ORIGINAL ARTICLE

Right atrial pressure represents cumulative cardiac burden in heart failure with preserved ejection fraction

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Abstract

Aims Right-sided filling pressure is elevated in some patients with heart failure (HF) and preserved ejection fraction (HFpEF). We hypothesized that right atrial pressure (RAP) would represent the cumulative burden of abnormalities in the left heart, pulmonary vasculature, and the right heart.

Methods and results Echocardiography was performed in 399 patients with HFpEF. RAP was estimated from inferior vena cava morphology and its respiratory change [estimated right atrial pressure (eRAP)], and patients were divided according to eRAP (3 or ≥8 mmHg). Patients with higher eRAP displayed more severe abnormalities in LV diastolic function as well as right heart structure and function than those with normal eRAP. Cardiac deaths or HF hospitalization occurred in 84 patients over a median follow-up of 19.0 months (interquartile range 6.7–36.9). The presence of higher eRAP was independently associated with an increased risk of the composite outcome (adjusted hazard ratio 2.20 vs. normal eRAP group, 95% confidence interval 1.34–3.62, $P = 0.002$). Kaplan–Meier curves separating the patients into four groups based on eRAP and E/e' ratio showed that event-free survival varied among the groups, providing an incremental prognostic value of eRAP over E/e' ratio. The classification and regression tree analysis demonstrated that eRAP was the strongest predictor of the outcome followed by right ventricular dimension, E/e' ratio, and estimated right ventricular systolic pressure, stratifying the patients into four risk groups (incident rate 8.8–72.2%).

Conclusions These data may provide new insights into the prognostic role of RAP in the complex pathophysiology of HFpEF and suggest the utility of eRAP for the risk stratification in patients with HFpEF.

Keywords Heart failure; Prognosis; Pulmonary hypertension; Right atrial pressure; Right heart

Introduction

More than half of patients with heart failure (HF) have a left ventricular (LV) preserved ejection fraction (HFpEF).[1,2] Increases in left heart filling pressure secondary to LV diastolic dysfunction is a fundamental abnormality in patients with HFpEF.[3–6] Elevations in LV filling pressure are associated with poor clinical outcomes, whether assessed by invasively measured pulmonary capillary wedge pressure (PCWP) or non-invasive estimates using Doppler echocardiography.[7–11]

Right-sided filling pressure is also elevated in some patients with HFpEF.[12–14] Elevated right heart filling pressure in HFpEF may be mediated by pulmonary hypertension (PH) due to high LV filling pressures, right ventricular (RV) dysfunction, worsening tricuspid insufficiency, right atrial (RA) dysfunction, and increasing burden of atrial fibrillation (AF), each of which is associated with adverse outcomes.[12,13,15–18]

Hence, we speculated that right-sided filling pressure may represent the cumulative burden of these cardiac abnormalities and may provide valuable information for risk stratification in HFpEF.[19] Right heart filling pressure can be readily estimated using echocardiography based on inferior vena cava (IVC) morphology,[20] but few studies have reported the prognostic value of estimated right atrial pressure (eRAP) in patients with HFpEF. Accordingly, the aims of the present study were to investigate the relationship between eRAP and clinical outcomes in HFpEF patients and to evaluate hierarchical relationship that could exist between eRAP and other echocardiographic markers indicating abnormalities in the left heart, pulmonary vasculature, and the right heart.

