diastolic hemodynamic parameters as well as potential for the clinical application in the assessment of overall cardiac performance.[18–21] The Tei index is calculated by the following formula: (isovolumic contraction time + isovolumic relaxation time)/ejection time. In adults, a left ventricle Tei index of less than 0.4 is considered normal. The higher index values correspond to more pathological states with overall cardiac dysfunction.

2.7. Left ventricular filling pressure (FP)

FP was estimated non-invasively from echocardiographic parameters as described elsewhere.[22–25] Briefly, FP was calculated by the following formula: [1.24 × (E/e') + 1.9] where E and e' are the early filling velocities of the mitral inflow and the tissue Doppler, respectively.

2.8. Statistical analysis

The values were expressed as the mean ± standard deviation. The parametric and non-parametric data were analyzed by independent T-test and Pearson's Chi Square test, respectively using the SPSS software, version 20. All statistical tests were two-sided, and P-value ≤0.01 was used to define statistical significance.

3. Results

3.1. Demographics of the study population

The demographics of the study population were summarized in Table 1. Patients were older in the LVH group than the non-LVH group (71.82 ± 13.49 vs. 68.27 ± 13.99; P = 0.006). Females and Caucasians were similarly dominant in both the LVH and non-LVH groups (P = 0.026 and 0.498, respectively). There was a difference in the prevalence of hypertension (P = 0.009), and systolic blood pressure was significantly higher in the LVH group than the non-LVH group (136.3 ± 20.6 mm Hg vs. 130.05 ± 18.14 mmHg, p < 0.001). There were no statistically significant differences in the distribution of patients with Grade I and II LVDD or other clinical characteristics between the two groups.

3.2. Echocardiographic parameters, FP, and Tei index

The results of echocardiographic parameters are summarized in Table 2 and Figs. 1 and 2. There was no difference in EF between the two groups (63.98 ± 6.98% in the LVH group and 65.14 ± 7.31% in the non-LVH group, P = 0.086). LV mass index was significantly higher in the LVH group compared to the non-LVH group (118.91 ± 27.49 g/m^2 vs. 72.47 ± 13.74 g/m^2, P < 0.0001). LV internal diameter in diastole (LVIDd) was greater in the LVH group compared to the non-LVH group (4.63 ± 0.69 cm vs. 4.10 ± 0.58 cm; P = 0.0001); however, relative wall thickness (RWT) was not significantly different between the two groups. Both groups had increased RWT, greater than 0.42, although there was no statistically significant difference. Compared to the non-LVH group, the LVH group had significantly higher FP (15.68 ± 4.50 mmHg vs. 14.07 ± 3.03 mmHg, P < 0.0001), larger left atrial size (3.77 ± 0.63 vs. 3.51 ± 0.65 cm, p < 0.0001), larger left atrial volume index (31.82 ± 11.38 ml/m^2 vs. 24.36 ± 9.68 ml/m^2, P < 0.0001), and longer IVRT (103.93 ± 23.93 vs. 95.94 ± 20.16, P < 0.0001). The Tei-index was abnormal (> 4.0) in the both groups, but significantly higher in the LVH group than the non-LVH group (0.58 ± 0.15 vs. 0.53 ± 0.15, P < 0.003), suggesting worsened global LV function in the LVH group. There were no significant differences in other echocardiographic parameters, such as pulmonary artery pressure, E and A wave velocities, E/A ratio, IVCT, ET, and DT between the two groups.

4. Discussion

LVDD is commonly observed in patients with advanced age, female gender, obesity, diabetes mellitus, hypertension, coronary artery disease, and LVH[6,26,27]. However, the clinical characteristics of the above conditions are different among patients. LVDD associated with aging and gender is considered among "biological" changes or differences. On

Table 1 Clinical characteristics of patients.

