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ORIGINAL RESEARCH ARTICLE

Prominent 'Y' descent is an ominous sign of a poorer prognosis in heart failure with preserved ejection fraction

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Abstract

Aims The heterogeneity of heart failure with preserved ejection fraction (HFpEF) represents different pathophysiological paths by which individual patients develop heart failure. The deterioration mechanisms are considered to be mainly left ventricular diastolic dysfunction, right ventricular (RV) systolic function, and RV afterload. It is unclear whether RV distensibility affects the deterioration of HFpEF. Our study aimed to clarify whether impaired RV distensibility is associated with the deterioration of HFpEF.

Methods and results We retrospectively enrolled 322 patients with HFpEF and examined their echocardiography results, electrocardiograms, phonocardiograms, and jugular venous pulse waves. Using signal-processing techniques, the prominent 'Y' descent of the jugular venous waveform was detected as an established haemodynamic sign of a less-distensible right ventricle. We defined cardiovascular events of HFpEF as follows: sudden death, death from heart failure, or hospitalization for HFpEF. During a mean follow-up period of 33 ± 20 months, 73 patients had cardiovascular events of HFpEF. The prevalence of a less-distensible right ventricle and the variables of RV systolic pressure were independent risk factors for cardiovascular events (hazard ratio, 2.046, $P = 0.005$, and hazard ratio, 1.032 per 1 mmHg, $P = 0.002$, respectively). The event-free rate of HFpEF was the lowest for HFpEF with a less-distensible right ventricle and elevated RV systolic pressure (≥35 mmHg) (P for trend <0.001).

Conclusions A less-distensible right ventricle and elevated RV systolic pressure were found to be closely associated with the deterioration of HFpEF. Assessment of a less-distensible right ventricle may help to stratify patients and improve therapeutic strategies for HFpEF.

Keywords HFpEF; Heart failure; Right ventricular distensibility; Jugular venous pulse; Right ventricular systolic pressure; Right ventricular dysfunction

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Introduction

The heterogeneity of heart failure with preserved ejection fraction (HFpEF) represents different pathophysiological paths by which individual patients develop heart failure.[1–3] The deterioration mechanisms are considered to be mainly left ventricular (LV) diastolic dysfunction, right ventricular (RV) systolic function, and RV afterload,[4–6] but it is unclear whether RV distensibility affects the deterioration of HFpEF. Recently, we reported that a less-distensible right ventricle due to aging and RV dysfunction were associated with congestive heart failure.[7] However, to our knowledge, it is unknown whether a less-distensible right ventricle is associated with cardiovascular events of HFpEF. Therefore, in the present study, we aimed to clarify whether impaired RV distensibility is associated with cardiovascular events of HFpEF. To identify a less-distensible right ventricle, we examined the jugular pulse waveform using the same signal-processing technique as in our previous study.[7]

Methods

Study population

Between January 2010 and December 2015, 5327 consecutive outpatients were referred to our hospital for echocardiographic examinations (Vivid 7, General Electric Healthcare, Wauwatosa, WI, USA) for cardiovascular disease. For 2011 outpatients (972 men; age range, 40–97 years; mean, 68 ± 12 years), we simultaneously recorded electrocardiograms, phonocardiograms, and the jugular venous pulse, and all data were stored in a hard disc memory system (echoPAC PC, General Electric Healthcare) for later analyses. In the present study, we defined patients with HFpEF as follows: having symptoms and/or signs of heart failure, preserved LV ejection fraction ≥50%, and two or more positive variables of LV diastolic function (*Figure 1*).[8] First, 1352 patients were excluded because of lack of data, such as LV ejection fraction, septal or lateral mitral annulus velocity, left atrial volume index, or RV systolic pressure, or incomplete detection of the jugular venous pulse waveform due to a fatty neck, tachycardia >90 b.p.m., or no apparent fluctuations. Second, patients were also excluded if they had normal LV diastolic function, constrictive pericarditis, cardiac amyloidosis, moderate or severe valvular heart disease, congenital heart disease, acute decompensate heart failure, acute coronary syndrome within 6 months, uncontrolled angina pectoris, LV ejection fraction <50%, or cardiac diastolic dysfunction with no symptoms and/or signs of heart failure (*Figure 1*). Patients with constrictive pericarditis are characterized by prominent Y descent and, in general, have a preserved LV ejection fraction and symptomatic heart failure. To exclude patients with constrictive pericarditis from this study, septal bounce, mitral inflow variation with respiration, and medial and lateral e′ velocity of the mitral annulus were assessed by echocardiography.[9,10] We performed computerized scans and/or inserted a cardiac catheter in patients suspected of constrictive pericarditis. We diagnosed 348 patients with HFpEF, but 26 were excluded because of follow up at another hospital. Thus, we retrospectively enrolled 322 patients in the present study. All patients have been taking chronic medication for 3 months. Blood sample tests were also performed on the same day as echocardiography for 233 of 322 patients. Informed consent was provided by all patients. This study complied with the Declaration of Helsinki and was approved by the Human Subject Review Committee at our institute.

