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Original Research

Renal implications of pulmonary arterial capacitance in acute heart failure with preserved ejection fraction

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Worsening renal function in patients with heart failure with preserved ejection fraction is associated with poor outcomes. Pulmonary arterial capacitance is a novel right heart catheterization derived hemodynamic metric representing pulmonary arterial tree distensibility and right ventricle afterload. Given the strong association between heart failure, pulmonary hypertension, and kidney function, the goal of this study is to investigate the correlation between Pulmonary arterial capacitance and long-term renal function in patients with heart failure with preserved ejection fraction. In this retrospective single center study, data from 951 patients with the diagnosis of heart failure, who underwent right heart catheterization were analyzed. Eight hundred and one patients with reduced ejection fraction, end-stage kidney disease on hemodialysis, acute myocardial infarction, and severe structural valvular disorders, were excluded. Pulmonary arterial capacitance was calculated as the stroke volume divided by pulmonary artery pulse pressure (mL/mmHg). Hemodynamic and clinical variables including baseline renal function were obtained at the time of the right heart catheterization, and renal function was also obtained at 3-5 years after right heart catheterization. The final cohort consisted of 150 subjects with a mean age 68 ($\pm$ 14.2) years, 93 (62%) were female. The mean value for Pulmonary arterial capacitance was 2.82 ($\pm$ 2.22) mL/mm Hg and the mean Glomerular Filtration Rate was 60.32 mL/min/l.73 m^2 ($\pm$ 28.36). After multivariate linear regression analysis (including baseline Estimated Glomerular Filtration Rate as one of the variates), only age and Pulmonary arterial capacitance greater than 2.22 mL/mm Hg were predictors of long term Glomerular Filtration Rate. Pulmonary arterial capacitance as a novel right heart catheterization index could be a predictor of long-term renal function in patients with heart failure with preserved ejection fraction.

Keywords

Right-heart catheterization; pulmonary arterial capacitance; renal function; heart failure

1. Introduction

Kidney dysfunction is a common co-morbid condition and independent risk factor for poor outcomes and increased mortality in heart failure (HF) (Grande et al., 2018). This association has been suggested to be more pronounced in heart failure with preserved ejection fraction (HFpEF) (Ter Maaten and Voors, 2016). Studies have shown high incidence of worsening renal function in HFpEF (as high as 40%), which was in turn associated with right and left ventricular dysfunction, worse cardiac mechanics, poor prognosis, and worse outcomes (Mukherjee et al., 2017; Schefold et al., 2016; Sharma et al., 2015; Unger et al., 2016). Several mechanistic pathways contribute to cardiorenal syndrome in HFpEF including neuro-hormonal activation, inflammatory cascade activation, renal venous hypertension and elevated intra-abdominal pressures (Rangaswami et al., 2019).

Pulmonary hypertension (PH) defined as mean pulmonary artery pressure of 25 mmHg and above measured via right heart catheterization (RHC), describes a group of hemodynamic disorders resulting from an increase in pulmonary blood flow, vascular resistance, or pulmonary venous pressure (Alves et al., 2017; Galie et al., 2015). PH can be idiopathic or secondary to variety of causes, most commonly due to left heart disease (50% of PH cases) (Guha et al., 2016). Pulmonary arterial capacitance (PAC) is a recently introduced invasive parameter of RHC, and is defined as the stroke volume (SV) divided by pulmonary artery pulse pressure (PP). It represents the distensibility of the pulmonary arterial tree, which in turn, is a determinant of right ventricular (RV) afterload. PAC has been shown to be associated with increased mortality and cardiac events in heart failure (Dragu et al., 2015; Dupont et al., 2012; Takatsuki et al., 2017). Recent studies have shown association between PH and kidney dysfunction using novel right heart catheterization measurements (Gajanana et al., 2017; Navaneethan et al., 2014).

The relationship between elevated right sided pressures and worsening kidney function in heart failure is well characterized (Mullens et al., 2009); however there is limited information on the impact of metrics of right ventricular (RV) function on long term renal function. We hypothesized that PAC as a more advanced

hemodynamic metric derived from RHC may have a predictive value for long-term renal function. The aim of this study is to investigate the correlation between PAC and long-term decline in GFR in subjects with HFpEF, given that they represent a growing but difficult to treat subset of patients with heart failure.

