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Ventricular Remodeling in Heart Failure with Preserved Ejection Fraction

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Abstract

Heart failure with preserved ejection fraction (HFpEF) is common, increasing in prevalence, and causes substantial morbidity and mortality. HFpEF has commonly been viewed as an expression of advanced hypertensive heart disease, with a cardiac phenotype characterized by an increase in wall thickness-to-chamber radius ratio (concentric hypertrophy). However, marked clinical heterogeneity within this syndrome is now well appreciated, and is mirrored in the variability in left ventricular structure. A review of larger imaging studies from epidemiology and clinical trial cohorts demonstrate that while concentric LV remodeling is common, it is by no means universal and many patients demonstrate normal LV geometry or even an eccentric pattern. More detailed assessment of cardiac structure and function in broader HFpEF populations will be necessary to better define the prevalence, determinants, and prognostic relevance of these measures, which may in turn serve as a foundation to identify pathophysiologically relevant sub-phenotypes within this diverse syndrome.

Keywords

Heart failure; Preserved Ejection Fraction; Ventricular Remodeling; Echocardiography

Introduction

Data from community-based studies have established that heart failure with preserved ejection fraction (HFpEF) accounts for up to 50% of HF cases and is increasing in prevalence.^{1,2} HFpEF is associated with rates of HF re-hospitalization and functional decline similar to HF with reduced EF (HFrEF),^{3,4} and carries a significantly higher risk of death compared to age-matched controls.^{5,6} However, no disease-specific therapy exists to improve prognosis in this heterogeneous syndrome, despite multiple randomized controlled trials.^{7,8,9} HFpEF has commonly been viewed as an expression of advanced hypertensive heart disease, with antecedent hypertension present in 60–90% of HFpEF cases in

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Conflict of Interest

Amil M. Shah declares that he has no conflict of interest.

Compliance with Ethics Guidelines

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

epidemiologic studies.^{10,11} The fundamental association between myocardial wall stress, ventricular hypertrophy, and chamber enlargement was described decades ago.^{12,13} LV shape, or geometry, can be described based on the LV mass (hypertrophy) and the relative wall thickness (RWT), which describes the relationship between wall thickness and cavity size (concentricity). LV hypertrophy can occur in the context of increased RWT (concentric hypertrophy) or normal to reduced RWT (eccentric hypertrophy). Increased concentricity can also occur in the absence of frank hypertrophy (concentric remodeling). In the context of hypertensive disease, sarcomere replication in parallel with associated increase in wall thickness-to-chamber radius ratio (concentric hypertrophy) would allow for normalization of LV peak systolic meridional wall stress, and would therefore be the expected pattern of remodeling in HFpEF. Supporting this model, several investigators have shown that HFpEF is associated with significantly increased LV wall thickness and reduced chamber dimension compared to healthy controls or hypertensive patients without HF.^{14,15} At the myocardial level, HFpEF patients demonstrate increased cardiomyocyte stiffness, elevated interstitial myocardial collagen content, and greater cardiomyocyte hypertrophy.¹⁶ Invasive hemodynamic studies of LV function in select HFpEF patients have demonstrated both impaired early diastolic active relaxation and increased passive stiffness.^{17,18}

Although this model accurately accounts for some patients with HFpEF, marked clinical heterogeneity within this syndrome is now well appreciated. In particular, beyond hypertension, the contribution of co-existing coronary artery disease, atrial fibrillation, and pulmonary dysfunction are being increasingly recognized.^{19,20,21} Mechanistically, measures of diastolic function have performed poorly in discriminating HFpEF patients from their comorbidity matched symptom-free counterparts,²² are absent in approximately one-third of HFpEF patients,^{23,24} and fail to reliably predict adverse events in HFpEF. Simultaneously, numerous additional pathophysiologic abnormalities have been described in HFpEF, including impaired systolic function despite preserved LVEF,^{25,26} increased ventricular dyssynchrony,^{27,28} impaired left atrial function,²⁹ pulmonary hypertension,³⁰ increased arterial stiffness,³¹ and impaired peripheral oxygen extraction.³² Similar heterogeneity in cardiac structure and function in HFpEF is also being increasingly recognized.³³ In prior studies, patient were often selected based on prior HF hospitalization and/or the presence of concentric structural remodeling which, together with limited sample size, may have limited the cardiac phenotype observed.^{14,15,34} In this review, we focus on larger imaging studies from epidemiology and clinical trial cohorts that included a broad population of HFpEF patients, in an attempt to capture the breadth of structural remodeling in HFpEF and mitigate the impact of inclusion bias.