Jugular venous waveform pattern of a less-distensible right ventricle

The methods to measure and judge the jugular venous pulse were the same as those in our previous report.[7] The jugular venous pulse was recorded in the supine position by well-trained cardiac sonographers. A pulse-wave transducer (TY-306, Fukuda Denshi, Tokyo, Japan) was placed over the neck, above and to the right of the junction of the right clavicle and the manubrium sterni, and held in place manually (*Figure 2*). The jugular venous waveform was recorded for at least 30 s and digitized at a sampling interval of 600 Hz. Using an offline moving average technique (Matlab version 14, Mathworks, Natick, MA, USA), respiratory baseline fluctuations (0.1–

Figure 1 Study flowchart for patient enrolment in the present study. HFpEF, heart failure with preserved left ventricular ejection fraction; LAVI, left atrial volume index; LVEF, left ventricular ejection fraction; TR, tricuspid regurgitation.

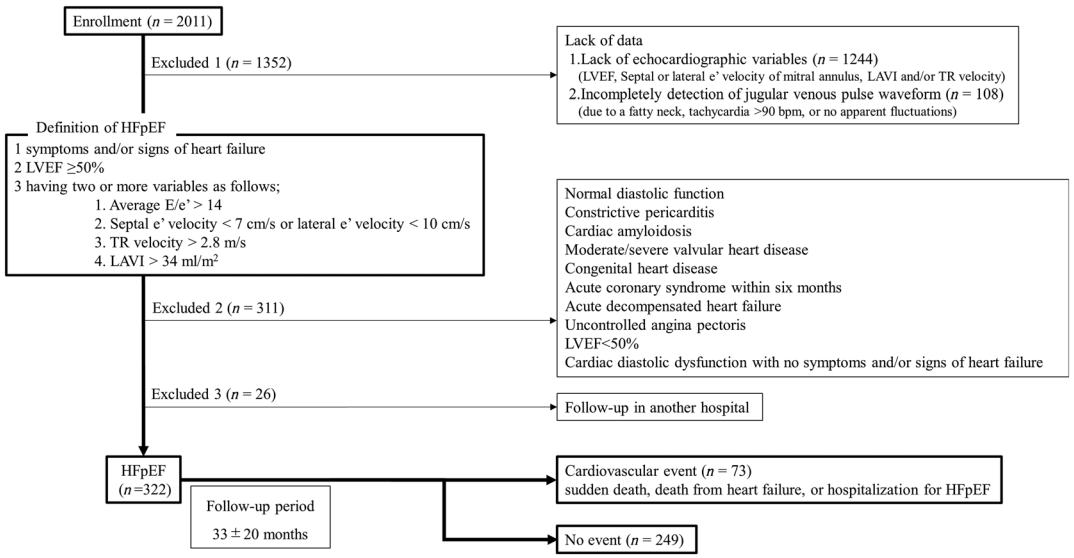
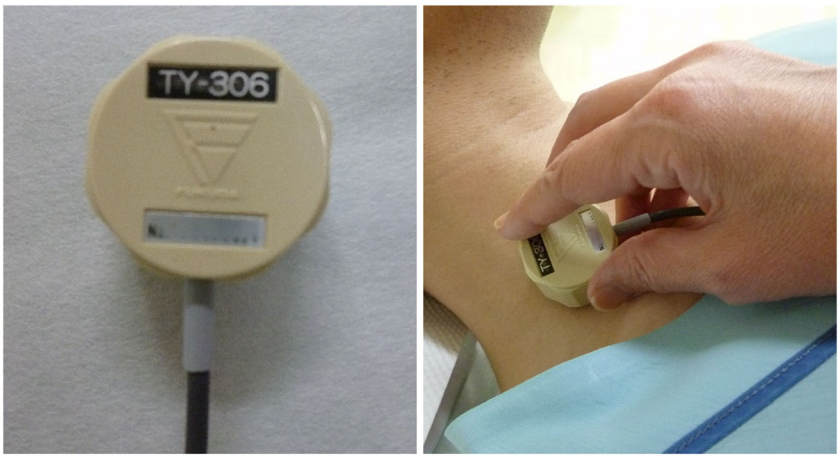


Figure 2 Jugular venous pulse. A pulse-wave transducer (left side) was placed over the neck, above and to the right of the junction of the right clavicle and the manubrium sterni, and held in place manually (right side).



