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Original Paper

Echocardiographic and Hemodynamic Parameters Associated with Diminishing Renal Filtration among Patients with Heart Failure with Preserved Ejection Fraction

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Keywords
Right ventricular dysfunction · Chronic kidney disease · Heart failure with preserved ejection fraction · Pulmonary artery pulsatility index

Abstract
Background: Renal dysfunction is an important predictor of poor outcomes in patients with heart failure with preserved ejection fraction (HFpEF). Right ventricular (RV) dysfunction is implicated as one of the explanations for worsening renal function in cardiorenal syndrome. Novel right heart catheterization (RHC) parameters such as pulmonary artery pulsatility index (PAPi) and right atrial to pulmonary capillary wedge pressure ratio (RA:PCWP) have been found as predictors of RV dysfunction. However, most studies investigating these parameters have been done in the setting of myocardial infarction or left ventricular assist device implantation, with limited data on these metrics in patients with HFpEF. ***Objective:*** The purpose of this study was to determine whether novel RHC parameters such as RA:PCWP and PAPi correlate with long-term renal outcomes among patients with HFpEF. ***Methods:*** A retrospective single-center study of adult patients with a documented diagnosis of heart failure who had RHC was performed between January 2006 and December 2010 at Einstein Medical Center Philadelphia. Selected patients also had a serum B-type natriuretic peptide level ≥100 pg/mL and a PCWP ≥15 mm Hg. Patients with an ejection fraction <50%, including those with recovered ejection fraction, and end-stage renal disease were excluded. ***Results:***

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A total of 81 patients with a clinical diagnosis of HFpEF were identified who met the inclusion criteria. On multivariate analysis, after adjusting for age, sex, race, diabetes, hypertension, and cardiac index, PAPi was associated with long-term estimated glomerular filtration rate (eGFR) (β = 3.43, 95% CI = 0.635–6.23, p = 0.017), and RA:PCWP showed a trend towards significance (β = 14.81, 95% CI = −0.096–29.73, p = 0.051). The results were unchanged after further adjustment for eGFR at the time of RHC. ***Conclusion:*** Novel hemodynamic indices obtained by RHC may have predictive value for long-term renal dysfunction in patients with HFpEF.

Introduction

According to the NHANES database from 2011 to 2014, an estimated 6.5 million Americans have heart failure (HF), and the number is expected to increase further in the coming years. The burden of disease mortality is high, with close to half of people diagnosed with HF dying within 5 years [1]. It is estimated that approximately half of patients diagnosed with HF have preserved ejection fraction [2].

There is a strong association between HF and worsening renal function [3]. A recent meta-analysis showed that among all subgroups of patients with HF, the presence of impaired renal function was significantly associated with mortality and had even greater prognostic significance among those with HF with preserved ejection fraction (HFpEF) [3]. Various studies have shown that HF, including HFpEF, is associated with worsening renal function [4–6], with right ventricular (RV) dysfunction and elevated right atrial (RA) pressures being implicated in the pathophysiology of progressive cardiorenal syndrome (CRS) [7, 8].

Recent studies have described novel hemodynamic parameters determined by right heart catheterization (RHC) such as pulmonary artery pulsatility index (PAPi) and RA to pulmonary capillary wedge pressure ratio (RA:PCWP) as predictors of RV dysfunction [9–14]. However, to date most of the studies investigating these novel parameters have been done in the setting of acute myocardial infarction or left ventricular assist device implantation. There are limited data on the association of these novel hemodynamic parameters with long-term renal function, especially in patients with HFpEF. The purpose of this study was to investigate whether novel hemodynamic parameters from RHC can predict long-term decline in renal function in patients with HFpEF.

Methods

Study Design and Patient Selection

This study was a retrospective single-center analysis of patients admitted with a clinical diagnosis of HF with characteristic symptoms of shortness of breath/orthopnea/paroxysmal nocturnal dyspnea and with clinical evidence of volume overload on physical examination as well as on imaging. Eligible subjects included those HF patients who underwent RHC at Einstein Medical Center Philadelphia between January 2006 and December 2010. From that group, we identified 311 subjects who had laboratory data available on long-term renal function. In addition, patients who qualified for inclusion had a serum B-type natriuretic peptide value ≥100 pg/mL and/or a PCWP ≥15 mm Hg. Finally, we excluded 230 patients with an ejection fraction <50% (including those with recovered ejection fraction) and patients with end-stage renal disease, leaving a final study sample of 81 subjects (Fig. 1).