Assessment of Ventricular Structure in HFpEF

While cardiac magnetic resonance imaging provides high resolution data on cardiac structure and complementary information on tissue characterization and fibrosis,³⁵ echocardiography has been the most commonly employed imaging modality in these larger clinical studies. It is the least expensive imaging modality, safe, portable, and able to evaluate cardiac structure, systolic and diastolic function, valvular function, and hemodynamics. However, image acquisition and measurement techniques are operator dependent, and both can be sources of variability. Fortunately, many large clinical studies of

HFpEF utilizing echocardiography have employed core laboratories to mitigate these sources of variability as recommended by professional societies,³⁶ although inter-laboratory measurement differences remain a potential source of between-study differences in cardiac structure and function.

Epidemiologic cohort studies offer the least biased view of HFpEF in the community, but have been limited by relatively small numbers of incident HFpEF cases. Hospital-based HFpEF registries obviate many of the inclusion biases inherent in clinical trial populations, particularly with regards to inclusion of patients with advanced co-morbidities – such as chronic kidney disease – who are often excluded from therapeutic trials for safety reasons. However, referral bias remains a significant consideration, as frequently only those admitted with acute decompensation are enrolled. In addition, the uniform implementation, analysis, and reporting of cardiac structure and function in most large HF registries has been limited. Finally, imaging sub-studies of HFpEF clinical trials have the unique advantages of large numbers of cases, robust clinical phenotyping, and prospective assessments. By necessity, clinical trials impose inclusion and exclusion criteria, and in HFpEF trials these frequently include echocardiographic criteria.^{8-9,37} Therefore, these studies are clearly not reflective of HFpEF epidemiology, and identify specific subsets of patients within the HFpEF syndrome.

Ventricular Remodeling in HFpEF in Epidemiologic Studies and Hospital Registries

Across epidemiologic studies, mean LV size tends to be normal, with variable degrees of LV wall thickening (Table 1). One of the largest and most comprehensive epidemiologic evaluations of cardiac structure and function in HFpEF is the Olmsted County cohort.³⁸ Among 244 HFpEF cases, ventricular hypertrophy was present in 42% of participants. Interestingly, while concentric hypertrophy or remodeling was present in 53%, eccentric hypertrophy was also noted in 16%. In addition, LV geometry was normal in nearly one-third of HFpEF cases (31%). The Cardiovascular Health Study, an older study of HFpEF cases of similar age and gender, demonstrated similar average LV mass index but somewhat larger ventricles with a lesser degree of concentric remodeling.³⁹

The Northwestern HFpEF Registry provides perhaps the most comprehensive assessment to date of cardiac structure and function in a registry setting (Table 1), and demonstrated greater concentric remodeling and higher prevalence of LV hypertrophy than most epidemiologic studies.⁴⁰ Interestingly, similar to the Olmsted County cohort, 12% of patients in this registry demonstrated an eccentric pattern of ventricular hypertrophy. This registry is also one of the few observational cohorts to report on left atrial remodeling and noted a high prevalence of left atrial enlargement with a mean LA volume index of 33.6 ml/m² (abnormal >29 ml/m²).

Ventricular Remodeling in HFpEF Clinical Trials

In HFpEF clinical trial imaging sub-studies, mean LV size tends to be normal, although appreciable within trial and between trial variability exists (Table 2). Similarly, LV wall thickness also varies between trials, with trials requiring elevated wall thickness for

inclusion demonstrating higher wall thickness and LV mass.⁸ As a result of these differences in chamber size and wall thickness, there is wide variability in the prevalence of both increased concentricity (wall thickness relative to chamber diameter) and LV hypertrophy, ranging from 14–49% and 21–59% respectively. Indeed, in the echocardiographic sub-study of the I-PRESERVE trial, the largest and most comprehensive study to date, nearly half (46%) of the 745 patients in the sub-study demonstrated normal LV geometry.²⁴ In addition, similar to the Olmsted County and Northwestern experiences, 7% of patients in the PARAMOUNT trial demonstrated an eccentric pattern of hypertrophy.⁴¹ Together, these observations highlight the marked heterogeneity of ventricular morphology found within this syndrome (Figure 1).