2. Methods

2.1 Subjects

This was a single center retrospective study of a total of 951 consecutive patients hospitalized with a clinical diagnosis of heart failure who underwent RHC between January 2010 and September 2015 at Einstein Medical Center, Philadelphia. Three hundred and ninety-nine patients were included based on age $\geq$ 18 years old and diagnosis of HFpEF. HFpEF was defined as EF $\geq$ 50%, and presence of signs and symptoms of heart failure, elevated brain natriuretic peptide (BNP), or evidence of diastolic dysfunction (DD) between grade I to IV (Ponikowski et al., 2016). Patients with end-stage renal disease on hemodialysis, acute myocardial infarction, severe structural valvular disorders, complex congenital heart disease, or severe chronic obstructive pulmonary disease (COPD) were excluded. Sixty-five subjects were also excluded due to lack of longitudinal data on long-term renal function (Fig. 1). The final cohort was made up of 150 patients. The study protocol was in conformity with the Declaration of Helsinki and was approved by the Institutional Review Board of Albert Einstein Health Network, Philadelphia, PA, USA.

Demographic and clinical data were obtained through medical records chart review. Laboratory data including creatinine was obtained form same admission of right heart catheterization and then from 3 to 5 years after that date. Glomerular filtration rate (GFR) was calculated using Cockroft-Gault formula (Cockcroft and Gault, 1976). Echocardiography data were obtained from measurements within 7 days from right heart catheterization.

Right Heart Catheterization was obtained in the cardiac catheterization laboratory in patients at rest in a supine position after minimal sedation. A balloon tipped catheter was used to obtain pressures including right atrium pressure (RAP), pulmonary capillary wedge pressure (PCWP), pulmonary artery systolic and diastolic pressure, and pulmonary artery oxygen saturation. Cardiac output (CO, L/min) was calculated using Fick equation and cardiac index (CI) was calculated based on CO divided by body surface area (BSA, m^2). Stroke volume was calculated as CO divided by heart rate (HR). Pulmonary artery capacitance (PAC) was calculated as stroke volume/pulmonary artery pulse pressure expressed in mL/mmHg.

2.2 Statistical Analysis

Data analysis was conducted using Statistical Package for the Social Sciences (SPSS)® version 24 (SPSS Corp, Chicago, IL, USA). Continuous variables were summarized using mean ± standard deviation. Categorical variables were summarized using frequencies and proportions. Patients were divided to two groups based on PAC median value (2.22 ml/mmHg). Baseline characteristics, comorbidities, laboratory, and hemodynamic data were compared between two groups using t-test. Cox proportional hazards models were used to estimate hazard ratios and their 95% confidence intervals for the association between clinical and hemodynamic factors. A P-value < 0.05 was considered significant.

3. Results

The final cohort consisted of 150 patients. The mean age was 68.49 (± 14.2) years. Of the 150 subjects, 93 (62%) were female, of which 66.7% were African American, 28% Caucasian, and 3.3% Hispanic. Mean Body Mass Index (BMI) was 33.7 ± 16.21 kg/m^2 and mean body surface area (BSA) was 2.03 ± 0.31 m^2. The mean and median PAC was 2.82 ± 2.22 and 2.22 ml/mmHg respectively, and the mean GFR was 60.32 ± 28.36 ml/min/1.73 m^2.

Patients were divided into two groups based on PAC median value: PAC < 2.22 ml/mmHg (n = 75) and PAC $\geq$ 2.22 ml/mmHg (n = 75). The range of PAC was 0.55-19.10 ml/mmHg. There was no significant difference between two groups regarding receiving medical therapy for heart failure including beta-blockers, ACE inhibitors/ARBs, diuretics, and nitrates. Table 1 summarized the baseline clinical characteristics, comorbidities, and baseline treatments of these two groups.

Baseline GFR was not significantly different between the two groups. The cardiac index was significantly higher in the high PAC group, whereas the right atrial pressure, mean arterial pressure (MAP), and mean pulmonary arterial pressure (MPAP) were all significantly higher in the low PAC group (Table 1).
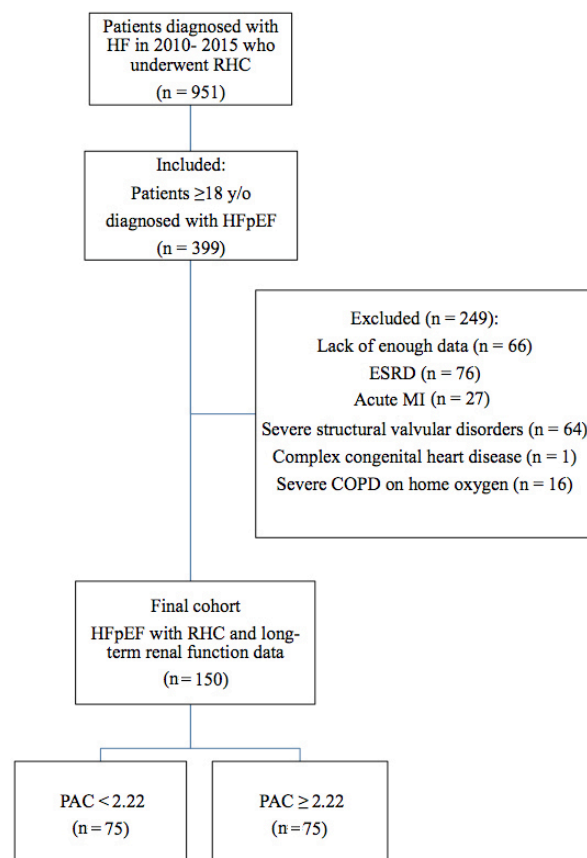

