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Associations between Subclinical Myocardial Dysfunction and Premature Fusion of Early and Late Diastolic Filling with Uncertain Cause

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Purpose: The fusion of early (E) and late diastolic filling (A) on mitral inflow Doppler, even in the absence of tachycardia, is often found during assessment of left ventricular (LV) diastolic function. We evaluated the echocardiographic characteristics and clinical implications of premature E-A fusion of uncertain cause in the absence of tachycardia.

Materials and Methods: We identified 1014 subjects who showed E-A fusion and normal LV ejection fraction (LVEF) between January 2019 and June 2021 at two tertiary hospitals. Among these, 105 (10.4%) subjects showed premature E-A fusion at heart rates less than 100 beats per minute (bpm). The conventional echocardiographic parameters and LV global longitudinal strain (GLS) were compared with 1:1 age-, sex-, and heart rate-matched controls without E-A fusion.

Results: The premature E-A fusion group had a heart rate of 96.4±3.7 bpm. Only 4 (3.8%) subjects were classified as having LV diastolic dysfunction according to current guidelines. The group showed prolonged isovolumic relaxation time (107.2±25.3 msec vs. 61.6±15.6 msec, p<0.001), increased Tei index (0.76±0.19 vs. 0.48±0.10, p<0.001), lower LVEF (63.8±7.0% vs. 67.3±5.6%, p<0.001) and lower absolute LV GLS (|LV GLS|) (17.0±4.2% vs. 19.7±3.3%, p<0.001) than controls. As the E-A fusion occurred at lower heart rate, the |LV GLS| was also lower (p for trend=0.002).

Conclusion: Premature E-A fusion at heart rates less than 100 bpm is associated with subclinical LV dysfunction. Time-based indices and LV GLS are helpful for evaluating this easily overlooked population.

Key Words: Heart failure, left ventricular dysfunction, diastole, doppler echocardiography

INTRODUCTION

Left ventricular (LV) diastolic dysfunction is an important prognostic factor in several patient populations.[1-3] Evaluating LV diastolic function is an important and unique role of Doppler echocardiography, along with other recent imaging modalities.[4-6] Among Doppler echocardiographic findings, variables from mitral inflow and mitral annular tissue velocity are fundamental for assessing LV diastolic function.[5,6] However, in clinical practice, it is often challenging to determine the degree of LV diastolic dysfunction, which is an important indicator of subclinical LV dysfunction.[7]

Sinus tachycardia, atrioventricular block, bundle branch block, paced rhythm, and heart transplants are associated with early (E) and late diastolic (A) wave fusion.[8-10] Fusion of E and A waves on mitral inflow Doppler is often found, even in the absence of tachycardia.[5] Current guidelines for the evaluation of LV diastolic function do not cover the assessment of LV diastolic function in subjects with premature E-A fusion because E/e' and e' velocity account for half of the diagnostic criteria.[5] In addition, it is difficult to apply the diastolic stress test to these

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subjects, and further evaluations to discriminate LV diastolic function are practically difficult.[11] Therefore, we hypothesized that there would be clinical and functional characteristics reflective of subjects who show premature E-A fusion of uncertain cause in the absence of tachycardia with a heart rate of less than 100 beats per minute (bpm). To test this hypothesis, we compared subjects who had premature E-A fusion with age-, sex-, and heart rate-matched controls with E-A separation. Furthermore, we sought to explore the clinical implications of premature E-A fusion, which is often observed when evaluating LV diastolic function.

