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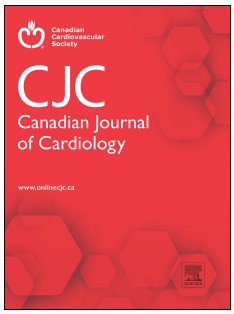

Right ventricular systolic and diastolic parameters based on pressure–volume loop theory in heart failure

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Right ventricular systolic and diastolic parameters based on pressure–volume loop theory in heart failure

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Short title: RHC-derived systolic/diastolic parameters in HF

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Abstract

Background: This study aimed to assess the clinical utility of right ventricular (RV) systolic and diastolic parameters derived from the RV pressure waveform obtained through right heart catheterization (RHC) based on pressure–volume (PV) loop theory in patients with heart failure (HF).

Methods: The study included patients hospitalized for advanced HF who underwent RHC at our institution. RV end-systolic elastance (Ees), RV arterial elastance (Ea), RVEes/Ea ratio and RV diastolic stiffness coefficient (β) were calculated from RV pressure waveforms. The prognostic value of these parameters was evaluated for the primary outcome defined as all-cause mortality or urgent HF-related hospitalization.

Results: A total of 254 patients were analyzed, including 141 with a left ventricular ejection fraction (LVEF) <40% and 113 with LVEF ≥40%. Among the RV systolic and diastolic parameters, a low RVEes/Ea ratio (<0.55) (hazard ratio [HR], 4.1; 95% confidence interval [CI], 2.4–6.9; $p < 0.001$) and an elevated RVβ (≥0.025) (HR, 4.8; 95% CI, 2.5–9.0; $p < 0.001$) were associated with a higher risk of the primary outcome. In those with LVEF <40%, a low RVEes/Ea ratio was a stronger independent predictor of the primary outcome (HR, 3.5; 95%CI, 1.6–7.5; $p = 0.002$), whereas in those with LVEF ≥40%, elevated RVβ was the more significant independent risk factor (HR, 3.0; 95%CI, 1.1–8.2; $p = 0.029$), even after multiple adjustments for covariate factors.

Conclusion: RV waveform evaluation based on PV loop theory was effective in predicting prognosis in HF patients, irrespective of LVEF.

Keywords

Right heart catheterization, pressure–volume loop, ventricular–arterial coupling (Ees/Ea), diastolic stiffness coefficient (β)

Introduction

Right heart catheterization (RHC) remains a fundamental technique among traditional evaluation methods for heart failure (HF). It is the most accurate approach for evaluating intra-cardiac pressure and provides unique diagnostic information that other tests cannot fully replace.[1] However, the utility of RHC data is often limited due to its susceptibility to volume status and incomplete representation of cardiac function. Notably, RHC—particularly its pressure waveform—is significantly influenced by right ventricular (RV) function, which has been linked to clinical outcomes in patients with left-sided HF, including both preserved ejection fraction (HFpEF) and reduced ejection fraction (HFrEF).[2, 3]

The role of RV dysfunction (RVD) in HF varies depending on the method used to assess right heart function evaluation and the characteristics of the patient population. Evaluating RV function via echocardiography presents challenges due to the complex shape of the right heart.[4, 5] In contrast, cardiac magnetic resonance (CMR) imaging provides a more precise assessment of RV function,[6] though its use is limited by factors such as implanted devices and the need for prolonged patient immobility. As research continues, efforts are focused on developing simpler and more practical methods for evaluating RV function.

We previously developed a novel method for assessing RV function using RHC based on pressure–volume (PV) loop theory.[7] This approach allowed for the evaluation of both systolic and diastolic RV functions, including RV end-systolic elastance (RVEes), RV arterial

elastance (RVEa), RV diastolic stiffness coefficient (RVβ), and RV end-diastolic elastance (RVEed), with demonstrated validity.

This study aimed to explore the additional prognostic value of this RV assessment method in patients with advanced HF, beyond established risk markers. Furthermore, we compared its prognostic impact between patients with HFpEF and those with HFrEF.

Methods

Patient Selection

This retrospective study included consecutive patients who underwent RHC with available RV pressure waveforms at our hospital between March 2019 and November 2023 for the evaluation of advanced HF. Our hospital is a specialized heart failure center that receives referrals from major institutions for patients with medically intractable HF requiring consideration for advanced interventions, such as left ventricular assist device (LVAD) implantation or heart transplantation, as previously we reported.[8] HF diagnosis was confirmed if it was documented as the primary reason for admission, based on physical examination findings, laboratory results, and radiologic assessments. Patients were excluded if they had moderate or severe tricuspid valve regurgitation (TR), had significant valvular disease, or had already received or were scheduled to receive mechanical circulatory support (MCS). Patients with moderate or severe TR were specifically excluded because such