Clinical characteristics		LVH Group*	Non-LVH Group*	P value
Age (years)		71.82 ± 13.498	68.27 ± 13.995	0.006**
Female		164 (72%)	142(63%)	0.026
African American		69 (31%)	70 (31%)	0.498
Caucasian		135 (60%)	143 (63%)	
Other Races		21 (9%)	12 (6%)	
BMI (Kg/m^2)		29.49 ± 8.44	29.69 ± 8.26	0.792
SBP (mmHg)		136.3 ± 20.653	130.05 ± 18.141	0.001**
DBP (mmHg)		70.10 ± 11.62	70.64 ± 10.87	0.627
Creatinine (mg/dl)		1.27 ± 1.19	1.12 ± 0.89	0.144
Tobacco abuse		90 (41%)	95 (45%)	0.431
COPD		49 (22%)	51(24%)	0.639
Dyslipidaemia		108 (50%)	96 (46%)	0.428
Diabetes		73 (32%)	63 (28%)	0.256
CAD		48 (22%)	42 (20%)	0.627
Hypertension		196 (88%)	167 (79%)	0.009**
ACE-I/ARB		99(44%)	97 (43%)	0.849
Diuretics		79 (35%)	73 (32%)	0.550
CCB		84 (39%)	63 (31%)	0.079
Beta-blocker		104(48%)	78 (38%)	0.030
Statins		107(49%)	91(44%)	0.251
Aspirin/Plavix		105(46%)	87(39%)	0.110
Diastolic Dysfunction grade	Grade I	94 (42%)	87 (39%)	0.501
	Grade II	131 (58%)	138 (61%)	

*Values are expressed as the mean ± 1SD or numbers (%). ** P values were significant at <0.01.
BMI: body mass index; COPD: chronic obstructive pulmonary disease; CAD: coronary artery disease; ACE-I: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker; CCB: calcium channel blocker; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure

the other hand, LVDD accompanied by obesity, diabetes mellitus, hypertension, and/or LVH is considered among "pathological" conditions. Our question was whether LVDD of different aetiologies is characteristically the same. In this report, we studied LVH-related LVDD, which is the most common pathological LVDD. We assessed whether LVH has any additional effect on LV diastolic function and overall cardiac function in mild-to-moderate LVDD patients.

In our study population, LVDD was observed more commonly in the patients with advanced age (over 70

Table 2 Echocardiographic characteristics of patients.

Echocardiographic Parameters	LVH Group*	Non-LVH Group*	P value	95% Confidence interval
LV mass Index (g/m^2)	118.91 ± 27.49	72.47 ± 13.74	0.0001**	42.61 to 50.25
LA size (cm)	3.77 ± 0.63	3.51 ± 0.65	0.0001**	0.13 to 0.37
LA Volume/BSA (ml/m^2)	31.82 ± 11.38	24.36 ± 9.68	0.0001**	5.50 to 9.42
LVIDd (cm)	4.63 ± 0.69	4.10 ± 0.58	0.0001**	0.41 to 0.65
LVIDd/BSA(cm/m^2)	2.47 ± 0.37	2.14 ± 0.32	0.0001**	0.25 to 0.38
Relative Wall Thickness	0.54 ± 0.13	0.51 ± 0.12	0.010	0.007 to 0.054
PAP (mmHg)	35.56 ± 10.93	33.86 ± 8.77	0.098	−0.31 to 3.71
EF (%)	63.98 ± 6.98	65.14 ± 7.31	0.086	−2.48 to 0.16
E/A	0.83 ± 0.19	0.83 ± 0.19	0.775	−0.041 to 0.308
E/e$^\times$	11.48 ± 3.75	10.283 ± 2.83	0.0001**	0.72 to 1.95
DT (msec)	246.43 ± 56.67	232.91 ± 57.77	0.013	2.912 to 24.119
IVCT (msec)	61.43 ± 21.01	56.14 ± 28.70	0.026	0.63 to 9.95
ET (msec)	292.65 ± 46.77	289.00 ± 43.06	0.389	−4.67 to 11.98
IVRT (msec)	103.93 ± 23.65	95.94 ± 20.16	0.0001**	3.91 to 12.06
FP (mmHg)	15.68 ± 4.50	14.07 ± 3.40	0.0001**	0.87 to 2.34
Tei index	0.58 ± 0.15	0.53 ± 0.15	0.003**	0.014 to 0.072