MATERIALS AND METHODS

Study subjects

Between January 2019 and June 2021, a total of 1014 consecutive patients with complete fusion of mitral E and A waves was identified at two tertiary hospitals (Severance Hospital and Gangnam Severance Hospital). We excluded patients with tachycardia (heart rate over 100 bpm, n=503), bundle branch block (n=127), any degree of atrioventricular block (n=122), significant mitral disease (at least moderate stenosis or regurgitation, n=31), pacemaker rhythm (n=11), transplanted hearts (n=40), LV ejection fraction (EF) under 50% (n=65), and regional wall motion abnormality (n=10). After exclusions, 105 subjects with premature E and A wave fusion were comprehensively reviewed. As the control group, we extracted 1:1 age-, sex-, and heart rate-matched subjects without E-A fusion from the same echocardiographic database. All performed electrocardiograms closest to index echocardiogram were analyzed. Atrioventricular block and bundle branch block were defined according to current guidelines.[12] Clinical information, such as comorbidities and reason for echocardiogram, was obtained from medical records. HFA-PEFF score was calculated using echocardiographic parameters, except biomarker parameters.[13] We compared clinical and echocardiographic characteristics between subjects with premature E-A fusion (n=105) and controls (n=105). In additional subgroup analysis, patients with heart rates less than 95 bpm were investigated. Subjects with premature E-A fusion were classified into three subgroups according to their heart rate on Doppler acquisition. Data from subjects who underwent follow-up echocardiogram after heart rate decreases within 6 months were analyzed. The Institutional Review Board of Severance Hospital approved this study (4-2022-0438), which was conducted in compliance with the Declaration of Helsinki. The need for informed consent was waived.

Two-dimensional, Doppler, speckle tracking echocardiography

All echocardiographic studies were performed using commercially available equipment with a 2.5–3.5-MHz probe and were retrospectively analyzed by two cardiologists blinded to clinical data according to current guidelines.[5,14,15] Standard echocardiographic measurements were performed according to the American Society of Echocardiography guidelines. The sample volume of pulse-waved Doppler was placed at the mitral tips in the apical four-chamber view while recording three to five cardiac cycles for mitral inflow. For the tissue Doppler, a sample volume was placed at the septal side of the mitral annulus in the apical four-chamber view, and tissue Doppler signal was recorded three to five cycles. Left ventricular ejection fraction (LVEF) and left atrial (LA) volume index were calculated by biplane methods. LV mass index and relative wall thickness were calculated using the Devereux formula.[16] LV diastolic function was assessed according to algorithms provided by current guidelines.[5] Isovolumetric relaxation time (IVRT), isovolumetric contraction time (IVCT), and ejection time (ET) were obtained from Doppler echocardiograms. We used the Tei index and LV global longitudinal strain (GLS) obtained by two-dimensional speckle echocardiography to evaluate LV myocardial performance.[17,18] The Tei index was measured as follows: (IVCT+IVRT)/ET. LV GLS was measured with two-dimensional speckle tracking analysis on apical two-, three-, and four-chamber views using 2D Cardiac Performance Analysis (TomTec Imaging System). Echocardiographic images were recorded for strain analysis at a frame rate between 50 and 70 frames/sec. We calculated global strain values by averaging values computed at the segmental level according to current recommendations.[15] The Tei index and LV GLS were measured independently to reduce bias. Patients with echocardiographic image quality too poor for GLS measurement were excluded from GLS analyses. Patients with absolute LV GLS values less than 16.0% were defined as having reduced LV GLS according to recommendations from the Heart Failure Association of the European Society of Cardiology.[13]

Statistical analysis

Continuous variables are expressed as means±standard deviations and were compared using Student's t-test. Categorical variables are presented as frequencies (percentages, %) and were compared using the chi-square test or Fisher's exact test. The Cochran–Armitage and Jonckheere–Terpstra tests were used to assess trends in clinical variables according to the heart rate at which E and A wave fusion occurred. Baseline and follow-up echocardiographic data from study subjects were compared by paired t-test or Wilcoxon signed rank test, whichever was appropriate. Two-sided p-values<0.05 were considered significant. Statistical analyses were conducted using SPSS software version 20 (SAS Institute Inc., Cary, NC, USA), R studio, and R version 4.1.0 (The R Foundation for Statistical Computing; www.R-project.org).

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RESULTS

Baseline characteristics

Table 1 shows the baseline demographic and clinical characteristics of the two groups. Age, sex, and heart rate were comparable between the two groups. The mean age was 63.9±17.7 years, and most patients were female (57.1%). The premature E-A fusion group had higher systolic (132±28.0 mm Hg vs. 125.0±21.3 mm Hg, p=0.043) and diastolic blood pressure (80.4±17.8 mm Hg vs. 74.3±15.1 mm Hg, p=0.009), more prolonged PR intervals (165.8±20.1 msec vs. 154.0±17.5 msec, p<0.001) and higher HFA-PEFF scores (1.7±1.1 vs. 1.3±1.2, p=0.007). In terms of comorbidities, the premature E-A fusion group included a higher proportion of patients with chronic kidney disease than the control group. The reasons for echocardiogram referral were not different between the groups. About half of the subjects did not have specific cardiovascular symptoms, and echocardiography was performed for screening cardiac dysfunction.