Racial/Ethnic Variation in Cardiac Structure and Function in HFpEF

Limited data is currently available regarding ethnic/racial variation in cardiac structure and function in HFpEF. Among Native Americans, the NHLBI Strong Heart Study suggests similar patterns of ventricular remodeling as observed in the Olmsted cohort.⁴² Data from the a relatively small Chinese referral cohort of HFpEF patients also suggests similar LV size and mass as observed in the Olmsted cohort,⁴³ although the ongoing prospective PEOPLE/SHEP study should help further clarify the extent and magnitude of ventricular remodeling among Asians with HFpEF.⁴⁴ Even less data is currently available in Hispanic populations.

A particularly important gap in our current understanding is the limited data available regarding cardiac structure and function among blacks, who carry a disproportionate share of the HF burden but are uniformly under-represented in clinical trials and most large epidemiologic cohort studies. Among U.S. cohorts, African Americans demonstrate particularly high HF prevalence⁴⁵ and incidence,⁴⁶ and experience higher mortality with HFpEF.⁴⁷ Comparative studies in non-hypertensive healthy subjects suggest that LV mass and relative wall thickness are higher in African Americans compared to whites,⁴⁸ and African Americans appear to develop greater degrees of diastolic dysfunction,⁴⁹ concentric remodeling,⁵⁰ and hypertrophy⁵¹ for a set degree of hypertension. Perhaps the most comprehensive data to date on cardiac structure and function among African Americans with HFpEF comes from the NHLBI Atherosclerosis Risk in Communities (ARIC) Study's Jackson, MS cohort.⁵² Among 2,445 African American participants, the 85 identified with HF tended to demonstrate smaller LV chambers, higher LV mass and relative wall thickness, and higher prevalence of concentric hypertrophy compared to other – albeit larger – cohort studies.

Prognostic Relevance of Ventricular Remodeling in HFpEF

The echocardiographic sub-study of the I-PRESERVE trial clearly demonstrated the prognostic relevance of LV hypertrophy for both all-cause mortality and HF mortality or hospitalization.²⁴ Even after multivariable adjustment, the presence of LV hypertrophy was associated with a hazard ratio of 1.59 (95% CI 1.17–2.16; $p=0.003$) for mortality. Similarly, in the Northwestern HFpEF Registry, LV hypertrophy was associated with a significantly higher incidence of death or cardiovascular hospitalization, although in this study no

significant difference in incidence rates was noted between those with a concentric pattern of hypertrophy compared to those with an eccentric pattern.⁴⁰ Along with ventricular remodeling, I-PRESERVE also demonstrated the prognostic importance of atrial remodeling in HFpEF. Left atrial enlargement, likely a marker of LV diastolic dysfunction and chronically elevated filling pressure,⁵³ was associated with a hazard ratio of 1.47 (95% CI 1.03–2.10, $p=0.03$) for death in multivariable adjusted models.²⁴ This finding contrasts with Doppler-based measures of diastolic function, which have only variably been associated with outcomes in HFpEF.^{23,24} Finally, data from the Olmsted cohort demonstrate the prognostic importance of pulmonary hypertension in HFpEF, which appears at least partially – though not fully – related to LV diastolic dysfunction.³⁰

Future Directions

Relationship of Structural Remodeling to Functional Impairment in HFpEF

The functional implications of LV structural remodeling in HFpEF are not well understood. Concentric remodeling has been associated with impaired diastolic function and increased diastolic LV stiffness.⁵⁴ However, several studies also suggest that concentric remodeling can mask impairments in myocardial systolic function despite preserved or even increased chamber-level measures of LV systolic function, such as ejection fraction and fractional shortening.^{55,56,57} More recent data using 2D speckle tracking indicate that progressive concentric remodeling is associated with reduced longitudinal deformation despite normal LVEF and increased circumferential deformation.⁵⁸ This emerging data using myocardial deformation imaging suggest a distinct pattern of LV dysfunction in conditions predisposing to HFpEF, such as hypertension and diabetes, characterized by impaired longitudinal systolic function with concomitant increase in circumferential systolic function, maintaining overall LVEF.^{59,60,61} However, the prevalence and independent prognostic relevance of impaired ventricular deformation despite preserved LVEF in HFpEF remain unclear.

