**INTRODUCTION**

Left ventricular (LV) diastolic dysfunction is an important prognostic factor in several patient populations. Evaluating LV diastolic function is an important and unique role of Doppler echocardiography, along with other recent imaging modalities. Among Doppler echocardiographic findings, variables from mitral inflow and mitral annular tissue velocity are fundamental for assessing LV diastolic function. 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.

Sinus tachycardia, atrioventricular block, bundle branch block, paced rhythm, and heart transplants are associated with early (E) and late diastolic (A) wave fusion. Fusion of E and A waves on mitral inflow Doppler is often found, even in the absence of tachycardia. 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. In addition, it is difficult to apply the diastolic stress test to these patients, which is a key component in the evaluation of LV diastolic function.

**Key Words:** Heart failure, left ventricular dysfunction, diastole, doppler echocardiography
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-A fusion were comprehensively reviewed. As the control group, we extracted 1:1 age-, sex-, and heart rate-matched controls without E-A fusion from the same echocardiographic database. All performed echocardiograms closest to index echocardiogram were analyzed. Atrioventricular block and bundle branch block were defined according to current guidelines. 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. 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. 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. LV diastolic function was assessed according to algorithms provided by current guidelines. 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. 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. 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.

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).
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 (123±28.0 mm Hg vs. 125.0±21.3 mm Hg, p=0.043) and diastolic blood pressure (80±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 systolic function, the premature E-A fusion group had higher ratios of e’/a’ and e’/e” and longer IVCT and IVRT, compared to the control group (Table 2).

| 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/m² | 85.6±26.1 | 97.8±27.8                   | 0.001   |
| Relative wall thickness | 0.41±0.09 | 0.45±0.10                   | 0.102   |
| LV hypertrophy  | 19 (18.1)      | 41 (39.1)                   | 0.001   |
| LA volume index, mL/m² | 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 function | 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  |

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

*HFA-PEFF score except biomarker.
Premature Fusion of Diastolic Filling

In the absence of tachycardia, 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. An association between subclinical LV dysfunction with HFpEF progression is well-established. 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. 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. 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-
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     | 0.080      |
| LA volume index, mL/m³           | 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. 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.
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 HFPEF 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.

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. Several previous studies have described PR prolongation as being associated with adverse cardiovascular events and decreased atrial conduction and function. 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, as the main parameters for determining subclinical LV dysfunction. The Tei index is a conventional index of myocardial performance that has been studied under various conditions and is reported to be independent of heart rate change. Normal cut-off values vary between studies, ranging from 0.3 to 0.5, through what is known as the reference range. 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. 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. 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. 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
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, Chi Young Shim, and Se-Joong Rim. Project administration: Kyu Kim and Chi Young Shim. Resources: Chi Young Shim, Ik sung 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.

**ORCID iDs**

Kyu Kim https://orcid.org/0000-0002-3632-0183
Jiwon Seo https://orcid.org/0000-0001-6927-5410
Ik sung Cho https://orcid.org/0000-0001-5927-3729
Eui-Young Choi https://orcid.org/0000-0003-4981-3304
Geu-Ru Hong https://orcid.org/0000-0003-8260-2958
Jong-Won Ha https://orcid.org/0000-0002-7631-5581
Se-Joong Rim https://orcid.org/0000-0002-7631-0136
Chi Young Shim https://orcid.org/0000-0002-6136-0136