conditions invalidate the isovolumic range assumption necessary for the single-beat method. This study protocol was reviewed and approved by Institutional Review Board (IRB) of the University of Tokyo in accordance with the principles of the Declaration of Helsinki (Approval No.: 2,650). As this study was retrospective, the IRB did not require patient consent. To assess the prognostic value of novel RV parameters across a broad range of left ventricular ejection fractions (LVEF), consecutive patients with HFpEF who underwent invasive RHC measurements were also included. The diagnoses of hypertrophic cardiomyopathy (HCM) and cardiac amyloidosis were made according to established clinical criteria. HCM was diagnosed based on echocardiographic or CMR imaging showing a maximum left ventricular wall thickness ≥15 mm. Secondary causes of myocardial hypertrophy—such as Fabry disease and cardiac amyloidosis—were excluded through comprehensive evaluation, including blood and urine tests, CMR, 99mTc-pyrophosphate scintigraphy, and, when indicated, endomyocardial biopsy. The diagnosis of cardiac amyloidosis was confirmed when suspected based on abnormal immunoglobulin levels, CMR, or scintigraphy findings, by performing an endomyocardial biopsy to establish a definitive diagnosis. These patients were included in the cohort because RHC was often performed before a definitive etiologic diagnosis was established. Their inclusion is expected to reflect real-world clinical conditions and enhances the generalizability of the findings.

RHC and Other Evaluations

A 7-Fr ballooned Swan–Ganz catheter (Edwards Lifesciences, Irvine, CA, USA) was inserted via the internal jugular vein for RHC. Measurements included right atrial pressure, RV pressure, pulmonary artery wedge pressure (PAWP), and pulmonary arterial pressure (PAP). All pressures were recorded with patients holding their breath at the end of expiration. Cardiac output (CO) and cardiac index were determined using the thermodilution method, while stroke volume (SV) was calculated by dividing CO by heart rate. Blood tests were performed at the time closest to the RHC procedure. Clinical data were extracted from medical records at the time of admission for RHC evaluation, including patient age, sex, body mass index, HF status, and the presence of coronary artery disease or atrial fibrillation. Coronary artery disease was defined as a history of myocardial infarction, percutaneous coronary intervention, or significant stenosis detected on coronary arteriography or computed tomography. Echocardiography was conducted at the time closest to the RHC procedure, assessing standard parameters such as LVEF, left ventricular end-diastolic diameter (LVDd), the ratio of the E wave to early diastolic velocity of the mitral annulus (E/e' ratio), left atrial diameter, RV fractional area change (RVFAC), and tricuspid annular plane systolic excursion (TAPSE). Medication data were collected from the medical records at the time of admission for RHC evaluation.

PV Analysis

RV pressure waveforms were digitally recorded using a polygraph (Cath Lab RMC5000; Nihon Kohden), and comma-separated values of 10–15 consecutive RV pressure waveforms were extracted at a sampling rate of 1,000 Hz. Three stable waveforms were selected for analysis using MATLAB software (R2024a, MathWorks, Natick, MA, USA Inc.). The method for estimating the end-systolic PV relationship (ESPVR) and the end-diastolic PV relationship (EDPVR) have been previously described[7] and are briefly outlined in Fig. 1. ESPVR parameters include RVEes, RVEa, and RVEes/Ea ratio, while EDPVR parameters consist of the RVβ and RVEed.

The isovolumic contraction and relaxation periods of the RV pressure waveforms were defined as the ranges from 1/5 dP/dt max to dP/dt max and dP/dt min to 1/5 dP/dt min, respectively.[9] Additionally, sine-curve fitting was performed using the Levenberg–Marquardt least squares algorithm, with the maximum sine-curve value designated as Pmax.

The ESPVR was approximated as a line passing through the two points: (end-systolic volume [ESV], end-systolic pressure [ESP]) and (end-diastolic volume [EDV], Pmax).

The ESP was calculated using the following formula:[10]

ESP = mean PAP + [(systolic PAP – mean PAP) x (time to RV systolic pressure (RVSP) − time to dP/dt max)/(time to dP/dt min − time to dP/dt max)]

The RVEes was determined as follows: RVEes = (Pmax − ESP)/SV. The RVEa was calculated as ESP/SV. Assuming that the ESPVR passes through the origin (0,0), ESV and EDV were computed as follows:

$$ESV = ESP \times SV/(Pmax - ESP)$$

$$EDV = Pmax \times SV/(Pmax - ESP)$$

The EDPVR was represented by an exponential curve passing through three points: (0,0), (ESV,1), (EDV, end-diastolic pressure [EDP] − beginning-diastolic pressure [BDP] + 1), following the equation below:

$$P = \alpha(e^{V\beta} - 1)$$

where *P* is pressure, α is the curve-fitting constant, *V* is volume, and β is the diastolic stiffness coefficient.[11]

The RVEed was calculated using the following equation:[12]

$$RVEed = \alpha \times \beta \times e^{\beta \cdot EDV}$$

Follow-Up and Outcomes

The primary endpoint was a composite of all-cause mortality or HF-related hospitalization. LVAD implantation was not included in the primary endpoint, as it always occurred as a subsequent event following HF hospitalization.

The secondary endpoint was defined as a composite of all-cause mortality and LVAD implantation ("hard events"). HF-related hospitalization was characterized by dyspnea and pulmonary edema observed on chest X-ray, with hospitalization decisions made according to standard clinical practice. The decision for LVAD implantation was determined by a multidisciplinary team of cardiologists, cardiac surgeons, and transplant coordinators, based on the following criteria: persistent HF symptoms and progressive circulatory collapse despite optimal pharmacologic and non-pharmacologic therapy escalation. Heart transplantation was not considered an endpoint, as no patients underwent transplantation without prior LVAD implantation.