Echocardiographic characteristics

Table 2 demonstrates the echocardiographic characteristics of the two groups. Compared to controls, subjects with premature E-A fusion had larger LV end-systolic dimension, lower LVEF, higher LV mass index and relative wall thickness, and larger LA volume index values. Thus, the percentages of patients who met the criteria for LV hypertrophy and LA enlargement in the premature E-A fusion group were significantly higher than those in the control group. These findings suggest that subjects with premature E-A fusion had structural abnormalities predisposing them for heart failure with preserved EF. In the premature E-A fusion group, 36 (34.3%) patients was available for e' velocity measurement, which was significantly lower in the premature E-A fusion group than in the control group (5.09±1.80 cm/s vs. 6.34±1.64 cm/s, p<0.001). The premature E-A fusion group comprised a higher proportion of individuals with indeterminate diastolic function, based on the current guidelines defining LV diastolic dysfunction in normal LVEF, than the control group (32.4% vs. 14.3%, p=0.004). Subgroup analysis of the patients with a heart rate less than 95 bpm showed similar findings (Supplementary Table 1, only online). Fig. 1 shows a representative case of premature E-A fusion.

In terms of time-derived variables for LV diastolic and sys-

Table 1. Baseline Characteristics of the Study Population

Characteristics	Control (n=105)	Premature E-A fusion (n=105)	*p* value
Age, yr	64±14	64±18	0.903
Sex, female	60 (57.1)	61 (57.1)	0.999
Body mass index, kg/m^2	24.4±4.9	23.6±5.3	0.297
Systolic blood pressure, mm Hg	125.0±21.3	132.0±28.0	0.043
Diastolic blood pressure, mm Hg	74.3±15.1	80.4±17.8	0.009
Heart rate, bpm	96.0±3.3	96.4±3.7	0.424
PR interval, msec	154.0±17.5	165.8±20.1	<0.001
QRS duration, msec	85.2±12.1	87.4±11.8	0.174
Comorbidities			
Hypertension	64 (61.0)	72 (68.6)	0.312
Diabetes mellitus	44 (41.9)	38 (36.2)	0.479
Dyslipidemia	30 (28.6)	21 (20.0)	0.198
Chronic kidney disease	12 (11.4)	24 (22.9)	0.044
Coronary artery disease	12 (11.4)	11 (10.5)	>0.999
Prior myocardial infarction	3 (2.9)	3 (2.9)	>0.999
Heart failure	23 (21.9)	33 (31.4)	0.160
HFA-PEFF score*	1.3±1.2	1.7±1.1	0.007
Referral reason for echo			0.261
Chest pain evaluation	14 (13.3)	8 (7.6)	
Dyspnea evaluation	28 (26.7)	37 (35.2)	
Syncope or palpitation evaluation	11 (10.5)	15 (14.3)	
Screening for cardiac function	52 (49.5)	45 (42.9)	

Data are presented as mean±standard deviation or n (%).
*HFA-PEFF score except biomarker.

Table 2. Echocardiographic Characteristics of the Study Population

Characteristics	Control (n=105)	Premature E-A fusion (n=105)	*p* value
LVEDD, mm	44.7±6.1	45.6±6.2	0.305
LVESD, mm	29.0±4.6	30.7±5.4	0.015
LVEF, %	67.3±5.6	63.8±7.0	<0.001
LV mass index, g/m^2	85.6±26.1	97.8±27.8	0.001
Relative wall thickness	0.41±0.09	0.45±0.10	0.012
LV hypertrophy	19 (18.1)	41 (39.1)	0.001
LA volume index, mL/m^2	25.5±9.7	28.4±9.4	0.033
LA enlargement	14 (13.9)	26 (24.8)	0.072
TR jet velocity, m/s	2.1±1.0	2.1±1.0	0.801
TR jet velocity >2.8 m/s	17 (16.2)	15 (14.3)	0.848
PASP, mm Hg	26.5±15.3	26.0±15.7	0.836
LV diastolic function			0.004
Normal	80 (76.2)	67 (63.8)	0.071
Indeterminate	15 (14.3)	34 (32.4)	0.003
Diastolic dysfunction	10 (9.5)	4 (3.8)	0.167
e' velocity, cm/s*	6.34±1.64	5.09±1.80	<0.001
IVCT, msec	58.9±11.1	78.5±20.9	<0.001
IVRT, msec	61.6±15.6	107.2±25.3	<0.001
Ejection time, msec	250.9±20.0	249.1±31.5	0.616
Tei index	0.48±0.10	0.76±0.19	<0.001
|LV GLS|, %	19.7±3.3	17.0±4.2	<0.001
|LV GLS| <16.0%	12 (11.4)	39 (37.1)	<0.001