Figure 1. Flow chart of the patient selection process of our study cohort. HF: heart failure, RHC: right heart catheterization, HFpEF: heart failure with preserved ejection fraction, ESRD: end-stage renal disease, MI: myocardial infarction, COPD: chronic obstructive pulmonary disease, PAC: pulmonary arterial capacitance.

Table 1. Baseline clinical characteristics, comorbidities, laboratory, treatments, and hemodynamic data based on the median PAC value.

	Total n = 150	PAC < 2.2 mL/mmHg	PAC ≥ 2.2	*P*-value
		n = 75	mL/mmHg n = 75	
Baseline clinical data				
Age (years)	68.49 ± 14.21	70.72 ± 12.64	66.25 ± 15.38	0.054
Female Sex (n, %)	93 (62%)	56 (75%)	37 (49%)	0.002*
Weight (kg)	91.18 ± 26.86	85.87 ± 24.84	96.49 ± 27.9	0.015*
Height (cm)	166.57 ± 12.4	162.35 ± 12.87	170.78 ± 10.4	0.001*
BMI (kg/m^2)	33.70 ± 16.21	34.38 ± 21.19	33.02 ± 8.91	0.61
BSA (m^2)	2.03 ± 0.31	1.94 ± 0.27	2.12 ± 0.33	0.001*
Comorbidities				
Hypertension (n, %)	127 (85%)	67 (89%)	60 (81%)	0.173
Hyperlipidemia (n, %)	79 (53%)	39 (52%)	40 (54%)	0.87
Diabetes Mellitus (n, %)	79 (53%)	46 (61%)	33 (45%)	0.049*
Smoking (n, %)	48 (32%)	24 (32.4%)	24 (32.4%)	1.000
Atrial Fibrillation (n, %)	43 (29%)	26 (35%)	17 (23%)	0.24
CAD (n, %)	64 (43%)	35 (47%)	29 (39%)	0.409
OSA (n, %)	15 (10%)	8 (11%)	7 (9%)	1.000
COPD (n, %)	15 (10%)	7 (9%)	8 (11%)	0.432
ILD (n, %)	2 (1.3%)	1 (1%)	1 (1%)	1.000
Laboratory data				
GFR (mL/min)	60.32 ± 28.36	60.21 ± 25.78	60.43 ± 30.90	0.961
GFR 3-5 years (mL/min)	55.08 ± 33.26	54.22 ± 31.37	55.83 ± 35.22	0.835
Hemodynamics				
PCWP	20.44 ± 8.75	21.73 ± 9.3	19.16 ± 8.03	0.076
Cardiac Index	2.52 ± 1.06	2.06 ± 0.62	2.98 ± 1.21	0.001*
RAP	12.95 ± 7.08	14.11 ± 7.4	11.8 ± 6.59	0.046*
MAP	94.78 ± 16.60	97.7 ± 14.5	91.85 ± 8.08	0.031*
MPAP	34.35 ± 12.60	38.88 ± 11.89	29.82 ± 11.7	0.001*
Medications				
Beta blocker	106 (71%)	58 (77%)	48 (64%)	0.074
Loop diuretics	96 (64%)	50 (67%)	46 (61%)	0.498
Spironolactone	14 (9%)	6 (8%)	8 (11%)	0.78
ACE/ARB	56 (37%)	28 (37%)	28 (37%)	1.000
nitrates	29 (19%)	18 (24%)	11 (15%)	0.142

*P-value < 0.05 significant.

t-test was used to compare means.

Numbers are expressed as either N (%) or Mean ± SD.

PAC: pulmonary arterial capacitance, BMI: body mass index, BSA: body surface area, CAD: coronary artery disease, OSA: obstructive sleep apnea, ILD: interstitial lung disease, GFR: glomerular filtration rate, PCWP: pulmonary capillary wedge pressure, RAP: right atrial pressure, MAP: mean arterial pressure, MPAP: mean pulmonary arterial pressure.