Statistical Analysis

Data were presented as medians with interquartile ranges (25th–75th percentile) or as frequencies with percentages. The Mann–Whitney U test was used to compare continuous variables, while Pearson's chi-squared test was applied to categorical variables.

Cox regression analysis was performed to identify significant predictors of the primary endpoint. The mean PAP cutoff value was set at 20 mmHg, based on pulmonary hypertension criteria.[13] The cutoff values for mean PAWP and cardiac index were set at 18 mmHg and 2.2 L/min/m^2, respectively, following Forrester's subset classification.[14] Cutoff values for other variables in the hazard analysis were determined using receiver operating characteristic

(ROC) curve analysis for the primary endpoint. Kaplan–Meier analysis and log-rank tests were performed to compare primary and secondary endpoints between groups, with time zero defined as the point of RHC.

Cox univariable and multivariable analyses were conducted to identify independent predictors of the primary endpoint. Multivariable analysis included a selection of parameters, ensuring an appropriate number based on gender and variables with high hazard ratios (HRs) and low *p*-values from the univariable analysis results. To validate the robustness of the findings, a sensitivity analysis was performed using alternative cutoff values for RV parameters or after patients were dividing into two groups whether they had pulmonary hypertension or not.

All statistical analyses were conducted using JMP software (version Pro 17.2.0; SAS Institute, Cary, NC, USA).

Results

Clinical Characteristics

During the study period, 349 patients underwent RHC, of whom 27 were excluded due to moderate or severe TR, 8 due to MCS implementation or scheduling, 13 due to unclear RV waveforms, and 47 due to significant valvular disease. Ultimately, 254 patients met the inclusion criteria, with 141 classified into the <40% LVEF group and 113 into the ≥40%-

LVEF group. Baseline characteristics of both groups are summarized in Table 1. The <40% LVEF group tended to be younger and exhibited larger LVDd on echocardiography. Brain natriuretic peptide (BNP) levels were comparable between the groups. Similarly, RHC parameters showed no significant differences, except for heart rate. A higher proportion of HF medications was administered to the <40% LVEF group. Among RV parameters derived from the PV loop theory, RVEes and RVEes/Ea were significantly different between the two groups. However, RVEa, RVβ, and RVEed showed no significant differences.

Association of RV Systolic and Diastolic Parameters with Primary and Secondary Outcomes

The median follow-up period was 913 [487–1,361] days. Among the 254 patients, 60 (23.6%) reached the primary endpoint during follow-up, while 22 (8.7%) died and five underwent LVAD implantation. Table 2 presents the HRs for RHC and RV systolic and diastolic parameters in relation to the primary endpoint. The optimal cutoff values for these parameters were determined using Youden index in ROC curves. Among RV systolic parameters, both RVEa and RVEes/Ea were significantly associated with the primary endpoint (RVEa, HR, 4.0; 95% confidence interval [CI], 2.4–6.7; $p < 0.001$; RVEes/Ea, HR, 4.1; 95% CI, 2.4–6.9; $p < 0.001$). Among RV diastolic parameters, RVβ and RVEed were also significantly associated with the primary events (RVβ, HR, 4.8; 95% CI, 2.5–9.0; $p <$

0.001; RVEed, HR, 2.8; 95% CI, 1.7–4.7; $p < 0.001$). Given the relatively high HRs of RVEes/Ea and RVβ, we defined RVD as RVEes/Ea <0.55 and diastolic RVD as RVβ ≥0.025. These classifications were used for further analysis. As illustrated in Fig. 2, the presence of either systolic or diastolic RVD was significantly associated with an increased risk of both the primary and secondary outcomes.

Association of RV Systolic and Diastolic Parameters with Clinical Prognosis in Different LVEF Groups

Fig. 3 illustrates the prevalence of systolic and diastolic RVD in two groups categorized by an LVEF threshold of 40%. The occurrence of systolic RVD differed significantly between the groups (22.7% in the <40% LVEF group vs. 8.0% in the ≥40% LVEF group, $p = 0.002$). In contrast, there was no significant difference in the prevalence of diastolic RVD between the groups (52.5% in the <40% LVEF group vs. 48.7% in the ≥40% LVEF group, $p = 0.546$). In the entire populations, age, creatinine and BNP were identified as poor prognostic parameters in the Cox proportional hazard analysis (Supplemental Table S1).

In the subgroup analysis of patients with LVEF <40%, both systolic and diastolic RVD remained independent predictors of the primary endpoint, even after adjusting for mean PAP. On the other hand, in the ≥40% LVEF group, only diastolic RVD was associated with an increased risk of the primary endpoint, in both unadjusted and adjusted models (Table 3).

Sensitivity Analyses

Cox regression analyses were performed using various thresholds of RVEes/Ea and RVβ as part of the sensitivity analyses (Supplemental Table S2). There have been various reports on the thresholds of RVEes/Ea and RVβ, but they have not been well established. [15,16] In this population, we performed a sensitivity analysis by varying the threshold value determined by the Youden index above and below. The findings indicated that all tested thresholds of RVEes/Ea and RVβ were associated with primary outcomes in the overall population. The consistency of these results supports the robustness of the association between RVD and the primary outcome. In addition, we also investigated about the association between RVD and the primary outcome after patients were divided into two groups by mean PAP =20 mmHg (Supplemental Table S3). The results showed that both RVEes/Ea and RVβ were associated with the primary outcome in patients with mean PAP <20 mmHg, whereas only RVEes/Ea remained significant in those with mean PAP ≥20 mmHg.