**REFERENCES**

1. Zile MR, Brutsaert DL. New concepts in diastolic dysfunction and diastolic heart failure: part I. Diagnosis, prognosis, and measurements of diastolic function. Circulation 2002;105:1387-93.
2. Kitzman DW, Litte WC. Left ventricle diastolic dysfunction and prognosis. Circulation 2012;125:743-5.
3. Nagueh SF. Left ventricular diastolic function: understanding pathophysiology, diagnosis, and prognosis with echocardiography. JACC Cardiaco Imaging 2020;13(1 Pt 2):228-44.
4. Marwick TH, Gimelli A, Plein S, Bax JJ, Charpin P, Delgado V, et al. Multimodality imaging approach to left ventricular dysfunction in diabetes: an expert consensus document from the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging 2022;23:e62-84.
5. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF 3rd, Dokainish H, Edvardsen T, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 2018;29:277-314.
6. Nagueh SF, Middleton KJ, Kopelen HA, Zoghbi WA, Quinones MA. Doppler tissue imaging: a noninvasive technique for evaluation of left ventricular relaxation and estimation of filling pressures. J Am Coll Cardiol 1997;30:1527-33.
7. Sitges M, Ajmone Marsan N, Cameli M, D’Andrea A, Carvalho BF; Holte E, et al. EACVI survey on the evaluation of left ventricular diastolic function. Eur Heart J Cardiovasc Imaging 2021;22:1098-105.
8. Sohn DW, Kim YJ, Kim HC, Chun HG, Park YB, Choi YS. Evaluation of left ventricular diastolic function when mitral E and A waves are completely fused: role of assessing mitral annulus velocity. J Am Soc Echocardiogr 1999;12:203-8.
9. Nagueh SF, Mikati I, Kopelen HA, Middleton KJ, Quinones MA, Zoghbi WA. Doppler estimation of left ventricular filling pressure in sinus tachycardia. A new application of tissue Doppler imaging. Circulation 1998;98:1644-50.
10. Rowan RA, Billingham ME. Myocardial innervation in long-term heart transplant survivors: a quantitative ultrastructural study. J Heart Transplant 1988;7:448-52.
11. Ha JW, Andersen OS, Smiseth OA. Diastolic stress test: invasive and noninvasive testing. JACC Cardiovasc Imaging 2020;13(1 Pt 2):272-82.
12. Kusumomo FM, Schoenfeld MH, Barrett C, Edgerton JR, Ellenbogen KA, Gold MR, et al. 2018 ACC/AHA/HRS guideline on the evaluation and management of patients with bradycardia and cardiac conduction delay: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines and the Heart Rhythm Society. Circulation 2019;140:E382-482.
13. Pieske B, Tschöpe C, de Boer RA, Fraser AG, Anker SD, Donal E, et al. How to diagnose heart failure with preserved ejection fraction: the HFA-PEFF diagnostic algorithm: a consensus recommendation from the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). Eur Heart J 2019;40:3297-317.
14. 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.
15. Voigt JU, Pedrizzetti G, Lysyansky P, Marwick TH, Houle H, Baumann R, et al. Definitions for a common standard for 2D speckle tracking echocardiography: consensus document of the EACVI/ASE/Industry Task Force to standardize deformation imaging. J Am Soc Echocardiogr 2015;28:183-93.
16. Devereux RB, Alonso DR, Lutas EM, Gottlieb GI, Campo E, Sachs I, et al. Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. Am J Cardiol 1986;57:450-8.
17. Poulsen SH, Nielson J, Andersen HR. The influence of heart rate on the Doppler-derived myocardial performance index. J Am Soc Echocardiogr 2000;13:379-84.
18. Geyer H, Caracciolo G, Abe H, Wilansky S, Careri S, Gentile F, et
al. Assessment of myocardial mechanics using speckle tracking echocardiography: fundamentals and clinical applications. J Am Soc Echocardiogr 2010;23:351-69; quiz 453-5.
19. van Riet EE, Hoes AW, Wagenaar KP, Limburg A, Landman MA, Rutten FH. Epidemiology of heart failure: the prevalence of heart failure and ventricular dysfunction in older adults over time. A systematic review. Eur J Heart Fail 2016;18:242-52.
20. Dahl JS, Magne J, Pellikka PA, Donal E, Marwick TH. Assessment of subclinical left ventricular dysfunction in aortic stenosis. JACC Cardiovasc Imaging 2019;12:163-71.