All pressures are expressed in mm/Hg. Cardiac index expressed in L/min/m^2.

On multivariate linear regression analysis, no factors were found to be associated with GFR on admission. Looking at factors associated with long-term 3-5-year GFR, only age ($P = 0.0001$) and PAC greater than 2.2 ml/mmHg ($P = 0.044$) were significantly associated with long term GFR. This was after taking into consideration baseline GFR on admission, which in itself was a strong predictor of subsequent long term GFR ($P = 0.0001$) (Table 2). Lastly, looking at the difference in GFR between admission and at 3-5 years, only PAC ≥ 2.2 ($P = 0.044$) and age ($P = 0.0001$) were significantly associated with the change in GFR after adjusting for baseline GFR on admission.

4. Discussion

In this study, we have demonstrated that PAC is a predictor of long-term GFR in subjects with HFpEF. Prior studies have shown significant high rates of worsening renal function in patients with HFpEF (Sharma et al., 2015), which is predictive of worse prognosis in these patients (Sato et al., 2019). However, it is difficult to distinguish whether HFpEF is causing renal dysfunction via vascular congestion or kidney disease is causing adverse cardiac remodeling leading to worsening cardiac dysfunction. This pathophysiology involves a bidirectional cross talk between heart and kidneys in CRS (Rangaswami et al., 2019).

Table 2. Regression analysis showing variables predictive of GFR on admission, GFR on 3-5 years, and change in GFR.

	Predictive of GFR on admission		Predictive of GFR 3-5 year		Predictive of difference of GFR between admission and 3-5 years	
	P-value	CI	P-value	CI	P-value	CI
Baseline clinical data						
Age (years)	0.781	-0.45 to 0.34	0.0001	-1.47 to -0.46	0.0001	0.46 to 1.47
Female Sex (n, %)	0.017	-22.96 to -2.33	0.085	-1.58 to 24.03	0.085	-24.03 to 1.58
Race, Black	referrant					
Race, White	0.933	-11.9 to 10.93	0.352	-8.21 to 22.72	0.352	-22.72 to 8.21
Race, Hispanic	0.873	-24.32 to 28.6	0.519	-46.31 to 23.62	0.519	-23.62 to 46.31
Race, Other	0.551	-42.82 to 22.95	0.080	-5.35 to 92.94	0.080	-92.94 to 5.35
Comorbidities						
Hypertension	0.171	-24.73 to 4.45	0.219	-6.23 to 26.66	0.219	-26.66 to 6.233
Diabetes Mellitus	0.191	-16.99 to 3.42	0.287	-19.1 to 5.75	0.287	-5.75 to 19.10
Hemodynamics						
PCWP	0.954	-0.69 to 0.65	0.984	-0.80 to 0.82	0.984	-0.821 to 0.804
RAP	0.763	-1.03 to 0.76	0.736	-1.44 to 1.03	0.736	-1.03 to 1.44
Cardiac Index	0.622	-6.29 to 3.78	0.158	-10.85 to 1.80	0.158	-1.80 to 10.85
PAC ≥ 2.2 mL/mmHg	0.394	-15.39 to 6.09	0.044*	0.338 to 26.3	0.044*	-26.3 to -0.338
Baseline GFR mL/min/l			0.0001*	0.608 to 1.001	0.051	-0.001 to 3.92

*P-value < 0.05 significant.

Cox regression analysis was used.

CI: confidence interval, PAC: pulmonary arterial capacitance, GFR: glomerular filtration rate, PCWP: pulmonary capillary wedge pressure,

RAP: right atrial pressure, MAP: mean arterial pressure, MPAP: mean pulmonary arterial pressure.

All pressures are expressed in mm/Hg. Cardiac index expressed in L/min/m^2.

In HFpEF elevated pulmonary capillary wedge pressure (PCWP) leads to structural remodeling of small pulmonary arteries over time, which increases pulmonary vascular resistance and in turn causes pulmonary hypertension and subsequent RV dysfunction. PAC represents distensibility of the pulmonary arterial tree, which is inversely correlated with RV afterload (Medrek et al., 2017). This index essentially combines the effects of pulmonary vascular resistance (PVR) and PCWP on RV afterload in one parameter, which reflects the pathophysiology of PH in HF. A strong inverse relationship has been demonstrated between PAC and PVR (Dupont et al., 2012).