0.5 Hz) were excluded from the jugular waveform to determine a relative depth of the nadirs of 'X' and 'Y' descent [*Figure 3A* and *3B*, right side]. According to the established significance of the jugular venous waveform,[11–13] two cardiologists who were blinded to the clinical data judged whether the jugular venous pulse had a dominant 'Y' descent, where the nadir of the 'Y' descent was deeper than that of the 'X' descent. A normal jugular venous waveform characterized by the highest 'A' wave and lowest 'X' descent within one cardiac cycle is shown in *Figure 3A*. In contrast, the dominant 'Y' descent with a lower nadir than that of the 'X' descent is shown in *Figure 3B*, a finding highly indicative of a less-distensible right ventricle.[11–13] Interobserver reproducibility in evaluation of RV distensibility was also investigated in this study. In our previous study, the waveform of the jugular venous pulse was compared and revealed to have high similarity with the waveform of right atrial pressure with right heart catheterization.[7]

Echocardiographic evaluation

To evaluate the diastolic properties of the left ventricle, we measured the mitral inflow E and A velocities, the deceleration time (DT) of early mitral flow, and the early diastolic velocities (e′) using a pulsed-wave tissue Doppler technique from the apical view (*Figure 3A* and *3B*, left side). We measured septal and lateral E/e′ and averaged the values for more reliable assessment of LV relaxation and filling pressure.[8] If the patients had atrial fibrillation, we estimated velocity measurements from 10 consecutive cardiac cycles.[8] The left atrial volume index was obtained using the biplane method from both the apical four-chamber and two-chamber views.[14] For patients with sinus rhythm, we determined the LV diastolic dysfunction according to the E/A ratio, average E/e′ ratio, tricuspid regurgitation velocity, and left atrial volume index.[8] In addition, tricuspid regurgitation jet was detected by the continuous Doppler technique to measure the RV systolic pressure. The peak pressure gradient from the right ventricle to the right atrium was calculated from the peak tricuspid regurgitant velocity (V) using the modified Bernoulli equation (pressure gradient = 4 V^2). The peak RV pressure was then calculated by adding the peak pressure gradient to the right atrial pressure, which was estimated from the echocardiographic characteristics of the inferior vena cava.[15] An RV systolic pressure of 35 mmHg or greater was defined as elevated RV systolic pressure, which is a non-invasive surrogate for RV afterload.