Discussion

This study validated the application of our novel method for analyzing RHC data using the PV loop technique, specifically highlighting its predictive value for HF events beyond conventional risk markers. A conceptual overview of the prognostic significance of

RVEes/Ea and RVβ derived from pressure waveform analysis is summarized in the Central Illustration. To our knowledge, this is the first study to simultaneously assess RV-specific systolic and diastolic function solely from RHC data and evaluate its prognostic significance. RVD has recently been recognized as a prognostic factor in HF patients.[2] Previous studies have reported RVD in 20%–50% of patients with HFpEF and 63%–76% of those with HFrEF.[17,18] Our findings underscore the utility of incorporating PV loop-derived RV evaluation alongside existing markers for a more precise prediction of HF progression, regardless of LVEF status.

Methods for Evaluating RV Function

Several modalities are used to assess RVD, with echocardiography and CMR being the most commonly employed. Key echocardiographic parameters include TAPSE, RVFAC, and TAPSE/pulmonary artery systolic pressure. In CMR imaging, RVEF and RV volume serve as primary indicators of RVD.[17,19] However, RV analysis can be challenging due to its complex anatomy, position in the thoracic cavity, and trabeculated myocardium, which makes it difficult to accurately trace the intra-cardiac border.[20] Alternatively, studies have been conducted to measure or estimate the PV loop in HF patients, primarily focusing on specific groups, such as those with HFrEF or PH.[10,21] Additionally, evaluating RV diastolic function using conventional methods remains complex,[22, 23] leading to limited available data.

In this study, we expanded the application of PV loop-based systolic and diastolic parameters for a broader HF population, irrespective of the LVEF or the presence of PH, which had not been previously reported. Our method enables the assessment of RV function using RHC alone, providing a more accurate prognosis prediction and potentially having a significant clinical impact. To further evaluate the clinical significance of our waveform-derived indices, we compared them with conventional echocardiographic markers of RV systolic function. As a result, RVFAC was significantly associated with the primary outcome in univariable analysis, whereas TAPSE was not. However, when included in a multivariable model adjusted for age, sex, BNP, creatinine, mean PAP, and RVEDP, RVFAC lost statistical significance, whereas both RVEes/Ea <0.55 and RV$\beta \geq 0.025$ remained independent predictors. These findings suggest that PV loop-derived indices offer incremental prognostic value beyond conventional echocardiographic RV parameters.

PV Loop Parameters of RVD

Among the systolic RV parameters analyzed, RVEes/Ea and RVEa have been identified as important predictors of the primary endpoint. RVEes/Ea, which reflects ventricular–arterial coupling, was lower in the HFrEF group, and a value below 0.55 was linked to poorer outcomes, particularly in HFrEF patients. The prognostic value of RVEes/Ea remained

consistent in HFrEF cases complicated by PH.[10, 21] These previous findings align closely with our results.

From a pathophysiological perspective, persistent pressure loading on the pulmonary arteries due to left-sided HF initially triggers pulmonary arterial remodeling, characterized by intimal hypertrophy, when RVD originates from left heart dysfunction.[24] This increased RV afterload leads to a rise in RVEa as a compensatory response. The RV myocardium undergoes hypertrophy to counteract the increased afterload, causing RVEes to rise along with RVEa in the early stage, thereby maintaining RVEes/Ea. However, as pathological changes progress, Ees declines, disrupting the balance between oxygen supply and demand and eventually leading to myocardial ischemia, collagen formation, fibrosis, and ventricular–vascular uncoupling.[25] The RVEes/Ea ratio reflects RV–pulmonary arterial coupling, representing the balance between contractility and afterload. Although a cutoff of <0.8 has been used previously based on its association with RV dysfunction,[10] it was not validated against outcomes. In our study, we used a data-driven threshold of 0.55 derived from ROC analysis, which better discriminated adverse events in this cohort. As noted, RVEa and RVEes/Ea serve as valuable prognostic indicators. While RVEa elevation occurs in the early stage of dysfunction, RVEes/Ea deterioration becomes evident in the later stage. The significantly lower RVEes and RVEes/Ea in the <40% LVEF group support this explanation (Table 1).

In this study, RVβ and RVEed emerged as significant prognostic indicators of diastolic function. These parameters are recognized as markers of ventricle-specific diastolic function, particularly in patients with PH.[11,12] Additionally, Tello K et al. reported that RVEed is linked to the extent of RV myocardial fibrosis.[26] Several HF studies utilizing conductance catheters have explored these parameters. One study found a notable increase in RVβ in HFpEF patients compared to controls,[27] while another reported a significant rise in RVEed in HFrEF patients with poor prognosis.[21] However, large-scale studies confirming the clinical benefit of these parameters in HF patients remain lacking. Our findings highlight RVβ as the valuable additional parameter for prognostic assessment, regardless of LVEF.