Methods

Study population

In this retrospective observational study, we evaluated the association between echocardiographic markers of RAP and clinical outcomes in stable patients with HFpEF. Some participant data from this study have been previously published,[16,18,21,22] but not as it relates to the prognostic value of eRAP. We identified patients who were admitted to either Gunma University Hospital in Maebashi, Japan, between January 2014 and June 2019 or Hokkaido University Hospital in Sapporo, Japan, between January 2014 and December 2018. Diagnosis of HFpEF was defined as the typical clinical symptoms of HF (exertional dyspnoea, fatigue, or peripheral oedema), an EF $\geq$ of 50%, and at least one of the following: directly measured PCWP $>$ 15 mmHg, B-type natriuretic peptide (BNP) levels $>$ 200 pg/mL, the ratio of early diastolic mitral inflow velocity to early diastolic mitral annular tissue velocity (E/e') $>$ 15, left atrial (LA) volume index $>$ 34 mL/m^2, or previous HF-related hospitalization.[23,24] We excluded subjects with reduced EF (EF $<$ 50%), recovered EF (previous EF $<$ 40%), non-group II PH, significant left-sided valvular heart disease (mild or greater stenosis or moderate or greater regurgitation), acute coronary syndrome, congenital heart disease, or cardiomyopathies. From this group, patients with comprehensive echocardiographic evaluation including IVC measurements in a compensated state of HF were included. The study was approved by our Institutional Review Board with the waiver of consent and was performed in accordance with the declaration of Helsinki. All authors have read and agreed to the manuscript as written. The data underlying this article will be shared on reasonable request to the corresponding author.

Cardiac structure and function assessment

Comprehensive echocardiography was performed according to the contemporary guidelines.[25] LV volumes (end-diastolic volume and end-systolic volume), LA volume, and EF were measured using the biplane method of disks. Stroke volume was calculated from the LV outflow dimension and pulse-Doppler wave, and cardiac output (CO) was then determined as the product of stroke volume and heart rate. LV diastolic function was assessed using mitral inflow velocities, mitral annular tissue velocities, and septal E/e' ratio. RAP was estimated based on IVC diameter and its respiratory changes (eRAP), coded as 3 mmHg (IVC diameter $<$ 2.1 cm that collapses $>$ 50% with a sniff), 8 mmHg (borderline cases who did not meet criteria indicating either 3 or 15 mmHg), 15 mmHg (IVC diameter $>$ 2.1 cm that collapses $<$ 50% with a sniff), according to the ASE/EACVI guidelines.[25] Our laboratory has demonstrated high intra-observer and inter-observer reproducibility of eRAP measurements (intra-observer and inter-observer intraclass correlation coefficients were 0.96 and 0.79 in 15 subjects) (Yang et al., in press). RV systolic pressure was then calculated as 4 × peak tricuspid regurgitation (TR) velocity^2 + eRAP (eRVSP).[25] RV systolic function was assessed by tricuspid annular plane systolic excursion (TAPSE). Due to the unavailability of M-mode images, TAPSE was measured using two-dimensional (2D) images in 94 patients as previously described.[26] The correlation between 2D and M-mode-derived TAPSE was examined in 20 patients, and a strong correlation was found between them (r = 0.95, P < 0.0001). RV basal, mid-cavity, and longitudinal dimensions were measured at end-diastole using RV-focused views, and RV dilation was defined as RV mid-cavity dimension $>$ 35 mm.[25] RA maximum volume was measured in the apical four-chamber view and indexed to the body surface area. RA enlargement was defined as RA volume index $>$ 39 mL/m^2 in men and $>$33 mL/m^2 in women, with cut-offs taken as 2 standard deviations from the mean of the normal values.[25]

Outcome assessment

Patient followed-up was initiated from the day of echocardiographic examination. The primary endpoint of this study was a composite of cardiovascular deaths or HF hospitalization. The HF hospitalization was defined as dyspnoea and pulmonary oedema on chest X-ray requiring intravenous diuretic treatment.

Statistical analysis

Data are reported as mean (SD), median (IQR), or number (%) unless otherwise specified. Between-group differences were compared by a χ^2, unpaired t-test, Mann–Whitney U-test, ANOVA, or Kruskal–Wallis test. Kaplan–Meier curve analysis was used to assess event-free rates, and univariable and multivariable Cox proportional hazards models were then applied