Clinical Data and Outcome Measures

Anonymized demographic, clinical, and RHC data were collected by review of medical records. PAPi was calculated as the difference of pulmonary systolic and diastolic pressures divided by RA pressure (Fig. 2).

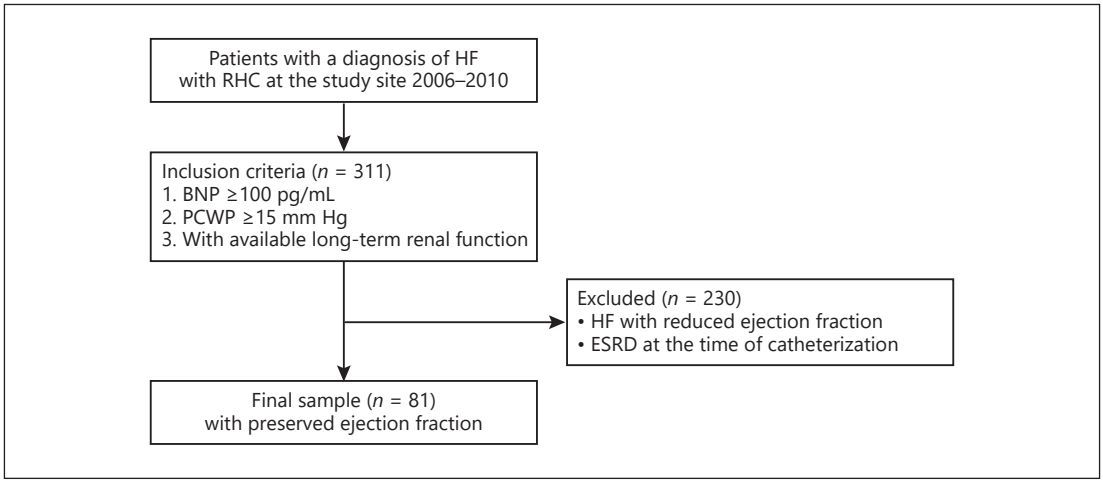

Fig. 1. Consort diagram showing the inclusion and exclusion criteria. BNP, B-type natriuretic peptide; ESRD, end-stage renal disease; HF, heart failure; PCWP, pulmonary capillary wedge pressure; RHC, right heart catheterization.

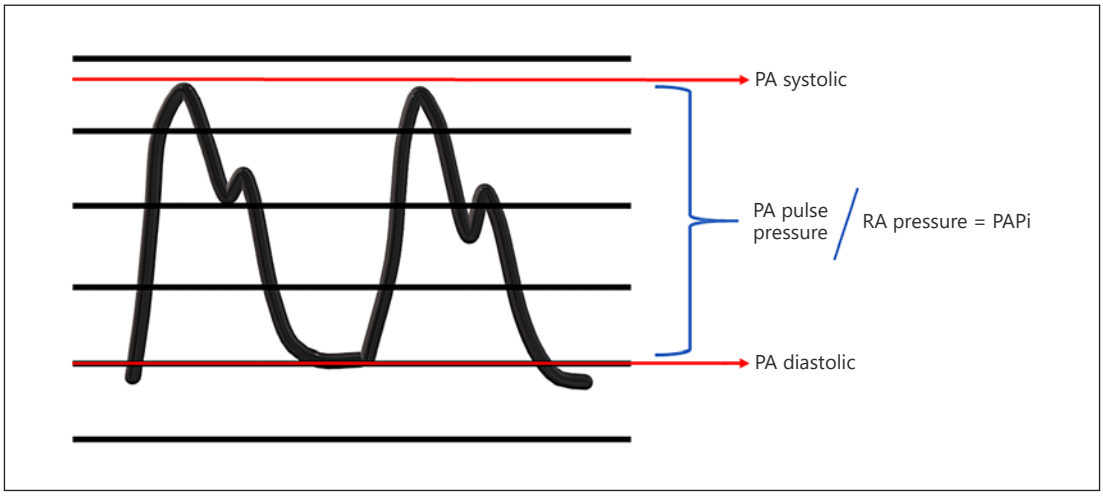

Fig. 2. Waveform tracing and computation for PAPi. PA, pulmonary artery; PAPi, pulmonary artery pulsatility index; RA, right atrial.