LVEDD, left ventricular end-diastolic dimension; LVESD, left ventricular end-systolic dimension; LVEF, left ventricular ejection fraction; LV, left ventricular; LA, left atrial; TR, tricuspid regurgitation; PASP, pulmonary artery systolic pressure; IVCT, isovolumic contraction time; IVRT, isovolumic relaxation time; GLS, global longitudinal strain.
Data are presented as mean±standard deviation or n (%).
*e' velocity measurement was available only in 36 (34.3%) patients in the premature fusion group.

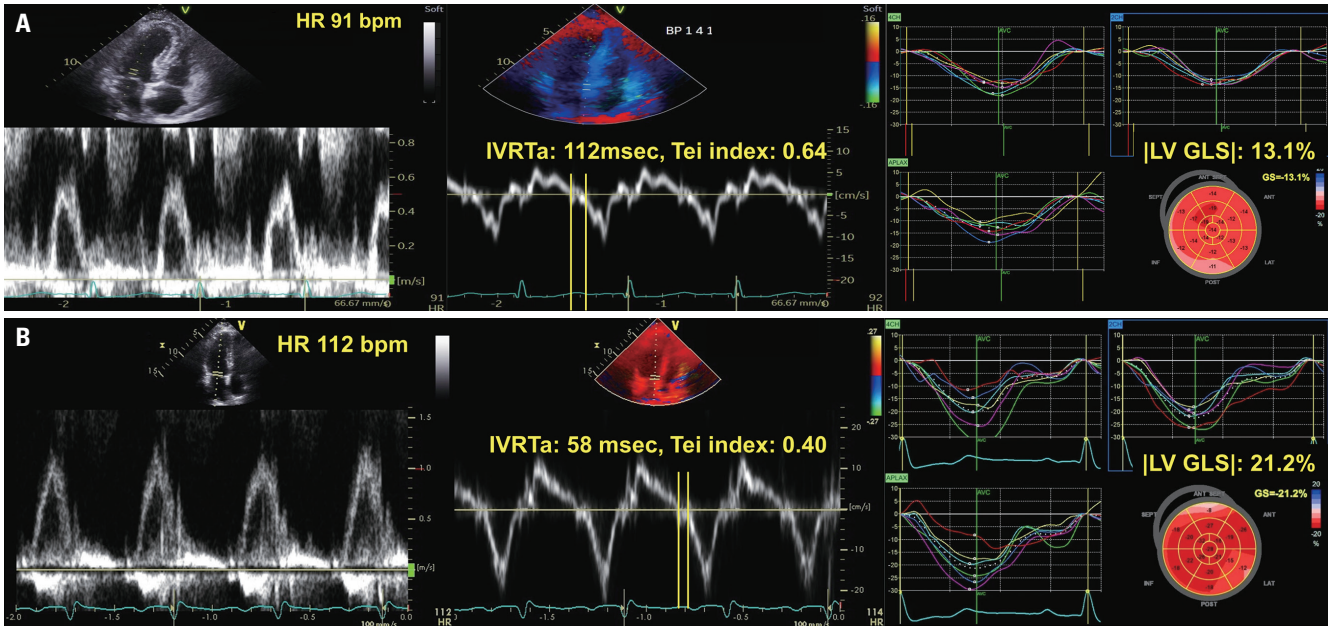

Fig. 1. Representative cases of premature E and A wave fusion. (A) Patients with premature E-A fusion. (B) Patients with E-A fusion due to tachycardia.

tolic function, the premature E-A fusion group had significantly prolonged IVRT (107.2±25.3 msec vs. 61.6±15.6 msec, p<0.001) and IVCT (78.5±20.9 msec vs. 58.9±11.1 msec, p<0.001), but similar ET values, compared with controls. The Tei index in the premature E-A fusion group was significantly higher than that in the controls (0.76±0.19 vs. 0.48±0.10, p<0.001) (Fig. 2). The mean |LV GLS| value in the premature E-A fusion group was significantly lower than that in the control group (17.0±4.2% vs. 19.7±3.3%, p<0.001). The proportion of decreased LV mechanical function, defined as |LV GLS|<16.0%, was higher in the premature E-A fusion group than in controls (37.1% vs. 11.4%, p< 0.001).