Right Ventricular Function and Pulmonary Vascular Disease in HFpEF

Pulmonary hypertension is a powerful risk factor for adverse outcomes in HFpEF. However, elevation in LV filling pressure does not appear able to fully account for pulmonary hypertension in HFpEF and concomitant elevations in pulmonary vascular resistance and pulmonary arterial stiffness have been suggested.³⁰ Similarly, while this review has focused on structural alterations in the LV in HFpEF, right ventricular dysfunction has demonstrated prognostic import in HF with reduced LVEF, LV dysfunction following myocardial infarction, and pulmonary arterial hypertension.^{62,63,64} However, little data to date exists regarding the prevalence, magnitude, and prognostic implications of both pulmonary vascular dysfunction and right ventricular dysfunction in HFpEF.

Using Cardiac Structure and Function to Identify HFpEF Sub-phenotypes

Phenotypic heterogeneity is now a well-recognized component of the HFpEF syndrome. A review of cardiac structure and function in HFpEF demonstrates similar diversity. While biases of study inclusion criteria and measurement variability contribute, this variability likely also reflects heterogeneity in underlying pathophysiology within this syndrome. Therefore, the ability to define sub-phenotypes within this heterogeneous syndrome may

allow for more effective targeting of treatments for this syndrome for which there are currently no efficacious therapies. Integration of quantitative measures of cardiac structure and function – including structural remodeling, biventricular systolic and diastolic function, and systemic and pulmonary vascular function – offers a promising foundation for the identification of such sub-groups.

Conclusions

Patients with the HFpEF syndrome demonstrate diverse patterns of ventricular remodeling, likely mirroring the clinical and pathophysiologic heterogeneity of this syndrome. While concentric LV remodeling is common, it is by no means universal and many patients demonstrate normal LV geometry or even an eccentric pattern. More detailed assessment of cardiac structure and function in broader HFpEF populations will be necessary to better define the prevalence, determinants, and prognostic relevance of these measures. This ‘deep phenotyping’ of structure and function may eventually serve as a foundation to identify pathophysiologically relevant sub-phenotypes within HFpEF, and promote more effective targeting and testing of therapies to ultimately reduce disease burden.

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Figure 1. Prevalence of ventricular geometric patterns in select epidemiology, registry, and clinical trial HFpEF cohorts demonstrating the heterogeneity in ventricular remodeling found in this syndrome.

Table 1

Cardiac structure and function in HFpEF in select epidemiology and registry studies.

	Ohmsted County ³⁸	CHS ³⁹	Strong Heart Study ⁴²	He et al. ⁴³	ARIC/Jackson ⁴²	NY HF Registry ⁴⁵	French Registry ⁴⁶	Northwestern Registry ⁴⁰	Reference Values
N	244	167	50	128	85	619	368	402	
LVEF cut-off	50%	55% [*]	>54%	>55%	50%	50%	50%	>50%	
Age (years)	76 (22–99)	76±7	64±8	72±10	61 (57–67)	71.7±14.1	76±10	64±12	
Female	55%	57%	84%	45%	85%	73%	53%	62%	
LV Structure									
EDD (cm)	NA	5.1±0.8	5.04±0.65	4.7±0.6	4.4 (4.1–4.7)	4.70±0.76	5.0±0.8	NA	-
ESD (cm)	NA	3.0±0.7	NA	3.1±0.5	2.6 (2.4–3.0)	3.21±0.73	3.3±0.7	NA	-
EDVi (ml/m ²)	56.4±14.4	69±22	NA	53±16	NA	NA	NA	40±10	>75
ESVi (ml/m ²)	NA	20±10	NA	20±8	NA	NA	NA	16±6	>30
Septal WT (cm)	NA	NA	0.99±0.14	1.2±0.2	1.2 (1.1–1.3)	NA	NA	NA	-
Posterior WT (cm)	NA	0.9±0.2	0.92±0.11	1.1±0.2	1.2 (1.1–1.4)				
LV Mass (g)	200.4±67.1	176±64	178±51	215±69	239 (202–285)	NA	NA	NA	-
LVMi (g/m ²)	102.1±29.0	98±34	96±24	118±36	NA	66 (53–85)	NA	NA	-
Hypertrophy	42%	NA	NA	NA	75%	NA	NA	60%	
RWT	0.45±1.0	0.36±0.11	0.37±0.06	NA	0.57 (0.51–0.62)	NA	NA	0.51±1.1	<0.42
LV geometry									
Normal	31%	NA	NA	NA	5%	NA	NA	12%	
Concentric remodeling	27%	NA	NA	NA	20%	NA	NA	28%	
Concentric hypertrophy	26%	NA	NA	NA	73%	NA	NA	48%	
Eccentric hypertrophy	16%	NA	NA	NA	2%	NA	NA	12%	
LV Systolic Function									
EF (%)	62±6	72±7	64±9	64±5	67 (59–75)	59.8±7.3	63±8	61±6	55
FS (%)	NA	42±7	NA	34±4	37 (31–44)	NA	34.5±7.8	NA	
Stroke volume index (ml/m ²)	42.3±10.0	50±14	NA	32±9	NA	NA	NA	NA	
LV Diastolic Function									