RA:PCWP was calculated as RA pressure divided by PCWP. All values for calculation were obtained from the index RHC reports. Estimated glomerular filtration rate (eGFR) values at the time of the RHC and the first available value between 3–5 years after the RHC were recorded. eGFR was calculated using the modified diet in renal disease equation.

Statistical Analysis

Continuous and categorical variables were described using descriptive statistics. Multivariate linear regression analysis was used to analyze the association between PAPi and RA:PCWP and long-term eGFR, after adjusting for age, race, sex, cardiac index, baseline eGFR, and comorbidities such as diabetes and hypertension. SPSS by IBM build 1.0.0.903 was used for all analyses.

Table 1. Demographic data and baseline clinical parameters

Age, years		63.33±12.84
Sex	Male	26 (32.1%)
	Female	55 (67.9%)
Race	African American	66 (81.5%)
	Caucasian	12 (14.8%)
	Hispanic	3 (3.7%)
	Others	0
Smoking		30 (47%)
Diabetes		46 (56.8%)
Hypertension		76 (93.8%)
COPD		20 (25%)
Mean A1c		6.74±2.06
Tricuspid regurgitation	None	47%
	Mild	31%
	Moderate	17%
	Severe	5%
RV systolic function	Normal	75%
	Mild dysfunction	6%
	Moderate dysfunction	16%
	Severe dysfunction	3%
TAPSE		1.6±0.6
Fractional area change		25.4±10.3
Left atrial size	Normal	45%
	Mild	22%
	Moderate	26%
	Severe	7%
Left ventricular size	Normal	89%
	Mild	4.7%
	Moderate	4.7%
	Severe	1.6%
Mitral regurgitation	None	67%
	Mild	19%
	Moderate	8%
	Severe	6%
Left ventricular hypertrophy	None	36%
	Mild	52%
	Moderate	12%
	Severe	0%
Ejection fraction		58.51±7.19
RA pressure, mm Hg		11.95±7.28
RV systolic pressure, mm Hg		52.45±16.36
RV diastolic pressure, mm Hg		7.63±6.80
PA systolic pressure, mm Hg		51.34±15.32
PA diastolic pressure, mm Hg		19.64±9.01
PA pressure, mm Hg		32.52±10.43
PCWP, mm Hg		18.96±8.04
Cardiac output, L/min		5.71±1.76
Cardiac index		2.85±0.81
PVR, dyn × s × cm^{-5}		216.94±155.46
PAPi		3.45±2.28
RA:PCWP		0.54±0.44
GFR at RHC (baseline eGFR)		74.93±32.87
Long-term eGFR, mL/min		74.7±38.67

Values are presented as mean ± standard deviation or *n* (%). COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; PA, pulmonary artery; PAPi, pulmonary artery pulsatility index; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RA, right atrial; RA:PCWP, right atrial to pulmonary capillary wedge pressure ratio; RHC, right heart catheterization; RV, right ventricular; TAPSE, tricuspid annular plane systolic excursion.

Table 2. Results of the multivariate linear regression model to assess the association between long-term eGFR and PAPi

Covariates	β (regression coefficient)	*p* value	CI
Age	–1.302	0.000	–1.81 to –0.791
Sex	–39.91	0.000	–54.71 to –25.11
Race	8.08	0.248	–5.75 to 21.92
Hypertension	1.376	0.916	–24.54 to 27.299
Diabetes	3.932	0.533	–8.57 to 16.44
PAPi	3.434	0.017	0.635 to 6.23
RA:PCWP	14.819	0.051	–0.096 to 29.73
Cardiac index	–3.523	0.391	–11.67 to 4.62

eGFR, estimated glomerular filtration rate; PAPi, pulmonary artery pulsatility index; RA:PCWP, right atrial to pulmonary capillary wedge pressure ratio.

Results

Patient Demographics

A total of 81 patients with a clinical diagnosis of HFpEF met the inclusion criteria. Mean age was 63.33 ± 12.84 years, and 81.5% of subjects were African American, 12% Caucasian, and 3% Hispanic; 56.8% had diabetes and 93.8% had hypertension. The time point where 3- to 5-year eGFR was measured was at a mean of 4.69 years. Representative indications for RHC included need for more accurate assessment of perfusion state, assessing the effect of concomitant valvopathy, and suboptimal response to diuresis in the backdrop of acute HF. The mean tricuspid annular plane systolic excursion was within the normal value of 1.6 cm, mean fractional area change was 25, and 75% of the population had normal RV function on echo assessment at baseline; these echo parameters of assessment of RV function were obtained according to guidelines [15]. For baseline clinical parameters and demographic data, see Table 1.