Table 3 shows data for subgroups according to heart rate tertiles within subjects with premature E-A fusion. The mean heart rates for successive tertiles were 91.7, 96.6, and 99.7 bpm, respectively. There were no significant trends in baseline characteristics according to heart rate. However, when E-A fusion occurred at a lower heart rate, decreased LVEF (p for trend=0.008) and |LV GLS| (p for trend=0.003) (Fig. 3) were observed. The proportion of individuals with reduced LV GLS increased in the lower heart rate subgroup (p for trend=0.015). In addition, IVCT (p for trend=0.044) and ET (p for trend= 0.017) also increased significantly as the heart rate at E-A fusion became lower in the three subgroups.

Table 4 presents the data of 31 subjects who underwent follow-up echocardiographic exams with lower heart rates within 6 months. The mean heart rate was 78.6±9.0 bpm and LVEF was 61.3±8.9%. Interestingly, 7 out of 9 (77.8%) subjects whose LV diastolic dysfunction could not be determined by previous examinations due to premature E-A fusion were reclassified as having diastolic dysfunction. The mean e' velocity was 5.7± 1.9 cm/s, and mean E/e' was 12.6±4.2. Time-derived variables, such as IVRT (101.2±27.1 msec) and Tei index (0.67±0.21), remained prolonged without significant interval changes in follow-up echocardiograms.

DISCUSSION

The main findings of the present study are as follows: 1) premature E-A fusion in the absence of tachycardia was not a rare finding when assessing LV diastolic function; 2) subjects with premature E-A fusion showed higher proportions of LV hypertrophy and LA enlargement, prolonged time-derived variables of LV dysfunction, and decreased |LV GLS|; and 3) as E and A wave fusion occurred at lower heart rates, |LV GLS| became more reduced.

The prevalence of heart failure with preserved EF (HFpEF) is increasing and accounts for more than half of all heart failure hospitalizations.[19] An association between subclinical LV dysfunction with HFpEF progression is well-established.[4,20-22] According to a recent survey from European Association of Cardiovascular Imaging, evaluation of LV diastolic function is challenging and particularly difficult to apply in certain subgroups of patients.[7] Thus, multimodal imaging approaches, such as LV GLS, cardiac magnetic resonance, or nuclear imaging, for detecting subclinical LV dysfunction has been reported to address shortcomings of current guidelines.[4] However, these imaging studies require significant time and resources, and their generalized application is limited. In the present study, we described specific subject groups that were not mentioned in previous studies and found an association with subclinical LV dysfunction via simple Doppler echocardiographic examination. Interestingly, most of the study subjects with in-