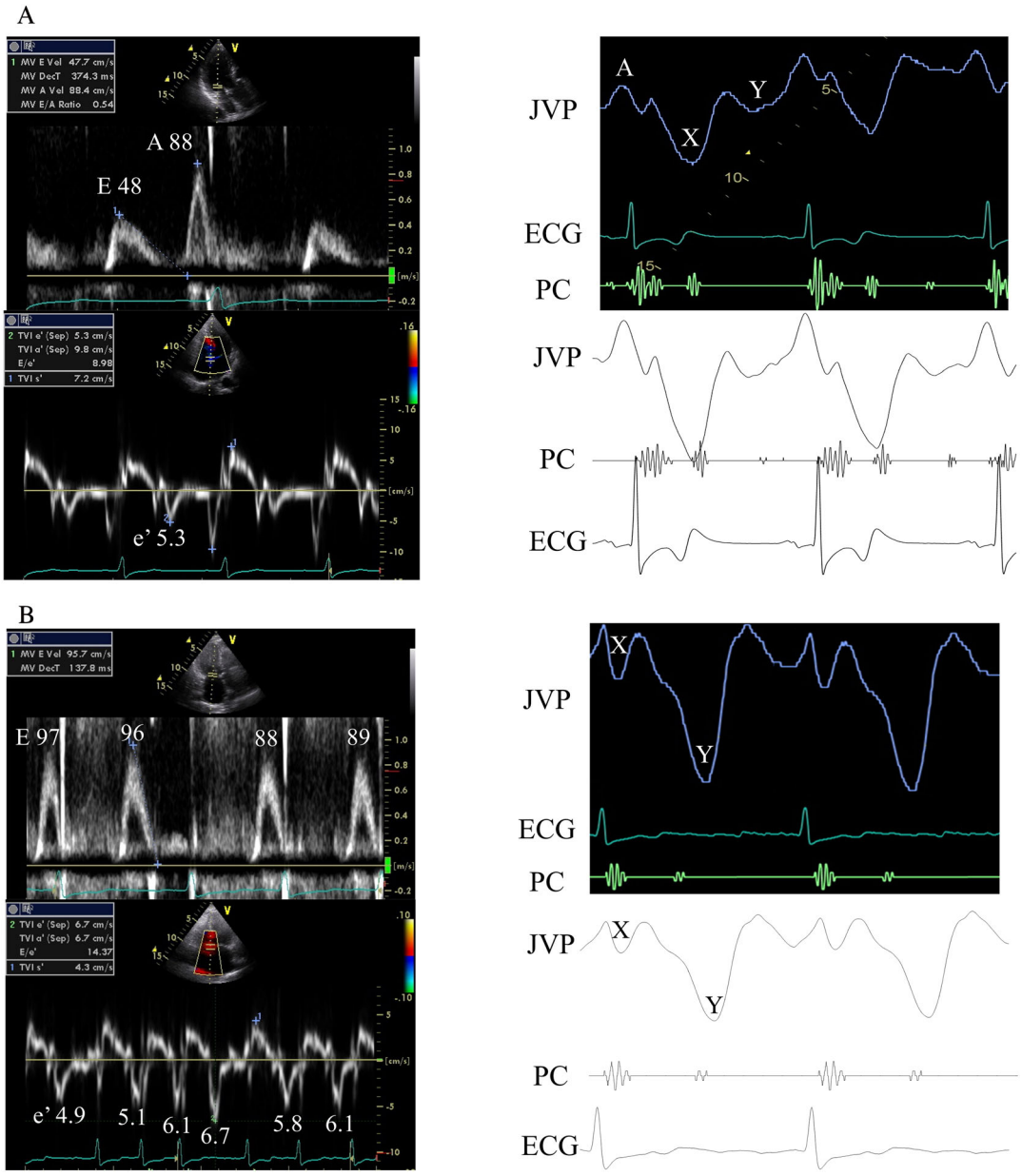
Documentation of endpoints

All 322 patients were followed up at the outpatient clinic of our hospital. We defined deterioration of HFpEF as follows: sudden death, death from heart failure, or hospitalization for HFpEF. These cardiovascular events were adjudicated by cardiologists at our hospital.

Statistical analysis

Results are expressed as mean ± standard deviation, median (interquartile range), or number (%). Interobserver reproducibility in evaluation of RV distensibility was examined using kappa coefficient. The unpaired *t*-test was used to compare numerical data between the two groups, and the χ^2 test or Fisher's exact test was used to compare non-parametric data between the two groups. Clinical, haemodynamic, and echocardiographic variables associated with cardiovascular events were identified by Cox regression analysis. In the multivariate analysis based on the Cox hazard model, we selected variables

Figure 3 Assessment of echocardiography and the jugular venous pulse. The mitral inflow (upper left) and the early diastolic velocities (e′) of the septum (lower left). Tracings of the jugular venous pulse, phonocardiogram, and electrocardiogram (upper right), with subtraction of baseline fluctuations (lower right). (A) A 73-year-old man with HFpEF and prior coronary revascularization had a distensible right ventricle characterized by the highest 'A' wave and the deepest 'X' descent within a single cardiac cycle. (B) An 86-year-old woman with HFpEF and chronic atrial fibrillation had a less-distensible right ventricle characterized by the dominant 'Y' descent, with a nadir deeper than that of 'X'. ECG, electrocardiogram; JVP, jugular venous pulse; PC, phonocardiogram.



with a *P* value <0.2 in the univariate analysis. Variables with the largest *P* value over 0.05 were removed using stepwise backward reduction to find the best final model. Cardiovascular events were estimated by the Kaplan–Meier method. Differences between event-free curves were examined using the log-rank χ^2 test. Significance was established at $P < 0.05$. All statistical analyses were carried out using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan).[16]

Results

At the end of the 33 ± 20 (range, 0.5–60)-month follow up, 73 (23%) of the 322 study patients had cardiovascular events (*Figure 1*). Contingency table for evaluation of RV distensibility is shown in *Table 1*. Kappa coefficient was 0.974 [95% confidence interval (CI), 0.949–0.999] in this study. The demographic and clinical characteristics of the patients are

Table 1 Contingency table for evaluation of RV distensibility

		Cardiologist B		
		Distensible right ventricle	Less-distensible right ventricle	Totals
Cardiologist A	Distensible right ventricle	193	3	196
	Less-distensible right ventricle	1	125	126
	Totals	194	128	322

shown in *Table 2*. Patients with a less-distensible right ventricle were older and had a higher New York Heart Association (NYHA) class and brain natriuretic peptide level than those with a distensible right ventricle. The rates of prior hospitalization for HFpEF, chronic atrial fibrillation, administration of diuretics, and symptoms and signs of systemic venous congestion were significantly higher, whereas the rate of diabetes mellitus and prior coronary revascularization were significantly lower for patients with a less-distensible right ventricle than those with a distensible right ventricle. The rates of cardiovascular events were also significantly higher for patients with a less-distensible right ventricle than for those with a distensible right ventricle.

Echocardiographic features according to right ventricular diastolic function

The echocardiographic features of the patients are shown in *Table 3*. Patients with a less-distensible right ventricle had a smaller LV end-diastolic dimension, larger left atrial volume index, higher E/A ratio of mitral and tricuspid inflow, shorter DT of mitral and tricuspid early inflow, slower average diastolic mitral annulus velocity, higher average mitral E/e′ ratio, larger right atrial end-systolic area, larger RV outflow tract, higher RV systolic pressure, shorter tricuspid annular plane systolic excursion (TAPSE), lower RV fractional area change (RVFAC), higher tricuspid E/e′ ratio, and bigger inferior vena cava than those with a distensible right ventricle.

Univariate and multivariate analyses of cardiovascular events

Univariate Cox proportional hazard analysis revealed that the variables of age, left atrial volume index, average mitral E/e′ ratio, RV systolic pressure, and inferior vena cava diameter were associated with cardiovascular events (*Table 4*). Prior hospitalization for HFpEF, chronic atrial fibrillation, diuretics, NYHA Class III, and a less-distensible right ventricle were also associated with cardiovascular events.