On multivariate linear regression analysis, after adjusting for age, sex, race, diabetes, hypertension, and cardiac index, PAPi was significantly associated with long-term eGFR (β = 3.43, 95% CI = 0.635–6.23, p = 0.017), and RA:PCWP showed a trend towards significance (β = 14.81, 95% CI = –0.096–29.73, p = 0.051). Cardiac index was included to help adjust for other hemodynamic factors such as systolic blood pressure, which may influence renal perfusion and potentially long-term renal outcomes. When the multivariate model included baseline eGFR, the results still held true for both parameters. This was true even on subsequent models tested when body mass index was included as a potential influencing factor for hemodynamics. As expected, baseline eGFR at the time of RHC was associated with eGFR at the 3- to 5-year timepoint. The results of the multivariate model (with and without baseline glomerular filtration rate) are shown in Tables 2 and 3.

Discussion

Various novel hemodynamic cardiac catheterization parameters in HF have been studied in the hope of eliciting underlying pathophysiologic mechanisms and deriving prognostic information on worsening renal function in patients with HF. Prior landmark data emphasizing the importance of the effect of elevated central venous and RA pressure in CRS have advanced our understanding of the impact of renal venous congestion on renal function in

Table 3. Results of the multivariate linear regression model to assess the association between long-term eGFR and PAPi adjusting for baseline eGFR

Covariates	β (regression coefficient)	*p* value	CI
Age	–1.073	0.000	–1.61 to –0.54
Sex	–31.90	0.000	–47.78 to –16.01
Race	6.456	0.767	–7.04 to 19.95
Hypertension	2.33	0.185	–22.83 to 27.49
Diabetes	3.49	0.568	–8.65 to 15.63
PAPi	2.852	0.043	0.092 to 5.613
RA:PCWP	13.27	0.073	–1.26 to 27.81
Cardiac index	–2.693	0.5	–10.62 to 5.24
Baseline eGFR	0.251	0.022	0.038 to 0.464

eGFR, estimated glomerular filtration rate; PAPi, pulmonary artery pulsatility index; RA:PCWP, right atrial to pulmonary capillary wedge pressure ratio.

patients with HF [16, 17]. The predictive value of novel hemodynamic parameters for RV dysfunction has been shown in prior studies in the setting of acute myocardial infarction, pre left ventricular assist device implantation, and the need for right ventricular assist device placement after left ventricular assist device placement [9–14]. A more recent analysis done by Gajanana et al. in 2017 [9] showed that among patients with pulmonary hypertension, novel parameters such as RA:PCWP can be used to predict worsening of short-term renal function. In this study, patients with an RA:PCWP >0.86 had higher serum creatinine levels and worsening short-term kidney function [9]. However, the prognostic significance of these parameters in long-term renal function is relatively unknown, particularly in HFpEF.

In our sample patient population, PAPi showed a direct and significant association with long-term eGFR, and RA:PCWP showed a trend towards association with long-term eGFR even after adjustment for age, sex, race, and risk factors for chronic kidney disease in the long term. This reiterates the link between RV dysfunction and worsening renal function in patients with HFpEF. This relationship was apparent even after adjusting for baseline eGFR, which is the strongest predictor of subsequent long-term decline in eGFR. Based on our analysis, PAPi was directly associated with long-term eGFR. The higher PAPi, the more preserved long-term eGFR. The fact that these hemodynamic metrics had incremental predictive value for long-term renal function in HFpEF over and above baseline eGFR emphasizes the key role that RV dysfunction may play. RV dysfunction not only contributes to acute hemodynamic changes and effects on renal function (type 1 CRS), but our study suggests that evidence of RV dysfunction may also play a role in the indolent phenotype of CRS (type 2 CRS) over time. This means that chronic abnormalities of right heart function may in the long term lead to progressive chronic kidney dysfunction consistent with type 2 CRS.