to evaluate the independent prognostic power of eRAP. We did not put eRVSP into a multivariable Cox model because it includes eRAP in its formula. To evaluate the additive prognostic value of eRAP over E/e′ ratio, the patients were divided into four groups according to the combinations of eRAP and E/e′ ratio: group 1, eRAP = 3 mmHg and E/e′ ratio ≤ 15; group 2, eRAP = 3 mmHg and E/e′ ratio > 15; group 3, eRAP ≥ 8 mmHg and E/e′ ratio ≤ 15; and group 4, eRAP ≥ 8 mmHg and E/e′ ratio > 15. The decision-tree model was created to evaluate the hierarchical relationships among echocardiographic variables. Classification and regression tree (CART) analysis was used to construct the decision tree,[27] where patients were split into binary groups with the highest contrast for the composite endpoints. Input variables were eRAP ≥ 8 mmHg, eRVSP ≥ 35 mmHg, E/e′ ratio > 15, the presence of AF, TAPSE < 17 mm, RV dilation, and RA enlargement. Detailed parameters of decision-tree classifier were as follows: max depth = 3, minimum sample split = 20, minimum sample leaf = 7, and ccp alfa = 0.005. In each level of the tree, the variable with the strongest relationship to the endpoint was selected. All tests were two-sided, with a *P* value of <0.05 considered significant. All analyses were performed with JMP 14.0.0 (SAS Institute, Cary, NC, USA) and Python programming language 3.8.5 (Python Software Foundation, Wilmington, DE, USA).

Results

Baseline characteristics

A total of 399 patients with HFpEF met inclusion criteria for the study. Supporting Information *Table S1* shows comparisons of clinical demographics and cardiac structure and function according to eRAP values. As expected, patients with eRAP of 15 mmHg had the greatest right heart remodelling and dysfunction, but those with eRAP of 8 mmHg displayed larger LV mass index and LA volume index, higher eRVSP, larger RV and RA size, and higher prevalence of significant TR (≥moderate) than those with eRAP of 3 mmHg. Given the presence of cardiac remodelling and dysfunction in HFpEF patients with eRAP of 8 mmHg, participants were divided into two groups based on eRAP: normal eRAP (eRAP of 3 mmHg) and higher eRAP (eRAP ≥ 8 mmHg).

Compared with patients with normal eRAP, those with higher eRAP were more likely to be men and had higher prevalence of systemic hypertension and AF (*Table 1*). Age, body mass index, blood pressures, heart rate, and other comorbidities were similar in the two groups. Usage of angiotensin-converting enzyme inhibitors/angiotensin-receptor blockers, diuretics, and mineralocorticoid receptor antagonists was more frequent in higher eRAP group than in

Table 1 Clinical demographics according to with and without higher eRAP

	Normal eRAP (*n* = 291)	Higher eRAP (*n* = 108)	*P* value
Age (years)	74 ± 12	75 ± 10	0.17
Female, *n* (%)	161 (55%)	41 (38%)	0.002
Body mass index (kg/m^2)	22.4 ± 4.1	22.9 ± 4.2	0.31
Vital signs			
Systolic BP (mmHg)	128 ± 21	129 ± 22	0.73
Diastolic BP (mmHg)	69 ± 15	67 ± 14	0.48
Heart rate (bpm)	74 ± 17	72 ± 17	0.43
Comorbidities			
Hypertension, *n* (%)	213 (73%)	90 (83%)	0.04
Coronary artery disease, *n* (%)	63 (22%)	24 (22%)	0.90
Atrial fibrillation, *n* (%)	131 (45%)	74 (69%)	<0.0001
Diabetes mellitus, *n* (%)	95 (33%)	38 (35%)	0.63
Medications			
ACEIs/ARBs, *n* (%)	131 (45%)	63 (58%)	0.02
Beta-blocker, *n* (%)	123 (42%)	41 (38%)	0.44
Diuretic, *n* (%)	178 (61%)	83 (77%)	0.003
MRA, *n* (%)	88 (30%)	48 (44%)	0.008
Laboratories			
Haemoglobin (g/dL)	11.7 ± 2.2	11.5 ± 2.0	0.49
Creatinine (mg/dL)	0.9 (0.7, 1.4)	1.0 (0.8, 1.3)	0.55
BNP (pg/mL), *n* = 347	191 (85, 356)	197 (114, 382)	0.52
AST (U/L)	23 (18, 29)	26 (19, 35)	0.008
ALT (U/L)	15 (11, 22)	17 (11, 25)	0.28
γGT (U/L)	28 (17, 55)	35 (19, 66)	0.06
ALP (U/mL)	237 (189, 318)	235 (201, 284)	1.0
T-bilirubin (mg/dL)	0.6 (0.5, 0.8)	0.8 (0.6, 1.1)	<0.0001