Combination of RV Systolic and Diastolic Parameters

The combination of RVEes/Ea and RVβ, which represent RV systolic and diastolic functions, respectively, may serve as a strong prognostic marker in HF patients. Recent studies using conductance catheters in both HFrEF and HFpEF patients have demonstrated that the simultaneous evaluation of load-independent RV systolic and diastolic function is valuable for monitoring HF progression across various clinical scenarios.[21,27]

Our study found a lower prevalence of systolic RVD in the ≥40% LVEF group, whereas diastolic RVD prevalence was similar between groups. Multivariate analysis indicated that RVEes/Ea was a stronger prognostic marker in patients with LVEF <40%, while RVβ was

more useful in those with LVEF ≥40%. This may be explained by differences in the distribution of systolic and diastolic RVD between groups, as previously noted. Regardless, incorporating both systolic and diastolic parameters alongside established biomarkers and RHC measurements enables a more comprehensive pathophysiological evaluation and enhances prognostic accuracy across all stages of HF.

In another subgroup analysis, we performed sex-based analyses to explore potential sex differences. While significant associations between RV systolic and diastolic dysfunction and primary outcomes were observed in both genders, results were less conclusive in females particularly in secondary outcomes, likely due to the smaller sample size (Supplemental Figure S1). The possibility of sex-specific differences in RV remodeling and prognosis cannot be excluded and warrants further investigation in larger cohorts with more balanced sex distribution.

These novel indices, derived from routine pressure waveform data during RHC, may allow clinicians to identify high-risk heart failure patients with RV systolic or diastolic dysfunction who would benefit from earlier intervention or more aggressive follow-up. Their incorporation into clinical hemodynamic assessments could augment existing risk stratification frameworks. In addition, we focused on the clinical relevance the RV function parameters calculated by only RHC data using the PV loop. After confirming the usefulness

of these parameters, we hope to combine them with existing parameters in future studies to examine a more practical formula that predicts prognosis more efficiently and accurately.

Study Limitations

First, this study was a single-center retrospective analysis, and the findings may be influenced by the patient population in this cohort. To validate these results, a larger multicenter study with a greater sample size is needed.

Second, our method relies on several approximate formulas, including the estimation of Pmax, ESP, and V_0. As a result, the parameters derived using this approach may differ from those obtained through the multiple-beat method with PV loop catheters. However, this study demonstrated the clinical utility of our method as a risk marker.

Third, the relatively low event rates observed in our study as compared with other studies with advanced HF [28,29]—23.6% for the primary endpoint and 8.7% for the secondary endpoint—may be partially explained by the exclusion criteria applied. We excluded patients with moderate or severe TR because such conditions invalidate the isovolumic range assumption required for the single-beat method. As most patients with HF have some degree of TR, our findings should be interpreted with caution when extrapolated to broader HF populations. The exclusion of patients with moderate or severe TR limits the applicability of our findings to patients with preserved tricuspid valve function. Notably, a substantial

number of patients with right ventricular enlargement were excluded, as moderate or severe TR is commonly observed in conditions such as arrhythmogenic right ventricular cardiomyopathy, which are characterized by primary RV dysfunction and dilation. In addition, patients scheduled to receive MCS and those with heart failure primarily due to valvular disease were excluded to ensure cohort integrity. Importantly, a considerable proportion of adverse events occurred in these excluded populations. Indeed, when analyzing the entire cohort of 349 patients prior to applying exclusion criteria, the incidence of the primary endpoint was 24.9%, and the secondary endpoint occurred in 12.3%. Although these patients were excluded for methodological and clinical reasons, it should be noted that moderate or severe TR is already an established marker of poor prognosis,[30] which can be recognized independently of PV loop-based assessment. Furthermore, there may have been bias in the selection of patients who were more stable. Indeed, RHC was limited to cases where the procedure could be performed under coordinated laboratory conditions. According to the limitation derived from this unique methodology, a small subset of RV pressure waveforms (13 cases) was excluded due to unreliable sine-curve fitting, leading to physiologically implausible estimates of Pmax or visibly poor waveform approximations. Such difficulties likely arouse from subtle waveform distortions related to valvular abnormalities, catheter artifacts, slight damping, or minimal air contamination. Despite the explicit exclusion of moderate or severe tricuspid regurgitation, these minor valvular or

technical factors occasionally compromised waveform quality, highlighting a practical limitation of this analytical method.

Fourth, the inclusion of patients with hypertrophic cardiomyopathy and cardiac amyloidosis enhances the external validity of our findings by reflecting the heterogeneous nature of HFpEF in clinical practice. However, we acknowledge that their presence may introduce etiologic heterogeneity and could potentially confound the interpretation of RV hemodynamic indices. Previous HFpEF studies have varied in how such conditions were handled, and many did not systematically screen for them at enrollment.[31] Our inclusion strategy mirrors real-world diagnostic uncertainty and improves the clinical applicability of our findings, while requiring careful interpretation when considering specific disease subtypes.

Fifth, this study did not include direct assessment of LV hemodynamics. The absence of LV pressure data limits the ability to evaluate biventricular coupling and may restrict the interpretation of RV parameters in the broader context of overall cardiac function.

Conclusion

Our novel method for assessing RV function, derived from RHC using PV loop theory, accurately predicts prognosis in patients with HF, irrespective of LVEF. These findings are

primarily applicable to patients with limited tricuspid regurgitation, due to the methodological requirements of the pressure waveform analysis.