Multivariate Cox proportional hazard analysis demonstrated that a less-distensible right ventricle [hazard ratio (HR), 2.046, 95% CI, 1.237–3.385, $P = 0.005$] and the variables of RV systolic pressure (HR, 1.032 per 1 mmHg, 95% CI, 1.012–1.052, $P = 0.002$) were independent risk factors for cardiovascular events (*Table 4*). The variables of age (HR, 1.029 per 1 year, 95% CI, 1.002–1.057, $P = 0.038$), prior hospitalization for HFpEF (HR, 3.185, 95% CI, 1.956–5.186, $P < 0.001$), administration of diuretics (HR, 2.187, 95% CI, 1.141–4.190, $P = 0.018$), and NYHA Class III (HR, 1.832, 95% CI, 1.100–3.049, $P = 0.020$) were also independent risk factors for cardiovascular events.

Event-free rate of heart failure with preserved ejection fraction according to right ventricular diastolic function and right ventricular systolic pressure

We divided the patients into four groups according to RV diastolic function and elevated RV systolic pressure in association with cardiovascular events. The Kaplan–Meier analysis is shown in *Figure 4*. The event-free rate was the lowest for HFpEF with a less-distensible right ventricle and elevated RV systolic pressure (P for trend <0.001).

Discussion

The present study revealed that a less-distensible right ventricle, as measured by jugular venous pulse waveform, and RV systolic pressure were independently associated with cardiovascular events of HFpEF. Moreover, the combination of a less-distensible right ventricle and elevated RV systolic pressure had the greatest effect on cardiovascular events.

It is unclear why RV distensibility is impaired in HFpEF. Abnormal LV relaxation elicited by aging or lifestyle-related diseases[8,17] is usually related to an increased LV filling pressure. Chronic elevated LV filling pressure influences left atrial dysfunction, which leads to pulmonary venous hypertension and increased RV afterload.[6] Deterioration of RV afterload may cause RV diastolic dysfunction, resulting in a less-distensible right ventricle. In our previous study, DT of mitral early flow was prolonged before the increase in the incidence of a less-distensible right ventricle and elevated RV systolic pressure.[7] Our previous data also support that a less-distensible right ventricle often originates from elevated RV afterload associated with LV diastolic dysfunction. Elevated LV filling pressure itself may directly influence RV

Table 2 Patient characteristics according to right ventricular distensiblity

	Total population (n = 322)	Distensible right ventricle (n = 193)	Less-distensible right ventricle (n = 129)	P value
Age, years	76 ± 11	73 ± 12	79 ± 10	<0.001
Men	146 (45)	92 (48)	54 (42)	0.361
Heart rate, b.p.m.	70 ± 11	70 ± 11	71 ± 11	0.165
Prior hospitalization for HFpEF	62 (19)	29 (12)	33 (45)	<0.001
Underlying disorders				
Hypertension	281 (87)	165 (85)	116 (90)	0.306
Diabetes mellitus	65 (20)	47 (24)	18 (14)	0.024
Chronic atrial fibrillation	74 (23)	7 (4)	67 (52)	<0.001
Prior coronary revascularization	85 (26)	62 (32)	23 (18)	0.005
Medications				
Beta-blockers	163 (51)	99 (51)	64 (50)	0.82
Calcium channel blockers	175 (54)	108 (56)	67 (52)	0.495
ACE/ARB inhibitors	228 (71)	131 (68)	97 (75)	0.17
Diuretics	163 (51)	54 (27)	109 (86)	<0.001
NYHA	2.3 ± 0.5	2.2 ± 0.4	2.4 ± 0.5	<0.001
I/II/III/IV	0/229/93/0	0/157/36/0	0/72/57/0	<0.001
Symptoms and signs of HFpEF				
Dyspnoea on exertion	304 (94)	186 (96)	118 (91)	0.082
Leg oedema	132 (41)	40 (21)	92 (71)	<0.001
Neck vein dilatation	90 (28)	23 (12)	67 (52)	<0.001
Pleural effusion	50 (16)	7 (4)	43 (33)	<0.001
BNP, pg/dL (n = 233)	181 (83, 318)	119 (67, 234) (n = 134)	262 (160, 460) (n = 99)	<0.001
Creatinine, mg/dL (n = 233)	0.87 (0.66, 1.11)	0.87 (0.64, 1.09) (n = 134)	0.88 (0.69, 1.15) (n = 99)	0.781
eGFR, mL/min (n = 233)	57 ± 24	59 ± 25 (n = 134)	56 ± 22 (n = 99)	0.354
Cardiovascular event	73 (23)	25 (13)	48 (37)	<0.001

Data are number of patients (%), median (interquartile range), or mean ± SD. ACE/ARB, angiotensin-converting enzyme inhibitors/angiotensin-receptor blockers; BNP, brain natriuretic peptide; HFpEF, heart failure with preserved left ventricular ejection fraction; NYHA, New York Heart Association.