Values are mean ± SD, median (interquartile range), or *n* (%).
ACEIs/ARBs, angiotensin-converting enzyme inhibitors/angiotensin-receptor blockers; ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; BNP, B-type natriuretic peptide; BP, blood pressure; E/e′, ratio of early diastolic mitral inflow velocity to early diastolic mitral annular tissue velocity; eRAP, estimated right atrial pressure; MRA, mineralocorticoid receptor antagonists; *r*; T-bilirubin, total bilirubin; γGT, γ-glutamyl transferase.

normal eRAP group. Compared to normal eRAP group, patients with higher eRAP displayed higher levels of serum aspartate transaminase and total bilirubin while other blood markers were similar between the groups.

## Comparisons of cardiac remodelling and dysfunction

Compared with subjects with normal eRAP, those with higher eRAP displayed larger LV mass index and end-diastolic volume while EF, mitral s' velocity, and CO were similar between the groups (Table 2). Mitral E-wave and LA volume index were larger in patients with higher eRAP group than in normal group, suggesting worse LV diastolic function. Prevalence of moderate mitral regurgitation was higher in higher eRAP group than in normal eRAP group. As expected, patients with higher eRAP displayed more severe abnormalities in the right heart structure and function than those with normal eRAP, including higher eRVSP, lower TAPSE, larger RV diameters and RA volume index, and higher prevalence of moderate or severe TR.

Outcome analysis

Over a median follow-up of 19.0 months (IQR 6.7–36.9), there were 84 composite outcomes (21%) in patients with HFpEF (78 HF hospitalization and 6 cardiac deaths). Kaplan––Meier curve analysis demonstrated that patients with higher

eRAP displayed higher rates of the combined events of cardiovascular death or HF hospitalization than those with normal eRAP (Figure 1). In an univariate Cox proportional hazards model, eRAP ≥ 8 mmHg was associated with more than a two-fold increased risk of adverse outcomes compared with normal eRAP (Table 3, hazard ratio 2.60 vs. eRAP

Figure 1 Kaplan–Meier survival curves for the composite outcome of cardiovascular (CV) mortality or heart failure (HF) hospitalization. Patients with higher estimated right atrial pressure (eRAP ≥ 8 mmHg) displayed higher rates of the outcomes than those with normal eRAP.
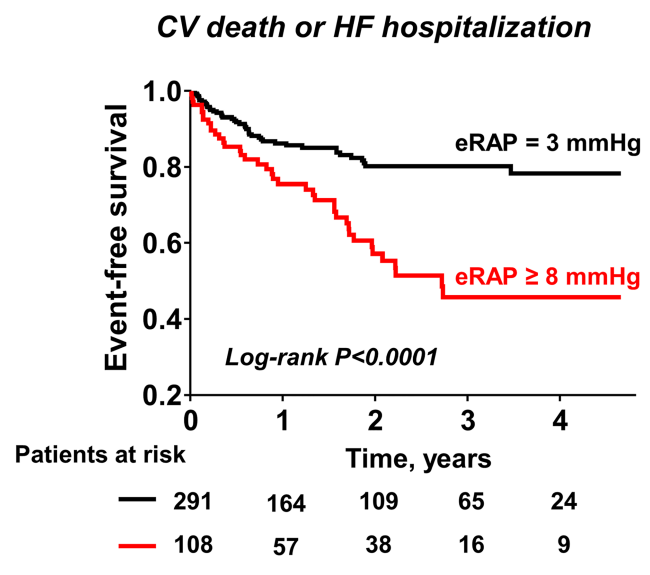
Table 2 Echocardiographic measurements according to eRAP values