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Disclosures

None.

Patient Consent Statements

The requirement for informed consent was waived due to the retrospective nature of the analysis, which was confirmed by the IRB.

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Table 1. Baseline characteristics of patients in each LVEF group

	LVEF < 40% (n = 141)	LVEF ≥ 40% (n = 113)	P-value
Age, years	50[41–63]	67 [54–78]	<0.001*
Male, n (%)	103, 73.1%	65, 57.5%	0.009*
BMI	23.1 [20.0–26.0]	22.9 [20.2–26.7]	0.682
NYHA III or IV, n (%)	40, 28.4%	24, 21.2%	0.191
Hypertension, n (%)	41, 29.1%	52, 46.0%	0.005*
SBP (mmHg)	112 [97–129]	124[107–139]	<0.001*
DBP (mmHg)	70 [62–82]	74 [61–83]	0.483
CKD, n (%)	56, 39.7%	55, 48.7%	0.153
DM, n (%)	33, 23.4%	32, 28.3%	0.372
CAD, n (%)	24, 17.0%	32, 28.3%	0.031*
AF, n (%)	24, 17.0%	25, 22.1%	0.307
Heart failure Etiology			
DCM, n (%)	82, 58.2%	15, 13.2%	<0.001*
HCM, n (%)	6, 4.3%	20, 17.7%	<0.001*
Amyloidosis, n (%)	10, 7.1%	26, 23.0%	<0.001*
ICM, n (%)	16, 11.4%	16, 14,2%	0.503
Others, n (%)	27, 19.2%	36, 31.9%	0.020*

Blood tests			
Hb (g/dL)	14.0 [12.5–15.4]	13.1 [11.6–14.7]	0.003*
Cre (mg/dL)	0.90 [0.76–1.22]	0.88 [0.74–1.13]	0.308
eGFR (mL/min/1.73m^2)	64.9 [49.1–79.3]	59.7 [46.0–74.8]	0.288
BNP (pg/mL)	198.0 [79.5–450.2]	198.0 [71.8–450.1]	0.796
HbA1c (%)	5.9 [5.5–6.3]	5.9 [5.6–6.5]	0.254
Echocardiography			
LVEF (%)	27 [21–34]	55 [47–67]	<0.001*
LVDd (mm)	60 [53–68]	46 [41–51]	<0.001*
E/e’	13.6 [9.9–19.7]	14.8 [9.8–20.0]	0.611
LAD (mm)	41 [35–48]	42 [35–46]	0.797
RVFAC (%)	36 [26–43]	38 [28–44]	0.191
TAPSE (mm)	16 [13–19]	17 [14–21]	0.170
Right heart catheterization			
mRAP (mmHg)	5 [3–7]	5 [4–7]	0.264
RVSP (mmHg)	27 [22–36]	28 [24–32]	0.881
RVEDP (mmHg)	6 [4–8]	6 [5–8]	0.189
mPAP (mmHg)	17 [13–25]	16 [13–21]	0.390
mPAWP (mmHg)	10 [6–17]	10 [7–14]	0.784

Heart Rate (/min)	71 [62–79]	67 [60–78]	0.049*
Cardiac Index, Thermo (liter/min/m^2)	2.5 [2.1–2.7]	2.5 [2.0–3.1]	0.495
PAPi	3.5 [2.4–5.8]	3.5 [2.4–5.0]	0.632
RA/PAWP ratio	0.50 [0.32–0.60]	0.50 [0.38–0.67]	0.190
RVSWI (g·m/m^2/beat)	6.0 [4.3–7.8]	6.0 [4.2–7.7]	0.828
Medication, n (%)			
Loop diuretics	87, 61.7%	55, 48.7%	0.038*
Tolvaptan	33, 23.4%	10, 8.9%	0.002*
Beta-blockers	122, 86.5%	74, 65.5%	<0.001*
ACEI/ ARB	95, 67.4%	63, 55.8%	0.058
ARNI	16, 11.4%	9, 8.0%	0.365
SGLT2i	47, 33.3%	29, 25.7%	0.183
MRAs	87, 61.7%	30, 26.6%	<0.001*
RV parameters derived from P-V loop analysis			
estimated RVEDV (mL)	135.2 [106.4–176.1]	120.4 [93.0–154.2]	0.014*
estimated RVESV (mL)	75.4 [51.1–102.4]	53.9 [36.4–79.1]	<0.001*
RVEes (mmHg/mL)	0.28 [0.20–0.42]	0.37 [0.23–0.50]	0.004*
RVEa (mmHg/mL)	0.34 [0.21–0.58]	0.30 [0.22–0.44]	0.246

RVEes/Ea	0.80 [0.57–1.17]	1.18 [0.79–1.65]	<0.001*
RVβ	0.025 [0.018–0.034]	0.025 [0.017–0.032]	0.490
RVEed (mmHg/mL)	0.139 [0.091–0.222]	0.147 [0.101–0.244]	0.395

Data are expressed as medians [interquartile ranges] or percent frequencies.