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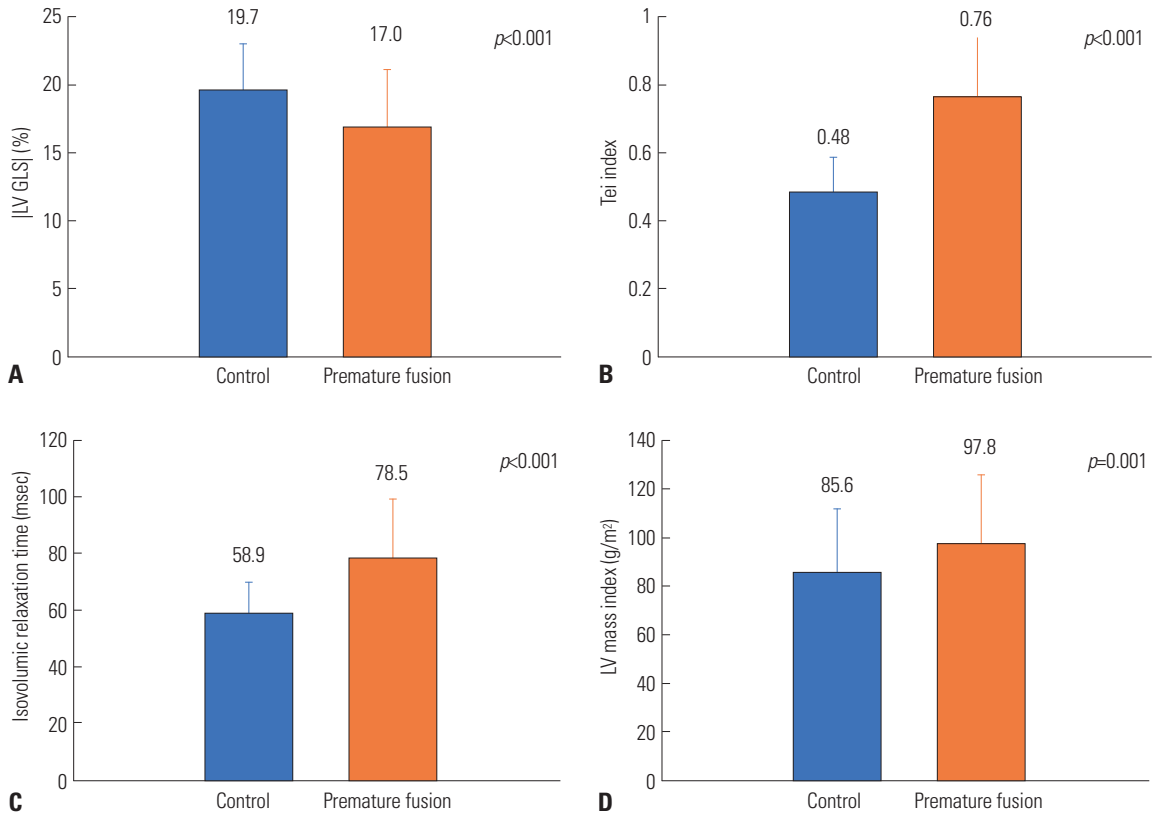

Fig. 2. Comparison of echocardiographic findings between premature fusion and matched controls. (A) Absolute value of LV GLS (%). (B) Tei index. (C) Isovolumic relaxation time (msec). (D) LV mass index (g/m²). LV, left ventricular; GLS, global longitudinal strain.

Table 3. Clinical Characteristics of Patients with Premature E-A Fusion according to Heart Rate Tertile

Characteristics	1st tertile (n=31)	2nd tertile (n=33)	3rd tertile (n=41)	*p* value	*p* for trend
Heart rate, bpm	91.7±2.9	96.6±1.1	99.7±0.5	<0.001	<0.001
Age, yr	65±21	62±17	66±16	0.837	0.934
Sex, female	20 (64.5)	18 (54.6)	22 (53.7)	0.612	
Body mass index, kg/m²	23.9±5.7	24.0±5.9	23.2±4.7	0.538	0.800
Systolic blood pressure, mm Hg	134.2±22.5	134.7±22.0	134.7±20.2	0.922	0.655
Diastolic blood pressure, mm Hg	82.2±14.3	82.6±14.6	81.2±13.5	0.747	0.785
LVEDD, mm	45.2±7.0	44.8±6.6	46.4±5.2	0.387	0.381
LVESD, mm	31.15±5.85	30.3±6.1	30.7±4.5	0.746	0.998
LVEF, %	61.8±6.9	63.8±6.9	65.3±6.9	0.035	0.015
LV mass index, g/m²	104.0±31.7	93.3±32.5	96.7±19.1	0.316	0.686
Relative wall thickness	0.47±0.11	0.46±0.11	0.42±0.08	0.056	0.090
LA volume index, mL/m²	31.6±9.8	25.4±9.0	28.3±8.8	0.185	0.522
TR jet velocity, m/s	2.1±0.9	2.1±1.0	2.0±1.1	0.511	0.693
PASP, mm Hg	26.3±16.7	26.9±15.1	25.1±15.7	0.721	0.658
IVCT, msec	83.1±19.6	80.9±22.4	73.1±20.0	0.039	0.027
IVRT, msec	108.1±31.5	104.4±22.4	108.8±22.5	0.862	0.730
Ejection time, msec	261.5±35.3	243.5±34.8	244.2±22.6	0.027	0.025
Tei index	0.75±0.20	0.79±0.23	0.75±0.13	0.981	0.734
|LV GLS|, %	15.8±3.6	16.2±4.5	18.9±3.8	0.002	0.002
|LV GLS| <16.0%	15 (48.4)	15 (45.5)	9 (22.0)	0.035	0.044