	Normal eRAP (n = 291)	Higher eRAP (n = 108)	P value
LV structure and volumes			
LV mass index (g/m^2)	102 ± 32	112 ± 28	0.002
LV end-diastolic volume (mL)	83 ± 33	95 ± 38	0.001
LV function			
LV ejection fraction (%)	61 ± 7	60 ± 7	0.22
Cardiac output (L/min)	4.1 ± 1.7	4.2 ± 1.6	0.45
Mitral E-wave (cm/s)	82 ± 25	98 ± 35	<0.0001
Mitral e' velocity (cm/s)	5.5 ± 2.1	6.0 ± 2.0	0.02
Mitral s' velocity (cm/s)	5.9 ± 1.7	5.6 ± 1.6	0.16
E/e' ratio	16.2 ± 5.9	17.0 ± 8.1	0.33
LA volume index (mL/m^2)	47 (33, 61)	62 (47, 83)	<0.0001
Moderate mitral regurgitation (%)	14 (5%)	12 (12%)	0.03
Right heart			
eRVSP (mmHg)	30 ± 9	41 ± 12	<0.0001
TAPSE (mm)	17.7 ± 4.8	15.8 ± 5.6	0.001
RV basal diameter (mm)	35 ± 7	38 ± 9	0.01
RV mid-diameter (mm)	28 ± 6	31 ± 7	0.008
RV long diameter (mm)	60 ± 8	63 ± 8	0.003
eRAP (mmHg)	3 ± 0	10 ± 3	—
RA volume index (mL/m^2)	23 (15, 33)	35 (20, 59)	<0.0001
Significant tricuspid regurgitation (%)	32 (11%)	36 (33%)	<0.0001

Values are mean ± SD, or median (interquartile range).
eRVSP, estimated right ventricular systolic pressure; LA, left atrial; LV, left ventricular; RA, right atrial; RV, right ventricular; TAPSE, tricuspid annular plane systolic excursion; and other abbreviations as in Table 1.

Table 3 Univariable and multivariable Cox proportional hazard models for prediction of adverse events

| Variables	Univariable analysis		Multivariable model	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age, per 1 year	1.03 (1.01–1.05)	0.01	1.00 (0.98–1.03)	0.78
Body mass index, per 1 kg/m^2	0.95 (0.89–1.00)	0.06	—	—
Atrial fibrillation, yes vs. no	2.09 (1.32–3.33)	0.002	1.06 (0.58–1.92)	0.85
Diuretic, yes vs. no	4.22 (2.18–8.16)	<0.0001	2.76 (1.35–5.65)	0.006
MRA, yes vs. no	1.32 (0.85–2.04)	0.21	—	—
Ln BNP, per 1 unit	1.63 (1.30–2.03)	<0.0001	1.58 (1.23–2.03)	0.0003
E/e' ratio, per 1 unit	1.03 (1.00–1.06)	0.03	1.01 (0.98–1.04)	0.50
LA volume index, per 1 mL/m^2	1.00 (1.00–1.01)	0.04	—	—
eRVSP, per 1 mmHg	1.05 (1.03–1.07)	<0.0001	—	—
TAPSE, per 1 mm	0.94 (0.91–0.98)	0.008	0.98 (0.93–1.03)	0.35
RV mid-diameter, per 1 mm	1.05 (1.02–1.08)	0.002	1.04 (1.01–1.08)	0.02
RA volume index, per 1 mL/m^2	1.01 (1.01–1.02)	<0.0001	—	—
eRAP, ≥8 mmHg vs. <8 mmHg	2.60 (1.70–4.00)	<0.0001	2.20 (1.34–3.62)	0.002

CI, confidence interval, HR hazard ratio, and other abbreviations as in *Tables 1* and *2*.

3 mmHg, 95% confidence interval 1.70–4.00, *P* < 0.0001). Age, the presence of AF, diuretic use, BNP levels, LA volume index, E/e' ratio, eRVSP, TAPSE, RV mid-cavity diameter, and RA volume index were also associated with incident end-points. In a multivariate analysis, the presence of higher eRAP remained independently associated with adverse outcomes after adjusting for age, AF, diuretics, BNP, E/e' ratio, TAPSE, and RV mid-diameter (hazard ratio 2.20 vs. normal eRAP group, 95% confidence interval 1.34–3.62, *P* = 0.002).