Table 3 Echocardiographic features according to right ventricular distensiblity

	Total population (n = 322)	Distensible right ventricle (n = 193)	Less-distensible right ventricle (n = 129)	P value
Left ventricular function				
LVEF, %	66 ± 8	66 ± 9	66 ± 8	0.715
LVEDD, mm	48 ± 5	49 ± 5	47 ± 6	0.004
LAVI, mL/m^2	41 ± 10	39 ± 7	44 ± 12	<0.001
E/A ratio of mitral inflow (n = 248)	0.97 ± 0.45	0.92 ± 0.38 (n = 186)	1.12 ± 0.59 (n = 62)	0.002
DT of mitral early inflow	217 ± 63	227 ± 58	202 ± 66	<0.001
Average mitral e′, cm/s	7.3 ± 1.8	7.5 ± 1.8	7.0 ± 1.7	0.021
Average mitral E/e′ ratio	11 ± 5	10 ± 5	13 ± 6	<0.001
Grade I/II/III diastolic dysfunction (n = 248)	155/83/10	127/54/5	28/29/5	0.003
Positive variables of left ventricular diastolic function	2.6 ± 0.7	2.4 ± 0.6	2.8 ± 0.7	<0.001
0–1/2/3/4	0/176/109/37	0/130/48/15	0/46/61/22	<0.001
Right ventricular function				
Right atrial end-systolic area, cm^2 (n = 247)	15 ± 6	13 ± 4	18 ± 8	<0.001
RVOT, mm	26 ± 5	25 ± 5	27 ± 5	0.002
RVSP, mmHg	33 ± 11	31 ± 11	36 ± 11	<0.001
TAPSE, mm (n = 255)	20 ± 4	21 ± 4 (n = 150)	18 ± 3 (n = 105)	<0.001
RVFAC, % (n = 247)	48 ± 12	53 ± 9 (n = 143)	42 ± 13 (n = 104)	<0.001
E/A ratio of tricuspid inflow (n = 76)	1.2 ± 0.3	1.1 ± 0.3 (n = 60)	1.3 ± 0.4 (n = 16)	0.019
DT of tricuspid early inflow, ms (n = 93)	182 ± 55	198 ± 50 (n = 60)	153 ± 54 (n = 33)	<0.001
Tricuspid e′, cm/s (n = 43)	10 ± 4	11 ± 4 (n = 26)	9 ± 3 (n = 17)	0.064
Tricuspid E/e′ ratio (n = 43)	5.4 ± 2.4	4.6 ± 1.2 (n = 26)	6.8 ± 3.0 (n = 17)	0.002
IVC, mm	15 ± 5	14 ± 4	16 ± 5	<0.001

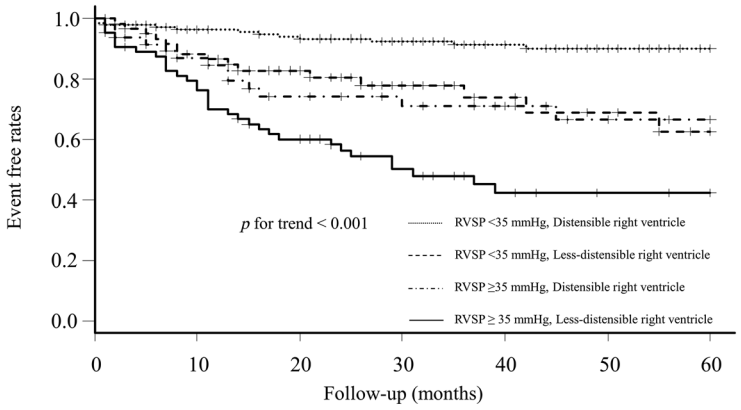
Data are number of patients (%) or mean ± SD. DT, deceleration time; IVC, inferior vena cava; LAVI, left atrial volume index; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; RVFAC, right ventricular fractional area change; RVOT, right ventricular outflow tract; RVSP, right ventricular systolic pressure; TAPSE, tricuspid annular systolic excursion.

Table 4 Multivariate analysis of cardiovascular events

	Univariate			Final model using stepwise backward reduction		
	Odds ratio	95% confidence interval	*P* value	Odds ratio	95% confidence interval	*P* value
Age (per 1 year)	1.076	1.048–1.104	<0.001	1.029	1.002–1.057	0.038
Men	0.696	0.434–1.117	0.133			
Heart rate (per 1 b.p.m.)	1.008	0.987–1.030	0.459			
Prior hospitalization for HFpEF	5.223	3.271–8.338	<0.001	3.185	1.956–5.186	<0.001
Hypertension	2.572	0.939–7.047	0.066			
Diabetes Mellitus	1.13	0.649–1.969	0.666			
Chronic atrial fibrillation	2.745	1.71–4.407	<0.001			
Prior coronary revascularization	0.779	0.452–1.342	0.369			
Beta-blockers	0.952	0.601–1.506	0.832			
Calcium channel blockers	1.194	0.750–1.899	0.455			
ACE/ARB inhibitors	1.354	0.795–2.306	0.264			
Diuretics	5.064	2.823–9.083	<0.001	2.187	1.141–4.190	0.018
NYHA III	4.706	2.946–7.519	<0.001	1.832	1.100–3.049	0.020
LVEF (per 1%)	0.976	0.948–1.001	0.063			
LVEDD (per 1 mm)	0.990	0.948–1.033	0.636			
LAVI (per 1 mL/m^2)	1.029	1.010–1.048	0.002			
Average mitral E/e′ ratio	1.058	1.024–1.094	<0.001			
RVOT (per 1 mm)	1.014	0.970–1.059	0.547			
RVSP (per 1 mmHg)	1.047	1.031–1.062	<0.001	1.032	1.012–1.052	0.002
IVC (per 1 mm)	1.107	1.059–1.158	<0.001			
Less-distensible right ventricle	3.554	2.185–5.781	<0.001	2.046	1.237–3.385	0.005