*Values are expressed in Mean ± 1SD or numbers (%). ** P value significant at <0.01.
LV: left ventricle; LA: left atrium; BSA: body surface area; LVIDd: LV internal diameter in diastole; PAP: pulmonary artery pressure; EF: ejection fraction; E: early diastolic filling on pulse wave Doppler; A: late diastolic filling on pulse wave Doppler; e$^\times$: early mitral annulus excursion on tissue Doppler; DT: deceleration time; ET: ejection time; IVRT: isovolumic ventricular relaxation time; IVCT: isovolumic contraction time; FP: left ventricle filling pressure.
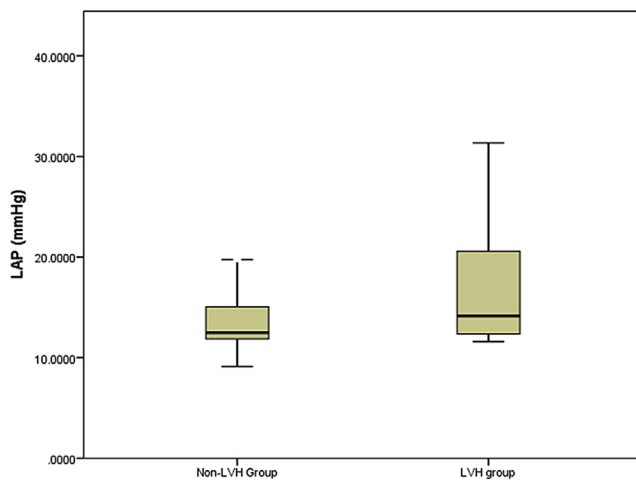
Figure 1   Box plot for LAP.

years), female gender, and obesity, as reported in previous studies.[1,6,8] The prevalence of medical conditions including CAD, dyslipidaemia, COPD, diabetes mellitus, and hypertension observed in our study groups was also similar to previous studies,[5−7] suggesting the appropriateness of our study population.

The prevalence of hypertension including the systolic blood pressure measured at the time of echocardiogram was significantly higher in the LVH group than the non-LVH group. However, this relationship was expected because LVH is recognized as hypertensive heart disease.[4,28] Both groups had increased RWT, suggesting the concentric nature of hypertrophy in the LVH group, and on the other hand, concentric remodelling in the non-LVH group given normal LV mass.[15]

The echocardiogram is a reliable tool to non-invasively assess left ventricular systolic function, diastolic function, and pulmonary artery pressure.[29] In addition to those conventional measurements, FP can also be fairly accurately estimated from the echocardiographic parameters with current echocardiographic parameters.[23−25,30,31] Our study demonstrated that FP was significantly higher when LVDD
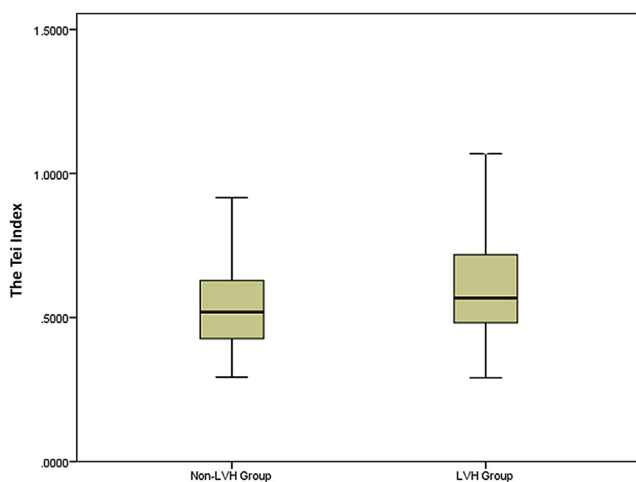

Figure 2   Box plot for Tei Index.

was accompanied by LVH. Higher FP was also reflected by the significantly larger left atrial size and higher left atrial volume index (ml/m^2) in the LVH group.