Tedford et al. (2012) showed that elevation in PCWP (which is the hallmark of HFpEF at rest, and particularly with exercise) decreases PA compliance for a given PA resistance and thus enhances RV pulsatile load, which is reflected in PAC. This can lead to decrease in RV ejection and elevation of right-sided filling pressures over time. Studies have shown right atrial pressure strongly correlates with kidney function in patients with different types of pulmonary hypertension including group II (PH associated with left heart disease), which is mediated by renal venous congestion (Kanjanahattakij et al., 2018; Navaneethan et al., 2014). In line with these findings, our study results showed that PAC as a surrogate of PA compliance and RV afterload had a predictive value on long term GFR. While high right sided filling pressures as mentioned above have been directly associated with worsening renal function in previous studies (Cockcroft and Gault, 1976; Guazzi and Borlaug, 2012), PAC as a combined hybrid hemodynamic parameter (Takatsuki et al., 2017) might actually reflect a totally different concept of not just volume or filling pressure but rather the adaptation of the right ventricular pulmonary arterial system to increasing filling pressures. This reflection of overall adaptation of the right ventricular pulmonary system in turn might have predictive value in subsequent net long term renal function as seen in our findings of more association with long term 3-5-year GFR and changes or differences of net renal function from baseline irrespective of absolute volume/filling pressures. This issue of right ventricular to pulmonary arterial system adaptation to that of a given volume or filling pressure is valuable to examine further as there is significant variability in RV adaptation to pulmonary hypertension in different individuals (Vonk-Noordegraaf et al., 2013), and thus potentially different end organ outcomes such as renal function. In fact, various invasive hemodynamic and echocardiographic surrogate markers of right ventricular to pulmonary arterial coupling have been studied and were related to worse outcomes such as hospitalization and mortality (Bellofiore and Chesler, 2013; Guazzi and Borlaug, 2012; Lo et al., 2019). PAC that reflects the potential imbalance between pulmonary arterial compliance for a given resistance or afterload in patients with HFpEF and pulmonary hypertension may therefore be considered in a similar way in this regard.

Similar to previous studies, our study showed lower RAP, MAP, and MPAP, and higher CI in higher PAC group. These parameters could independently have relationship with CKD. However, the predictive effect of PAC on long-term GFR was calculated after adjusting for them, indicating the independent predictive value of PAC on GFR.

Our study is also of particular importance as it represents an urban population of predominantly black patients (66%). While this population has been shown to have higher rates of heart failure and comorbidities including renal dysfunction than other ethnic populations, they are underrepresented in clinical trials especially regarding HFpEF (Blair et al., 2013; Lekavich and Barksdale, 2016). Achieving better understanding of the unique pathophysiology of HFpEF and renal dysfunction via new diagnostic and predictive parameters would help clinicians to better target their medical management towards preventing complications. Needless to say, future comparative population specific studies are needed for this purpose.

To the best of our knowledge, this is the first study to investigate the role of a novel hemodynamic parameter, PAC as a surrogate of RV function in predicting long-term kidney function in patients with HF with preserved EF. Although different cut-offs have been suggested, definitive cut-off value of PAC for prediction of kidney dysfunction has not been determined yet (Al-Naamani et al., 2015; Pellegrini et al., 2014). These findings could help clinicians recognize high probability of worsening kidney dysfunction in HFpEF patients and optimize medical management (such as early diuresis) towards preventing it. There are also non-invasive ways of measuring PAC via echocardiography which could be used towards this purpose (Papolos et al., 2019). In addition, wireless pulmonary artery pressure monitoring sensors are frequently implanted in these patients. Using a combination of stroke volume assessment from an echocardiogram and pulmonary artery pulse pressure from the wireless sensor, it may be possible to assess the impact of various therapies on PAC and their impact on renal function.

5. Limitations

There are some limitations to the present study due to the intrinsic nature of single center retrospective analysis, with relatively small final cohort size. Our data was collected from electronic medical records where it relies on adequate reporting and documentation. Also, this study could not imply cause and effect given the retrospective nature of the study. While PAC had predictive value for long-term GFR, the effects of other possible confounding risk factors for chronic kidney disease such as medications, compliance, and optimal control of existing comorbidities cannot be completely excluded in this association. The influence of medications such as diuretics, ACE inhibitors, and ARBs on the subsequent 3-5-year GFR were not accounted for as we were unable to ascertain the exact rates of medication use during these time periods mostly due to the inherent retrospective nature of the study. A future prospective study can help fully account for the individual patient's medical therapy regimen and minimize possible confounding factors.

6. Conclusion

Novel hemodynamic index of pulmonary artery stiffness as PAC obtained by right heart catheterization could have a predictive value to determine long-term renal dysfunction in patients with HFpEF. Further prospective studies are necessary focusing on RV function assessment and adaptation with determination of long-term kidney function in patients with HFpEF to better understand the causality of this association.

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