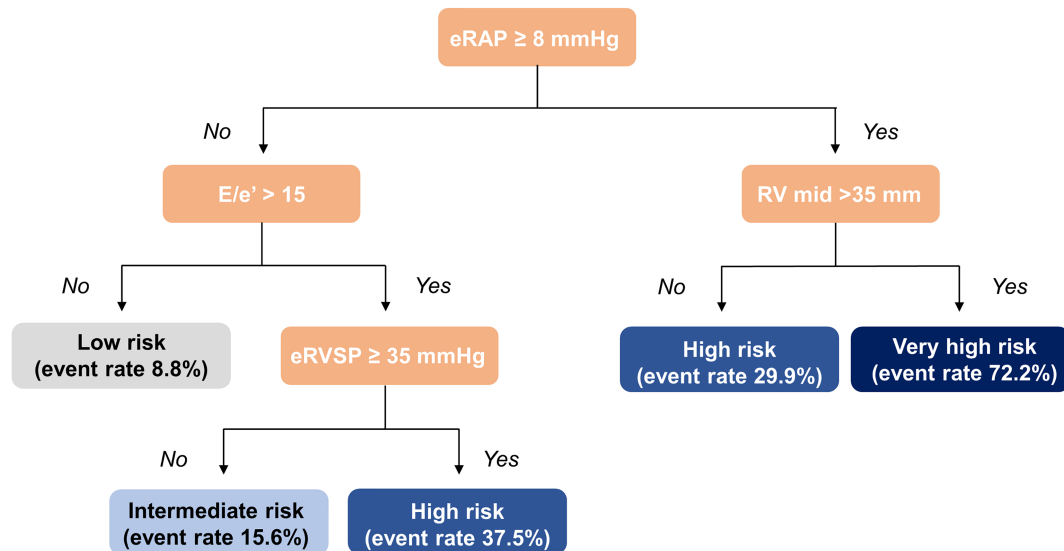Kaplan–Meier curves show that event-free survival varied among the groups based on the eRAP and E/e' ratio (log-rank *P* < 0.0001, *Figure 2*). Patients in Group 4 (eRAP ≥ 8 mmHg and E/e' ratio > 15) displayed higher event rates than those in Group 2 (normal eRAP and E/e' ratio > 15) (*P* = 0.004), suggesting an incremental prognostic value of eRAP over E/e' ratio in patients with HFpEF. In the CART analysis, eRAP ≥ 8 mmHg was the strongest predictor followed by RV mid-diameter (>35 mm), E/e' ratio (>15), and eRVSP (≥35 mmHg) while the presence of AF, TAPSE, and RA dilation was not selected. This model defined four risk groups: low (event rates 8.8%), intermediate (15.6%), high (29.9–37.5%), and very high risk (72.2%) (*Figure 3*).

Figure 2 Kaplan–Meier curves separating the patients according to eRAP and E/e' ratio. The risk of the composite outcome increased with progression of eRAP and E/e' ratio (log-rank *P* < 0.0001). Patients in Group 4 (higher eRAP and E/e' ratio > 15) displayed higher event rates than those in Group 2 (normal eRAP and E/e' ratio > 15, *P* = 0.004) and Group 1 (normal eRAP and E/e' ratio ≤ 15, *P* = <0.001). E/e', ratio of early diastolic mitral inflow velocity to early diastolic mitral tissue velocity; and other abbreviations as in *Figure 1*.