ACEI, angiotensin converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; BMI, body mass index; BNP, brain natriuretic peptide; CAD, coronary artery disease; CKD, chronic kidney disease; Cre, creatinine; DBP, diastolic blood pressure; DCM, dilated cardiomyopathy; DM, diabetes mellitus; E, early mitral flow velocity; e, early diastolic velocity of the septal mitral annulus; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; HCM, hypertrophic cardiomyopathy; ICM, ischemic cardiomyopathy; LAD, left atrial diameter; LVDd, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; mPAP, mean pulmonary arterial pressure; mPAWP, mean pulmonary artery wedge pressure; mRAP, mean right atrial pressure; MRAs, mineralocorticoid receptor antagonists; NYHA, New York Heart Association; PAPi, pulmonary artery pulsatility index; PVR, pulmonary vascular resistance; RA/PAWP ratio, median right arterial to pulmonary artery wedge pressure ratio; RVβ, right ventricular diastolic stiffness coefficient; RVEa, right ventricular arterial elastance; RVEDP, right ventricular end-diastolic pressure; RVEDV, right ventricular end-diastolic volume; RVEed, right ventricular end-diastolic elastance; RVEes, right ventricular end-systolic elastance; RVESV, right ventricular end-systolic volume; RVFAC, right ventricular fractional area change; RVSP, right ventricular systolic pressure; RVSWI, right

ventricular stroke work index; TAPSE, tricuspid annular plane systolic excursion; SBP, systolic blood pressure; SGLT2i, sodium-glucose cotransporter 2 inhibitor; Thermo, thermodilution method.

*P < 0.05.

Table 2. Hazard ratios of RHC parameters and RV systolic and diastolic parameters for the primary endpoint

	HR	95% CI	P-value
mPAP (mmHg)			
≥ 20 vs. < 20	2.9	1.7–4.8	<0.001*
mPAWP (mmHg)			
≥ 18 vs. < 18	2.2	1.3–3.8	0.004*
RVEDP (mmHg)			
≥ 9 vs. < 9	2.7	1.6–4.6	<0.001*
Cardiac index (liter/min/m^2)			
< 2.2 vs. ≥ 2.2	1.7	1.1–2.9	0.032*
PAPi			
< 2.25 vs. ≥ 2.25	1.6	0.95–2.9	0.078
RA/PAWP ratio			

≥ 0.93 vs. <0.93	2.5	0.91–7.0	0.075
RVSWI (g·m/m^2/beat)			
≥ 7.77 vs. < 7.77	2.5	1.5–4.1	0.001*
RVEes (mmHg/mL)			
≥ 0.25 vs. < 0.25	1.9	1.1–3.5	0.027*
RVEa (mmHg/mL)			
≥ 0.44 vs. < 0.44	4.0	2.4–6.7	<0.001*
RVEes/Ea			
< 0.55 vs. ≥ 0.55	4.1	2.4–6.9	<0.001*
RVβ			
≥ 0.025 vs. < 0.025	4.8	2.5–9.0	<0.001*
RVEed (mmHg/mL)			
≥ 0.17 vs. < 0.17	2.8	1.7–4.7	<0.001*

The cutoff value of mPAP was derived from the criteria for pulmonary hypertension. The cutoff values of mPAWP and cardiac index were derived from the criteria for pulmonary hypertension and Forrester's subset. The cutoff values of RV systolic and diastolic parameters were derived from a receiver operating characteristic curve for the primary endpoint.

CI, confidence interval; HR, hazard ratio; RHC, right heart catheterization; RV, right ventricular. Other abbreviations are as defined in Table1.

*P < 0.05.

Table 3. The unadjusted and adjusted analysis of RV systolic and diastolic parameters for the primary endpoint, incorporating other heart failure risk factors, in whole cohort and different LVEF groups

	Whole cohort		**LVEF < 40%**		**LVEF ≧ 40%**	
	HR (95% CI)	**P-value**	**HR (95% CI)**	**P-value**	**HR (95% CI)**	**P-value**
RVEes/Ea						
Unadjusted	**4.1 (2.4, 6.9)**	**<0.001***	**5.5 (2.7, 10.8)**	**<0.001***	**3.2 (1.2, 8.5)**	**0.019***
Adjusted model 1	**3.1 (1.8, 5.4)**	**<0.001***	**3.9 (1.9, 8.0)**	**<0.001***	**2.8 (0.98, 7.8)**	**0.054**
Adjusted model 2	**3.0 (1.7, 5.3)**	**<0.001***	**3.5 (1.6, 7.5)**	**0.002***	**2.8 (0.99, 7.8)**	**0.052**
Adjusted model 3	**2.7 (1.5, 4.9)**	**0.001***	**3.3 (1.4, 7.5)**	**0.005***	**2.2 (0.71, 6.8)**	**0.173**
RVβ						
Unadjusted	**4.8 (2.5, 9.0)**	**<0.001***	**5.0 (2.1, 12.1)**	**0.001***	**4.5 (1.8, 11.3)**	**0.001***
Adjusted model 1	**3.1 (1.6, 5.8)**	**0.001***	**3.5 (1.4, 8.6)**	**0.006***	**2.8 (1.1, 7.3)**	**0.034***

Adjusted model 2	**3.1 (1.6, 6.1)**	**0.001***	**3.1 (1.2, 8.0)**	**0.023***	**3.0 (1.1, 8.2)**	**0.029***
Adjusted model 3	**2.9 (1.4, 5.8)**	**0.003***	**2.9 (1.1, 7.8)**	**0.029***	**2.8 (1.01, 7.8)**	**0.048***

Abbreviations are as defined in Table 2.