	Olmsted County ³⁸	CHS ³⁹	Strong Heart Study ⁴²	He et al. ⁴³	ARIC/Jackson ⁵²	NY HF Registry ⁶⁵	French Registry ⁶⁶	Northwestern Registry ⁴⁰	Reference Values
LAVi (ml/m ²)	NA	NA	NA	NA	NA	NA	NA	33.6±14.1	16–29
LA Area (cm ²)	NA	NA	NA	NA	NA	NA	NA	NA	20
LA diameter (cm)	NA	NA	NA	3.9±0.5	3.4 (3.1–3.8)		4.1±0.7	NA	
E/A ratio	1.21±0.69	1.3±1.2	0.75±0.28	1.1±0.8	0.94 (0.79–1.12)	NA	NA	1.3±0.7	0.8–1.5
TDI E’ septal (cm/s)	6.0±2.1	NA	NA	8±2	NA	NA	NA	7.0±2.5	10.4±2.1 (6.2–14.6)
TDI E’ lateral (cm/s)	NA	NA	NA	NA	NA	NA	NA	9.2±3.7	12.9±3.5 (5.9–19.9)
E/E’ ratio (septal)	18.4±9.7	NA	NA	10	NA	NA	NA	15±8	8
E/E’ ratio (lateral)	NA	NA	NA	NA	NA	NA	NA	NA	8
Diastolic Dfxn (y/n)	NA	NA	NA	NA	27%	NA	NA	NA	
Diastolic Dfxn grade	NA	NA	NA	NA	NA	NA	NA	NA	
Pulmonary Pressure									
TR velocity (m/sec)	NA	NA	NA	NA	NA	PASP: 47±17	NA	NA	<2.9

Values in italics were estimated by the author from primary data provided in the referenced manuscripts.

* History of hypertension also required for inclusion.

EDD-LV end-diastolic dimension; ESD-LV end-systolic dimension; EDVi-LV end-diastolic volume indexed to BSA; EDVi-LV end-systolic volume indexed to BSA; LVEF - LV ejection fraction; WT – wall thickness; LVMI-LV mass index; RWT – relative wall thickness; FS – fractional shortening; LAVi – left atrial volume indexed to BSA; E wave – peak early diastolic transmitral flow velocity; A wave – peak late diastolic transmitral flow velocity; E’ lateral – peak early diastolic mitral annular tissue velocity at lateral mitral annulus; E’ septal – peak early diastolic mitral annular tissue velocity at septal mitral annulus; TR – tricuspid regurgitation.

Table 2

Cardiac structure and function in select HFpEF clinical trials enrolling at least 100 patients.