CV deaths or HF hospitalization
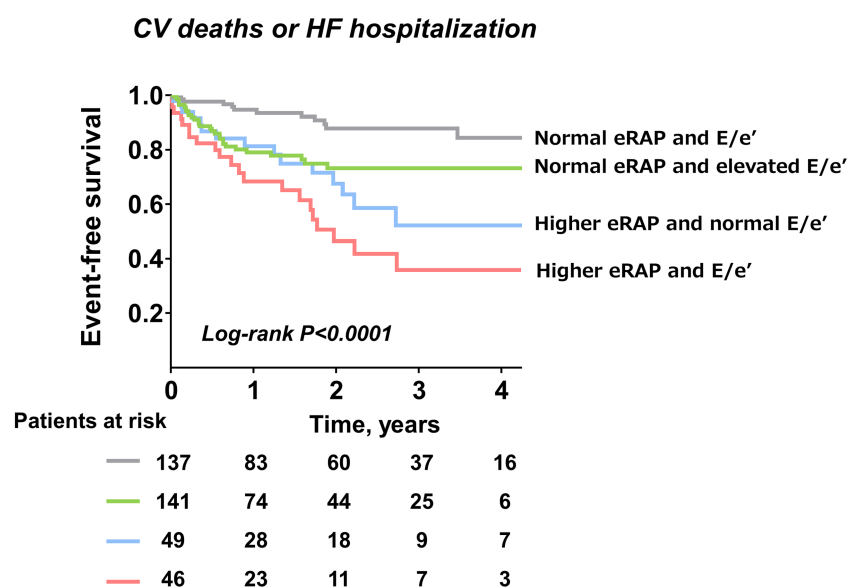
Figure 3 Classification and regression tree analysis. Higher eRAP was the strongest predictor followed by right ventricular (RV) mid-cavity diameter, E/e' ratio (>15), and estimated right ventricular systolic pressure (eRVSP), defining four risk groups: low (event rates 8.8%), intermediate (15.6%), high (29.9–37.5%), and very high risk (72.2%). Abbreviations as in *Figures 1* and *2*.

Discussion

In this study, we investigated the relationship between eRAP and clinical outcomes in patients with HFpEF. We demonstrated that patients with eRAP ≥ 8 mmHg displayed more severe abnormalities in LV diastolic function as well as right heart structure and function than those with normal eRAP. The presence of higher eRAP was independently associated with higher rates of the composite outcome. Kaplan–Meier curves show that event-free survival varied among the four groups based on the eRAP and E/e' ratio, providing an incremental prognostic value of eRAP over E/e' ratio. The CART analysis demonstrated that eRAP was the strongest predictor of the outcome followed by RV diameter, E/e', and eRVSP, stratifying the patients into four risk groups (incident rate 8.8–72.2%). These data may provide new insights into the prognostic role of RA hypertension in the complex pathophysiology of HFpEF and suggest the utility of eRAP for the risk stratification in patients with HFpEF.

Did right atrial pressure reflect the cumulative burden of cardiac dysfunction in HFpEF?

While increases in LV filling pressure secondary to LV diastolic dysfunction is a central abnormality, RAP is also often elevated in patients with HFpEF.[12–14] The potential mechanisms of RAP elevation in HFpEF can be multifactorial. Secondary PH due to high LV filling pressures and pulmonary

vascular disease may play a dominant role for this by mediating RV dysfunction and remodelling.[12,13,28] This may reduce RV compliance and increase RV filling pressure and thus RAP.[29] TR is also common in HFpEF, causing elevations in RAP through RA volume overload.[16,30] In both circumstances, RA remodelling may progress and RA compliance may decrease, leading to a further increase in RAP. AF may compromise RA compliance as well by inducing myocardial fibrosis and remodelling.[17] In the present study, patients with higher eRAP displayed more severe abnormalities in LV diastolic function evidenced by higher E velocity and larger LA volume, higher eRVSP, larger RV and RA size, and higher prevalence of significant TR than those with normal eRAP (*Table 2*). We also observed that left and right heart remodelling were present in patients with eRAP of 8 mmHg and that higher eRAP was associated with worsening cardiac remodelling and dysfunction (*Table S1*). These findings are consistent with the mechanisms underlying elevation in RAP as described above.

We demonstrated that higher eRAP was independently associated with an increased risk of the composite outcome. This is consistent with a prior study demonstrating the association between invasively measured RAP and adverse outcomes in HFpEF.[19] Multiple studies have examined the association between RV dysfunction, RV-pulmonary artery (PA) uncoupling, and clinical outcomes in patients with HFpEF,[31–33] but surprisingly, no data are available focusing on the prognostic value of echocardiographic estimates of RAP (i.e. eRAP) in HFpEF. It is of note that the CART analysis demonstrated that eRAP was the strongest predictor of the

outcome followed by RV mid-diameter, E/e' ratio, and eRVSP, stratifying the patient's risk. PH and right heart abnormalities may develop over time in patients with HFpEF that initially present with isolated LV dysfunction.[12,34] The RA is the upstream chamber of the heart. Rather than a single abnormality, we speculate that RAP may reflect the cumulative burden of pathological processes in the left heart, pulmonary vasculature, and the right heart, and this may be a part of the explanation for the prognostic superiority of eRAP.