LVEDD, left ventricular end-diastolic dimension; LVESD, left ventricular end-systolic dimension; LVEF, left ventricular ejection fraction; LV, left ventricular; LA, left atrial; TR, tricuspid regurgitation; PASP, pulmonary artery systolic pressure; IVCT, isovolumic contraction time; IVRT, isovolumic relaxation time; GLS, global longitudinal strain. Data are presented as mean±standard deviation or n (%).

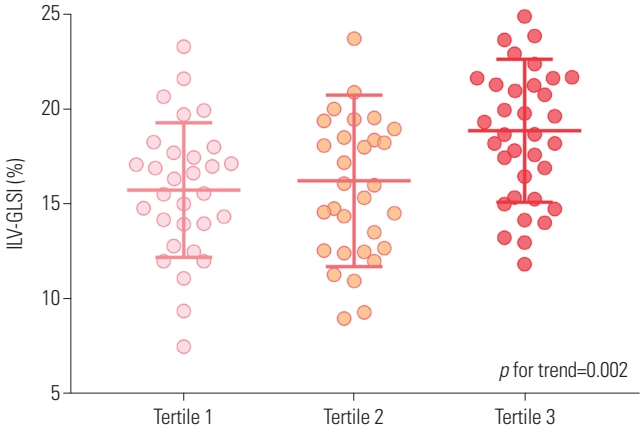

Fig. 3. Trends in left ventricular (LV) global longitudinal strain (GLS) according to the heart rate at which fusion occurred.

Table 4. Patients with Premature E-A Fusion and Echocardiographic Follow-Up (n=31)

	Premature E-A fusion	Follow-up	*p* value
Heart rate, bpm	95.9±3.8	78.6±9.0	<0.001
LVEF, %	62.2±5.7	61.3±8.9	0.595
LA volume index, mL/m^2	28.6±8.3	29.8±9.8	0.143
Diastolic function			0.229
Normal	20 (64.5)	20 (64.5)	>0.999
Dysfunction	2 (6.5)	9 (29.0)	0.032
Indeterminate	9 (29.0)	2 (6.5)	0.017
E velocity, m/s	NA	0.67±0.20	
A velocity, m/s	NA	0.89±0.19	
e' velocity, cm/s	NA	5.69±1.94	
a' velocity, cm/s	NA	9.2±2.6	
E/e'	NA	12.6±4.2	
TR jet velocity, m/s	2.1±0.9	2.3±0.4	0.230
IVCT, msec	75.3±23.6	78.8±22.7	0.496
IVRT, msec	105.3±30.7	101.2±27.1	0.540
Ejection time, msec	255.8±30.7	274.6±38.4	0.006
Tei index	0.72±0.19	0.67±0.21	0.247

LVEF, left ventricular ejection fraction; LA, left atrial; TR, tricuspid regurgitation; IVCT, isovolumic contraction time; IVRT, isovolumic relaxation time.
Data are presented as mean±standard deviation or n (%).

determinate LV diastolic function were classified with diastolic dysfunction and turned out to have reduced e' velocity after their heart rates were decreased.

The study subjects with premature E-A fusion were predominantly female and had higher blood pressure, higher HFA-PEFF score, more prolonged PR interval and IVCT, and more hypertrophied LV wall than matched controls. The female dominance in HFpEF that we observed has been reported in previous studies and shown to be associated with increased arterial stiffness, which is one of the mechanisms underlying heart failure progression.[23-26] Our study subjects had characteristics similar to patients with HFpEF or subclinical LV dysfunction. Prolonged IVCT has been reported to result from decreased LV contractility, increased LV end-diastolic pressure, or increased afterload.[27] Several previous studies have described PR prolongation as being associated with adverse cardiovascular events and decreased atrial conduction and function.[28,29] Our study showed that the premature fusion group had relatively prolonged PR interval despite excluding patients with atrioventricular block. There is the possibility that subclinical LV dysfunction might affect atrial dysfunction, thereby resulting in relative PR prolongation and premature summation. Future studies are needed to elucidate these mechanisms.