ACE/ARB, angiotensin-converting enzyme inhibitors/angiotensin-receptor blockers; HFpEF, heart failure with preserved left ventricular ejection fraction; IVC, inferior vena cava; LAVI, left atrial volume index; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; RVOT, right ventricular outflow tract; RVSP, right ventricular systolic pressure.

Figure 4 Kaplan–Meier curves for event-free rates according to right ventricular distensibility and right ventricular systolic pressure. The patients with a less-distensible right ventricle and elevated right ventricular systolic pressure had the lowest event-free rate among the four groups. RVSP, right ventricular systolic pressure.



No. of patients at risk

RVSP <35 mmHg, Distensible right ventricle	145	129	121	98	76	58	42
RVSP <35 mmHg, Less-distensible right ventricle	64	51	39	24	19	14	12
RVSP ≥35 mmHg, Distensible right ventricle	48	36	27	24	19	14	12
RVSP ≥ 35 mmHg, Less-distensible right ventricle	65	50	36	23	15	10	9

distensibility through diastolic ventricular interaction.[18] Age-related change may also affect RV distensibility.[7] Olivetti *et al*. found that aging was accompanied by a decrease in myocyte nuclei of 14 million/year and an increase in reactive cellular hypertrophy of the right ventricle.[19] Hodkinson *et al*. reported that amyloid deposition was detected in nearly half of the patients over 70 years old.[20] Thus, a less-distensible right ventricle may occur due to increased RV afterload, diastolic ventricular interaction, and/or age-related change of the myocardium in HFpEF.

The physiological properties of the right ventricle are a lower contractility and higher compliance than the left ventricle, which means that RV ejection depends more on the Frank–Starling mechanism than on contractility.[21] A less-

distensible right ventricle shifts the RV pressure–volume relationship to the upside, leading to a higher RV filling pressure and right atrial pressure. Moreover, when RV preload reserves are lost, the stroke volume is decreased with an increased RV afterload, resulting in RV afterload mismatch and further deterioration of the haemodynamics of HFpEF. The loss of high compliance, the greatest feature of the right ventricle, and the higher RV afterload complicate the pathophysiology of HFpEF. Indeed, RV dysfunction is associated with the severity of heart failure, independent of the LV ejection fraction[5,22,23] Therefore, as found in this study, the combination of a less-distensible right ventricle and elevated RV systolic pressure may lead to refractory HFpEF.

On the other hand, it is well known that a high average mitral E/e′ ratio reflects an elevated LV filling pressure and is an important prognostic factor for HFpEF,[5] but our results are inconsistent with those of a previous study. An elevated left atrial pressure evokes pulmonary oedema and may be related to cardiovascular events; however, compensative mechanisms for an elevated left atrial pressure occur in patients with chronic heart failure.[24] Aschauer *et al*. recently reported that RV indices, but not LV indices, measured by magnetic resonance imaging were associated with cardiovascular events.[25] Moreover, right-sided heart failure often masks apparent left-sided heart failure. Therefore, LV indices may have influenced RV dysfunction, but not cardiovascular events, in the present study. It is also well known that other RV parameters, such as TAPSE and RVFAC, are independent prognostic values important for HFpEF.[26] Although RV function can be assessed by echocardiography in a limited number of patients in this study, we must discuss the relationship between a less-distensible RV and other RV parameters. First, patients with a less-distensible right ventricle may have RV systolic dysfunction, as indicated by a lower TAPSE and RVFAC. Second, the impairment of RV contractility can decrease RV elastic recoil and be related to RV relaxation abnormality. Indeed, tricuspid e′, the index of RV relaxation ability, was slightly slower in patients with a less-distensible right ventricle than in those with a distensible right ventricle. Lastly, patients with a less-distensible right ventricle had a higher tricuspid E/e′, the index of RV filling pressure. The main factors contributing to ventricular diastolic function are ventricular relaxation and distensibility. Ventricular relaxation is an active energy-dependent process and influences lowering speed of ventricular pressure in isovolumic relaxation and the rapid filling phase. On the other hand, ventricular distensibility is passive stiffness of ventricle. Here, we should consider whether the main cause of high RV filling pressure is a decrease in RV distensibility itself or incomplete RV relaxation because these abnormalities in the early diastolic phase are related to a high RV filling pressure and may be targets for HFpEF treatment. In general, incomplete ventricular relaxation is evoked by tachyarrhythmia or exercise-induced tachycardia. Recently, Borlaug *et al*. revealed that restrictive RV physiology is related to exercise intolerance in patients with HFpEF.[27] In their study, the right atrial pressure was higher in patients with HFpEF than in normal subjects, although the tricuspid e′ at rest was the same between the two groups. Moreover, the inability to enhance RV relaxation ability with exercise was directly correlated with a greater increase in right heart filling pressure. These results suggest that a decrease in RV distensibility is the main cause of a high filling RV pressure at rest and the complication of incomplete RV relaxation evoked by exercise-induced tachycardia causes to the increased RV filling pressure during exercise. A less-distensible right ventricle rather than incomplete RV relaxation may have led to the high tricuspid E/e′ at rest in our study. Therefore, our RV indices as examined by echocardiography suggest that patients with a less-distensible right ventricle had more advanced RV dysfunction, as evidenced by not only the higher RV filling pressure but also the lower RV contractility and greater decrease in RV relaxation ability.