The predictive values of PAPi and RA:PCWP on renal function are likely determined by the degree and phenotype of HF (heart failure with reduced ejection fraction vs. HFpEF). The relatively smaller sample size in this study may have limited the ability to demonstrate a relationship between RA:PCWP and renal function as a predictor of long-term eGFR. Morine et al. [12] showed that PAPi performed better in identifying RV dysfunction and exceeded the predictive value of RA:PCWP, RV stroke work index, or RA pressure alone. However, in the study done by Gajanana et al. in 2017 [9], RA:PCWP was more predictive than PAPi of short-term renal function, but this study was conducted on advanced HF patients with reduced ejection fraction who had a greater degree of left ventricular failure with higher resting left-

sided filling pressures (PCWP). PAPi, a purely right-sided heart measurement, contrasts with RA:PCWP (which examines left- and right-sided filling pressures). It thus assesses RV systolic effectiveness and is hemodynamically more separated from the influence of the left-sided hemodynamics. Thus, PAPi might be a more sensitive hemodynamic parameter in detecting long-term decline in renal function caused by RV dysfunction when compared to the other parameters, especially in the setting of HFpEF.

RV dysfunction has long been implicated as a central factor in the progression of renal dysfunction. In the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial, among all hemodynamic parameters measured in patients randomized to the pulmonary artery catheterization arm, only RA pressure correlated with baseline serum creatinine and eGFR [16]. In another study of patients with HFpEF, RV fractional area change on echocardiography (a measure of RV function) was significantly lower in those with worsening renal function during hospitalization for acute decompensated HF [18]. Other data have demonstrated that patients with pulmonary hypertension prior to kidney transplantation had a higher risk of early graft dysfunction [19] and reduced patient survival after kidney transplantation [20]. These data outline the significant effect of progressive RV dysfunction as a cause of subsequent renal dysfunction and overall mortality.

The bidirectional relationship between the heart and kidney is complex, and new mechanisms and pathophysiologic explanations are continually being brought to light. In a prospective study done by Unger et al. [21], patients with chronic kidney disease had greater diastolic dysfunction and myocardial wall strain, thereby leading to a higher burden of HFpEF and overall worse outcomes. Possible mechanisms of chronic kidney disease leading to worse HFpEF outcomes include derangements in circulating factors causing an activated systemic inflammatory state and endothelial dysfunction leading to myocardial fibrosis and hypertrophy [22]. In a reverse association model, various studies have also in turn shown that HF, including HFpEF, is associated with worsening renal function. There are various explanations for this observation, but increased central venous pressure and resultant decreased renal perfusion have emerged as the main pathophysiologic factors driving renal dysfunction [6]. To this end, the effect of the contribution of RV dysfunction towards declining long-term renal function in CRS represents an important area of future study and targeted treatments.

Limitations

To the best to our knowledge, this study is the first one to investigate the association between novel hemodynamic invasive parameters of RV dysfunction on long-term renal function among patients with HFpEF. It reinforces the role of RV function in affecting long-term kidney function in HF, including patients with preserved ejection fraction. Our study is limited by the intrinsic nature of a retrospective analysis and a relatively small sample size. No blinding was done. There is a possibility of referral bias as the study was done in a tertiary medical center where patients admitted might not necessarily reflect the general population. There are also other factors such as long-term blood pressure and glucose control as well as medication compliance, which may influence decline in renal function in the long term and cannot be entirely controlled despite multivariate regression. Proteinuria is a major factor that is responsible for accelerated decline in kidney function over time, and data on serial urine microalbumin quantification were unavailable in this study and may represent a confounding factor. Finally, the hemodynamic metrics outlined represent a snapshot in time of RV function that was captured in this cohort and may not fully represent the sequential changes that may occur with progressive CRS over time. Furthermore, the use of sedation during the actual cardiac catheterization may also affect the hemodynamic parameters. However, given the relatively stringent inclusion/exclusion criteria, these findings are hypothesis-generating and contribute to the knowledge behind the pathophysiology of renal

function decline among patients with HFpEF. This study opens possibilities for future research focusing on outlining the role of RV function in predicting long-term kidney function in patients with HFpEF.

In conclusion, novel hemodynamic indices obtained by RHC may have predictive value for long-term renal dysfunction in patients with HFpEF.

Statement of Ethics

The study protocol was approved by the local institutional review board.

Disclosure Statement

The authors declare no conflicts of interest. There was no monetary or material support for this research investigation.

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