Among the echocardiographic parameters reflective of LV dysfunction, the present study used the Tei index and LV GLS, the most commonly used parameters to improve classification within the indeterminate diastolic function group,[7] as the main parameters for determining subclinical LV dysfunction.[30] The Tei index is a conventional index of myocardial performance that has been studied under various conditions[31-34] and is reported to be independent of heart rate change.[17] Normal cut-off values vary between studies, ranging from 0.3 to 0.5, through what is known as the reference range.[31-34] Our study population had a mean Tei index value of 0.76±0.19, significantly higher than matched controls at 0.48±0.10. Furthermore, follow-up echocardiograms after heart rate decreased showed prolongation remaining in IVRT and Tei index values. LV GLS, which is measured by speckle-tracking echocardiography, has clinical utility in detecting subclinical LV dysfunction in various conditions.[30,35-37] Previous large-scale studies have reported normal reference values for LV GLS, and the European Society of Cardiology suggests -16.0% as minor criteria for HFpEF.[13,38,39] In the present study we used TomTec 2D cardiac performance analysis, which was used in previous large-scale studies, and found that 37.1% of the premature fusion group had significantly reduced LV GLS values.[38,39] Subgroup analysis revealed a consistent decreasing trend in LV GLS according to heart rate, even with our relatively small number of study subjects. There were no significant trends in Tei index and IVRT, although IVCT showed a significant trend according to heart rate. The subgroup analysis in the present study depended on the heart rate at the time of echocardiogram. Some patients might have had premature E and A wave fusion at relatively lower heart rates, and this may have resulted in bias in the present study. Although the exact mechanism for premature E-A wave fusion is not able to be explained in this study, we assume that combined delayed relaxation (explained by prolonged IVRT) and relatively reduced myocardial contractility (explained by prolonged IVCT and reduced LV GLS) cause premature fusion. Future studies including invasive hemodynamics are needed to verify the mechanism of this phenomenon and clinical impact in this population.

The present study has several limitations. Our study design was retrospective and cross-sectional and is therefore inevitable from selection and referral bias. Second, we were not able to obtain data on medication and prognosis. In the present

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study, we focused on echocardiographic findings rather than clinical characteristics in this newly introduced population because sonographers in routine echocardiography laboratories sometimes examine subjects without having clinical information. A consecutive study examining clinical prognosis among subjects with premature E-A wave fusion is needed in future. Third, the present study did not have gold standard parameters with which to estimate LV diastolic dysfunction, such as LV end diastolic pressure or pulmonary capillary wedge pressure, which are derived from invasive catheterization. Fourth, among echocardiographic measurements, the core laboratory was not available in the present study. However, all echocardiographic data were transmitted to two experienced cardiologists and analyzed separately. Fifth, only a small number of study subjects underwent follow-up exams. This indicates that the subjects in this study might be neglected clinically. Sixth, we used only LV GLS and Tei index values for determining LV dysfunction in this study. Future studies with robust echocardiographic parameters, such as left atrial strain or strain rate, are needed to clarify the findings of our study.

In conclusion, the phenomenon of premature E-A fusion is associated with subclinical LV dysfunction. Further evaluations of time-derived variables for LV performance or LV GLS might be helpful for detecting subclinical LV dysfunction.

AUTHOR CONTRIBUTIONS

Conceptualization: Kyu Kim. Data curation: Kyu Kim. Formal analysis: Kyu Kim. Investigation: Kyu Kim. Methodology: Kyu Kim, Chi Young Shim, and Se-Joong Rim. Project administration: Kyu Kim and Chi Young Shim. Resources: Chi Young Shim, Iksung Cho, Geu-Ru Hong, Jong-Won Ha, Jiwon Seo, Eui-Young Choi, and Se-Joong Rim. Supervision: Chi Young Shim and Se-Joong Rim. Validation: Kyu Kim and Jiwon Seo. Visualization: Kyu Kim and Chi Young Shim. Writing-original draft: Kyu Kim and Chi Young Shim. Writing-review & editing: Chi Young Shim and Se-Joong Rim. Approval of final manuscript: all authors.

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