Is elevated right atrial pressure driving poor clinical outcomes in HFpEF?

Rather than simply reflecting the disease severity, elevated RAP might contribute to adverse outcomes in patients with HFpEF.[35] Elevated RAP can decrease venous return and cause systemic congestion in the upstream organs (the liver, kidney, and gut).[36] Our findings showing elevations in hepatic enzymes in patients with higher eRAP and others may support this hypothesis.[22,37] Elevated RAP can deteriorate tricuspid insufficiency through annular dilations, forming a vicious circle.[12] Conversely, these data suggest that therapies reducing RAP might improve clinical outcomes in patients with HFpEF. These may include diuretics to reduce volume overload and PA pressures, interventions to reduce tricuspid insufficiency, and maintenance or restoration of AF.[16,38] Sodium-glucose co-transporter 2 inhibitors may be effective for reducing volume overload and RAP.[39] Further studies are warranted to determine how to optimally treat RA hypertension in patients with HFpEF.

Utility of eRAP for risk stratification in HFpEF

Patients with HFpEF suffer from high morbidity and mortality, and repeated hospitalization for worsening HF is strongly associated with poor prognosis.[40] Hence, risk stratification is crucial for optimal treatment strategy in patients with HFpEF. Our CART model based on eRAP, RV size, eRVSP, and E/e' stratified the patients into subgroups with event rates ranging from 8.8% to 72.2%. Of note, eRAP assessment is performed in routine echocardiographic examinations, and the technique is straightforward and has low observer variability, with no requirement of specific software packages like those for 2D speckle tracking. Our findings suggest that assessment of eRAP may further enhance risk stratification in HFpEF patients and could be utilized to guide therapy such as diuretics. In this regard, a previous trial reported a reduction in HF hospitalization with PA pressure-guided therapy in patients with HFpEF.[38] Further clinical trials are warranted to determine if

eRAP-guided treatment strategy could improve outcomes in HFpEF.

Limitation

This is a retrospective study from tertiary referral centres, introducing selection and referral bias. The sample size was relatively small and further studies are required to confirm the current findings. Although the current study and our previous one both focused on the RA in HFpEF,[18] the two studies are different in three main perspectives: the aim, study design, and population. The aims of the previous study were to characterize patients with RA structural abnormality (i.e. RA dilation) in HFpEF and to evaluate the association between RA enlargement and clinical outcomes.[18] On the other hand, the aim of the present was to investigate whether eRAP would predict adverse outcomes in HFpEF. The current study also sought to determine whether there would be any hierarchical relationship between eRAP and other echocardiographic markers. Regarding the population, the previous study included patients from a single centre, whereas this study included patients from two centres although there is overlap (66%). The diagnosis of HFpEF was defined by PCWP, BNP levels, echocardiographic indices of diastolic function, or previous HF hospitalization. There might be heterogeneity across the different definitions, which could cause bias in the results.[41] RAP was not directly measured, but estimated non-invasively using echocardiography. However, the use of echocardiography allows for a more widespread application of the current results in clinical practice. Hepatic vein Doppler profile was not available in most patients. RV function was assessed by TAPSE alone based upon image availability.

Conclusions

Higher eRAP was independently associated with an increased risk of the composite outcome, with an incremental prognostic value over E/e' ratio. We also demonstrated that eRAP ≥ 8 mmHg was the strongest predictor of the outcome followed by RV mid-diameter, E/e' ratio, and eRVSP, stratifying the patient's risk. Our data may provide new insights into the prognostic role of RA hypertension in the complex pathophysiology of HFpEF and suggest the prognostic utility of eRAP.

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Conflict of interest

None declared.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Clinical demographics and cardiac structure and function according to eRA*P* value.

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