The Tei index assesses the overall cardiac performance, including both the systolic and diastolic function of the heart.[18] Higher index values correspond to more pathological states with overall cardiac dysfunction. The Tei index also carries a significant prognostic value. As Tei index increases, the cardiovascular mortality increases.[19−21] In our study, the Tei index was abnormal (high) in the both groups. This was most likely due to the presence of LVDD because the EF was preserved in both groups. Moreover, the index was significantly higher in the LVH group than in the non-LVH group.

The Tei index is known to be independent of FP and the ventricular geometry.[32] Because there were no significant differences in LV systolic function (EF) in both groups, a higher Tei index (worsened overall LV function) was considered solely due to worsened LV diastolic function in the LVH group. This hypothesis is also supported by the fact that the LVH group had significantly longer IVRT, which was consistent with worsened LV relaxation. Because worsening of diastolic function is an independent predictor of mortality in patients with normal baseline EF,[9,33] the patients with LVDD with co-existing LVH may be at higher cardiovascular risk than those without LVH.

There are a few limitations in our study. Firstly, we did not confirm FP using invasive methods. Cardiac catheterization was not indicated in most of our patients. The echocardiographic FP estimation has a strong correlation with invasive FP measurement.[23,24] However, it has also been reported that the non-invasive estimation of FP may not be accurate in patients with tachycardia, mitral valvular disease, recent myocardial infraction, and hypertrophic cardiomyopathy.[12−14] Although those patients were excluded from our study, validation of the echocardiographic FP estimation may require invasive measurements.

Secondly, our echo laboratory usually performs tissue Doppler for the medial mitral annulus only. The correlations of the FP with the medial annulus measurements have been reported to be consistent with or better than the lateral annulus measurements or the combination of both measurements.[22,23] However, the LV regional wall motion abnormality and/or intraventricular conduction delay may alter LV basal septal wall motion in the apical 4-chamber view, which possibly affects the tissue Doppler measurement of the medial mitral annular velocity.

Thirdly, the direct effect of higher systolic blood pressure on FP and the Tei index in the LVH group cannot be excluded. It is important to prove the higher FP and Tei index are solely due to worsened LVDD by LVH, but not due to higher systolic blood pressure. However, LVH is usually the consequence of poor blood pressure control. Because of this close correlation between LVH and hypertension, it may be difficult to discuss these two factors separately. Additionally, the LA volumes and size in LVH patient populations, but not in the non-LVH population, are only slightly abnormal; it is likely that these patient populations exhibit an early disease process or have significant variation among groups.

Lastly, because of the nature of any cross-sectional study, the clinical implications of LVH, such as transition to

more severe LVDD and the development of clinical diastolic heart failure, remain undetermined. However, because the presence of LVH was associated with worsened LV diastolic function in the mild-to-moderate LVDD population, we speculate that these patients are at higher risk of developing severe LVDD and diastolic heart failure when mild-to-moderate LVDD is associated with LVH.

In conclusion, our study demonstrated that the patients with mild to moderate LVDD had higher FP and worsened global LV function with worsened LV diastolic function when LVH co-existed. Because worsened LVDD is an independent predictor of mortality, the patients with mild-to-moderate LVDD may benefit from close monitoring and more aggressive hypertension management when LVH co-exists. Large-scale prospective studies are required before this concept is validated clinically.

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Conflict of interest

Authors have no conflicts of interest.

Author contributions

Kattel S contributed in the design of the study, data collection, manuscript preparation and literature review. Saito Y contributed in manuscript preparation and literature review. Memon S, Saito K and Narula J contributed in literature review.

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