21. Oikonomou EK, Kokkinidis DG, Kampaktsis PN, Amir EA, Marwick TH, Gupta D, et al. Assessment of prognostic value of left ventricular global longitudinal strain for early prediction of chemotherapy-induced cardiotoxicity: a systematic review and meta-analysis. JAMA Cardiol 2019;4:1007-18.
22. Russo C, Jin Z, Homma S, Elkind MS, Rundek T; Yoshita M, et al. Subclinical left ventricular dysfunction and silent cerebrovascular disease: the cardiovascular abnormalities and brain lesions (CABL) study. Circulation 2013;128:1105-11.
23. Gerber Y, Weston SA, Redfield MM, Chamberlain AM, Manemann SM, Jiang R, et al. A contemporary appraisal of the heart failure epidemic in Olmsted County, Minnesota, 2000 to 2010. JAMA Intern Med 2015;175:996-1004.
24. Vasan RS, Xanthakis V, Lyass A, Andersson C, Tsao C, Cheng S, et al. Epidemiology of left ventricular systolic dysfunction and heart failure in the Framingham study: an echocardiographic study over 3 decades. JACC Cardiovasc Imaging 2018;11:1-11.
25. Yoshida Y, Nakashishi K, Daimon M, Ishiwata J, Sawada N, Hirokawa M, et al. Sex-specific difference in the association between arterial stiffness and subclinical left ventricular dysfunction. Eur Heart J Cardiovasc Imaging 2021;22:817-23.
26. Shim CY, Park S, Choi D, Yang WI, Cho IJ, Choi EY, et al. Sex differences in central hemodynamics and their relationship to left ventricular diastolic function. J Am Coll Cardiol 2011;57:1226-33.
27. Hirschfeld S, Meyer R, Korfhagen J, Kaplan S, Liebman J. The isovolumic contraction time of the left ventricle: An echographic study. Circulation 1976;54:751-6.
28. Kwok CS, Rashid M, Beynon R, Barker D, Patwala A, Morley-Davies A, et al. Prolonged PR interval, first-degree heart block and adverse cardiovascular outcomes: a systematic review and meta-analysis. Heart 2016;102:672-80.
29. Magnani JW, Wang N, Nelson KP, Connelly S, Deo R, Rodondi N, et al. Electrocardiographic PR interval and adverse outcomes in older adults: the health, aging, and body composition study. Circ Arrhythm Electrophysiol 2013;6:84-90.
30. Kraigher-Krainer E, Shah AM, Gupta DK, Santos A, Claggett B, Pieske B, et al. Impaired systolic function by strain imaging in heart failure with preserved ejection fraction. J Am Coll Cardiol 2014;63:447-56.
31. Tei C. New non-invasive index for combined systolic and diastolic ventricular function. J Cardiovasc Imaging 1995;26:135-6.
32. Poulsen SH, Jensen SE, Tei C, Seward JB, Egstrup K. Value of the Doppler index of myocardial performance in the early phase of acute myocardial infarction. J Am Soc Echocardiogr 2000;13:723-30.
33. Dujardin KS, Tei C, Yeo TC, Hodge DO, Rossi A, Seward JB. Prognostic value of a Doppler index combining systolic and diastolic performance in idiopathic-dilated cardiomyopathy. Am J Cardiol 1998;82:1071-6.
34. Harjai KJ, Scott L, Vivekananthan K, Nunez E, Edupuganti R. The Tei index: a new prognostic index for patients with symptomatic heart failure. J Am Soc Echocardiogr 2002;15:864-8.
35. Morris DA, Boldt LH, Eichstaedt H, Ozcelik C, Haverkamp W. Myocardial systolic and diastolic performance derived by 2-dimensional speckle tracking echocardiography in heart failure with normal left ventricular ejection fraction. Circ Heart Fail 2012;5:610-20.
36. Colak A, Muderrisoglu H, Pirat B, Eroglu S, Aydinalp A, Sezgin A, et al. Longitudinal strain and strain rate for estimating left ventricular filling pressure in heart transplant recipients. Am J Cardiol 2020;137:63-70.
37. Laufer-Perl M, Derakhshesh M, Milvidsky A, Mor L, Ravid D, Amrami N, et al. Usefulness of global longitudinal strain for early identification of subclinical left ventricular dysfunction in patients with active cancer. Am J Cardiol 2018;122:1784-9.
38. Morris DA, Otani K, Bekfani T, Takigiku K, Izumi C, Yuda S, et al. Multidirectional global left ventricular systolic function in normal subjects and patients with hypertension: multicenter evaluation. J Am Soc Echocardiogr 2014;27:493-500.
39. Sugimoto T, Dulgheru R, Bernard A, Ilardi F, Contu L, Addetia K, et al. Echocardiographic reference ranges for normal left ventricular 2D strain: results from the EACVI NORRE study. Eur Heart J Cardiovasc Imaging 2017;18:833-40.