Assessment of RV distensibility may be useful for planning therapeutic strategies for patients with HFpEF and a less-distensible right ventricle. If patients have a less-distensible right ventricle, symptomatic therapy for restrictive RV physiology may be adopted.[12] Diuretics may improve symptoms and possibly the HFpEF haemodynamics, but excessive use of diuretics may reduce the RV filling pressure, resulting in a decreased stroke volume. Recently, tolvaptan, a water diuretic, was reported to effectively improve venous congestion and the long-term prognosis without lowering the cardiac index in patients with HFpEF.[28,29] Tolvaptan may be suitable for patients with HFpEF and restrictive RV physiology. The atrial contribution to RV filling is removed by the development of atrial fibrillation. Atrial fibrillation may also worsen existing diastolic dysfunction. Indeed, chronic atrial fibrillation was independently associated with a less-distensible right ventricle in our previous study.[7] Therefore, maintaining sinus rhythm may play an important role in patients with HFpEF and a less-distensible right ventricle. As the augmentation of cardiac output in restrictive RV physiology depends on the heart rate, it will need to be supported.[1,30] Heart rate reduction to prevent incomplete ventricular relaxation may be useful for HFpEF with LV relaxation abnormality; however, its effectiveness is controversial.[31,32] Restrictive RV physiology may attenuate the efficacy of a lower heart rate to prevent incomplete ventricular relaxation. Reducing pulmonary artery pressure may improve the haemodynamics of HFpEF with a less-distensible right ventricle through restoration of RV afterload mismatch, but the effectiveness of pulmonary artery vasoactive drugs, such as cyclic guanosine monophosphate, or endothelin pathway drugs is also controversial.[26] The heterogeneity of HFpEF syndrome may be a major factor underlying the failure of prior clinical trials, which have thus far essentially used a one-size-fits-all approach, and precision medicine may be needed for the heterogeneity of this syndrome.[33] Indeed,

patients with HFpEF and a less-distensible right ventricle had many facies and more advanced HFpEF, as evidenced by RV dysfunction and higher brain natriuretic peptide levels, NYHA class, prevalence of atrial fibrillation, LV filling pressure, and greater use of diuretics in this study. Such heterogeneity also leads to refractory HFpEF. It is unclear whether referring symptomatic therapy for restrictive haemodynamics can improve cardiovascular events of refractory HFpEF, but assessment of RV distensibility may be needed for planning therapeutic strategies for HFpEF. Moreover, not a one-size-fits-all approach, but precision medicine may be required for patients with HFpEF and a less-distensible right ventricle.

Study limitations

Several methodological limitations must be considered. First, this was a retrospective study that was conducted at a single centre and performed on consecutive patients matching eligibility criteria. As we required satisfactory imaging of echocardiography and jugular venous pulse, some patients, such as obese patients with limited windows or fatty neck, may have been underrepresented. Moreover, patients with tachycardia may also have been excluded because of difficulty in separating the E and A wave in the mitral inflow or the 'X' and 'Y' descent of the jugular venous pulse. Second, it is well known that wild-type transthyretin amyloidosis is an underdiagnosed cause of HFpEF.[34] Although we excluded patients with overt amyloid heart, those with subclinical amyloidosis may have been included in the present study. Third, we focused on RV compliance and afterload, which were examined non-invasively, and found them to be associated with the cardiovascular events of HFpEF independently of clinical characteristics and LV indices. However, we were unable to fully examine echocardiographic RV contractile and diastolic parameters and their relationships with a less-distensible right ventricle because the echocardiographic quantitative assessment of RV function was often difficult due to the complex RV anatomy.[35] Moreover, we were unable to examine the right atrial and ventricular pressure using the right cardiac catheter at rest or after exercise. Further clinical studies are warranted to clarify the pathophysiological importance of a less-distensible right ventricle as evaluated by the jugular venous pulse waveform in patients with HFpEF.

Conclusions

A less-distensible right ventricle and elevated RV systolic pressure are closely associated with the deterioration of HFpEF. Assessment of a less-distensible right ventricle may help to stratify patients and improve therapeutic strategies for HFpEF.

Conflict of interest

None declared.

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