Adjusted models include parameters as follow.

model 1 = age, gender, BNP, Cre

model 2 = age, gender, BNP, Cre, mPAP

model 3 = age, gender, BNP, Cre, mPAP, RVEDP

The cutoff values of RVEes/Ea, RVβ, BNP, age, Cre and RVEDP were derived from a receiver operating characteristic curve for the primary endpoint. The cutoff value of mPAP was derived from the criteria for pulmonary hypertension.

*$P < 0.05$.

Figure Legends

Central Illustration: Waveform-Derived RV Systolic and Diastolic Parameters and Their Prognostic Utility in Heart Failure

Waveform-derived RV systolic and diastolic parameters and their prognostic significance. This central illustration summarizes the conceptual framework and prognostic value of RVEes/Ea and RVβ derived from right heart catheterization in patients with heart failure. BDP, beginning-diastolic pressure; CI, confidence interval; EDP, end-diastolic pressure; EDPVR, end-diastolic pressure–volume relationship; ESP, end-systolic pressure; ESPVR, end-systolic pressure–volume relationship; RVβ, right ventricular diastolic stiffness coefficient; RVEa, right ventricular–arterial elastance; RVEed, right ventricular end-diastolic elastance; RVEes, right ventricular end-systolic elastance.

Fig. 1 Estimation of the end-systolic pressure–volume relationship (ESPVR) and end-diastolic pressure–volume relationship (EDPVR)

Pmax represents the maximum sine-curve fitting value of the isovolumic phases of RV waveforms

ESP is calculated as follows:

ESP = mean PAP + (systolic PAP – mean PAP) x (time to RVSP – time to dP/dt max) / (time to dP/dt min – time to dP/dt max)

ESPVR is expressed as a linear relationship passing through (0,0)

RVEDV is derived using:

$RVEDV = ESP \times SV/(Pmax - ESP)$

RVESV is determined as:

$RVESV = Pmax \times SV/(Pmax - ESP)$

EDPVR is modeled as an exponential function:

$P = \alpha(e^{(V\beta)} - 1)$,

where β represents the diastolic stiffness coefficient (RVβ). The curve is approximated using three reference points: (0,0), (RVESV, 1), and (RVEDV, normalized RVEDP [RVEDP – RVBDP + 1])

EDPVR, end-diastolic pressure–volume relationship; ESP, end-systolic pressure; ESPVR, end-systolic pressure–volume relationship; PAP, pulmonary artery pressure; RVβ, right ventricular diastolic stiffness coefficient; RVBDP, right ventricular beginning-diastolic pressure; RVEa, right ventricular–arterial elastance; RVEDP, right ventricular end-diastolic pressure; RVEDV, right ventricular end-diastolic volume; RVEed, right ventricular end-diastolic elastance; RVEes, right ventricular end-systolic elastance; RVESV, right ventricular end-systolic volume; RVSP, right ventricular systolic pressure

Fig. 2 Kaplan–Meier survival curves for primary and secondary endpoints

Panels (A) and (B) categorize the population based on RVEes/Ea, while panels (C) and (D) categorize them based on RVβ

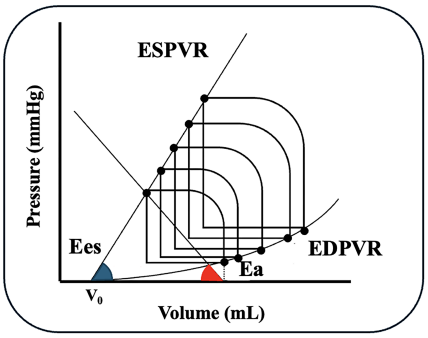
RVD, right ventricular dysfunction. Other abbreviations are as defined in Fig. 1

Fig. 3 Distribution of systolic and diastolic RVD stratified by LVEF

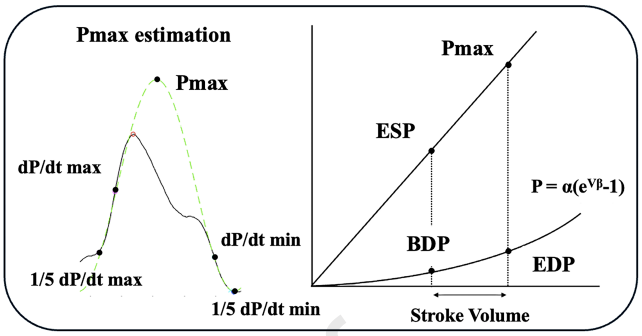
LVEF, left ventricular ejection fraction. Other abbreviations are as defined in Fig. 2

Central Illustration: Waveform-Derived RV Systolic and Diastolic Parameters and Their Prognostic Utility in Heart Failure

Conventional methods: Using Pressure-Volume Catheters



Our method: Using Right Heart Catheterization Data Alone



Systolic function
RVEes: Systolic capacity
RVEa: Arterial elastance
RVEes/Ea: Coupling or Uncoupling

Diastolic function
RVβ : Ventricular wall stiffness
RVEed

Utility in Heart Failure Patients