	PARAMOUNT ⁴¹	Aldo-DHF ³⁷	RELAX ⁶⁷	I- PRESERVE ²⁴	CHARMES ²³	PEP-CHF8	Reference Values
N	292	422	216	745	312	850	
Key Inclusion Criteria	LVEF 45% NT-pBNP>400	LVEF 50% Echo DD or AF pV02 25	LVEF 50% NT-pBNP>400 pV02<60% pred	LVEF 45% NSR at echo	LVEF>40%	LVEF>40% DHF by clin, echo criteria	
Age (years)	70.6±9.1	67 ± 8	69.62–77	72±7	66±11	75, 72–79	
Female	56%	52%	48%	62%	34%	56%	
LV Structure							
EDD (cm)	4.64±0.48	4.65±0.62	4.6, 4.3–5.1	4.8±0.6	5.4±0.7	4.6, 4.2–5.1	-
ESD (cm)	2.99±0.70	2.55±0.64	NA	3.2±0.7	3.6±0.7	NA	-
EDVi (ml/m)	61.4±15.4	NA	NA	49±14	NA	NA	>75
ESVi (ml/m)	26.5±10.4	NA	NA	18±9	NA	NA	>30
MWT (cm)	0.91±0.16	NA	NA	0.93±0.15	NA	1.3 (1.2–1.5)	-
LV Mass (g)	148±43	NA	NA	164±48	237±91	NA	-
LV Mass Index (g/m ²)	79.1±22.2	109±28	78, 62–94	NA	117±42	NA	
Hypertrophy	14%	NA	48%	29%	NA	NA	
RWT	0.38±0.08	NA	NA	0.40±0.08	NA	NA	<0.42
Concentric form of remodeling	21%	NA	46%	54%	NA	NA	
LV geometry							
Normal	72%	NA	NA	46%	NA	NA	
Concentric remodeling	14%	NA	NA	25%	NA	NA	
Concentric hypertrophy	7%	NA	NA	29%	NA	NA	
Eccentric hypertrophy	7%	NA	NA	0%	NA	NA	
LV Systolic Function							
EF (%)	57.7±7.9	67 ± 8	60, 56–65	64±9	50, 18–65	65 (56–66)	55
LV Diastolic Function							
LAVi (ml/m ²)	35.9±13.5	28.0±8.4	44, 36–59	-	41.3±14.7	NA	16–29
LA Area (cm ²)	21±5	-	-	23±6	NA	NA	20

	PARAMOUNT ⁴¹	Aldo-DHF ³⁷	RELAX ⁶⁷	I- PRESERVE ²⁴	CHARMES ²³	PEP-CHF8	Reference Values
LA Diameter (cm)	3.7±0.5	NA	NA	NA	NA	4.5 (4.1–4.8)	<4.0
E/A ratio	1.1±0.62	0.91±0.33	1.5, 1.0–2.1	1.05±0.74	1.1±0.7	0.7 (0.6–0.9)	0.8–1.5
TDI E' septal (cm/s)	5.8±2.0	5.9±1.3	6, 5–8	7.2±2.9	NA	NA	10.4±2.1 (6.2–14.6)
TDI E' lateral (cm/s)	7.5±2.8	-	-	9.1±3.4	NA	NA	12.9±3.5 (5.9–19.9)
E/E' ratio (septal)	15.9±7.3	12.8±4.0	16, 11–24	-	NA	NA	8
E/E' ratio (lateral)	12.7±7.4	-	-	10.0±4.5	NA	NA	8
Diastolic Dysfxn (y/n)	92%	100%	NA	69%	67%	NA	
None	8%	0%	NA	31%	33%	NA	
Grade 1	31%	77%	NA	29%	22%	NA	
Grade 2	43%	21%	NA	36%	37%	NA	
Grade 3	18%	2%	NA	4%	7%	NA	
Pulmonary Pressure							
TR velocity (m/sec)	2.5±0.4	NA	41, 33–53 (RVSP)	37±13 (RVSP)	NA	NA	<2.9

Values in italics were estimated by the author from primary data provided in the referenced manuscripts.

EDD – LV end-diastolic dimension; ESD – LV end-systolic dimension; EDVi – LV end-diastolic volume indexed to BSA; EDVi – LV end-systolic volume indexed to BSA; LVEF – LV ejection fraction; WT – wall thickness; LVMI – LV mass index; RWT – relative wall thickness; FS – fractional shortening; LAVi – left atrial volume indexed to BSA; E wave – peak early diastolic transmitral flow velocity; A wave – peak late diastolic transmitral flow velocity; E' lateral – peak early diastolic mitral annular tissue velocity at lateral mitral annulus; E' septal – peak early diastolic mitral annular tissue velocity at septal mitral annulus; TR – tricuspid regurgitation.