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Original Paper

Pulmonary Catherization Data Correlate Poorly with Renal Function in Heart Failure

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Heart failure · Cardiorenal syndromes · Heart catherization · Renal failure

Abstract
Background: The mechanisms of renal dysfunction in heart failure are poorly understood. We chose to explore the relationship of cardiac filling pressures and cardiac index (CI) in relation to renal dysfunction in advanced heart failure. ***Objectives:*** To determine the relationship between renal function and cardiac filling pressures using the United Network of Organ Sharing (UNOS) pulmonary artery catherization registry. ***Methods:*** Patients over the age of 18 years who were listed for single-organ heart transplantation were included. Exclusion criteria included a history of mechanical circulatory support, previous transplantation, any use of renal replacement therapy, prior history of malignancy, and cardiac surgery, amongst others. Correlations between serum creatinine (SCr) and CI, pulmonary capillary wedge pressure (PCWP), pulmonary artery systolic pressure (PASP), and pulmonary artery diastolic pressure (PADP) were assessed by Pearson correlation coefficients and simple linear regression coefficients. ***Results:*** Pearson correlation coefficients between SCr and PCWP, PASP, and PADP were near zero with values of 0.1, 0.07, and 0.08, respectively ($p < 0.0001$). A weak negative correlation coefficient between SCr and CI was found (correlation coefficient, –0.045, $p = 0.027$). In a subgroup of young patients unlikely to have noncardiac etiologies, no significant correlations between these values were identified. ***Conclusion:*** These findings suggest that, as assessed by pulmonary artery catherization, none of the factors – PCWP, PASP, PADP, or CI – play a prominent role in cardiorenal syndromes.

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Introduction

Renal dysfunction in heart failure is unfortunately too common. It is estimated that between 32 and 63% of all heart failure patients have significant renal dysfunction [1–3] compared to just 4.5% of the general population [4]. Furthermore, concomitant renal and heart failure powerfully predicts negative clinical outcomes [1] including a marked elevation in all-cause mortality (estimated odds ratios ranging from 1.7 to 6.58) compared to similar patients with isolated heart failure. It has also has been observed that often with the treatment of heart failure alone concurrent renal dysfunction is dynamic and may improve or worsen considerably [5]. The mechanisms of these interactions are unclear and both hemodynamic and nonhemodynamic processes have been implicated. In terms of hemodynamic factors, two potential theories of renal injury are commonly proposed: a low forward flow state hypothesis and a central venous pressure (CVP) elevation hypothesis. The former refers to the notion that decreases in cardiac index (CI) result in inadequate renal perfusion and ultimately organ dysfunction. However clinical trials aimed at improving CI with inotropic therapy such as the ROSE trial [6] and large observational series [7–10] have increasingly failed to support this theory, the latter finding no notable epidemiologic association between baseline CI and renal dysfunction.

The evidence for the alternative hemodynamic theory is somewhat sturdier, and this is the theory perhaps most commonly accepted and taught by clinicians on a daily basis. Animal models that mechanically raise renal vein pressures consistently demonstrate acute renal dysfunction [11, 12]. However, these models are unspecific as almost any organ will fail in the setting of acute venous obstruction. Few studies have reviewed this relationship epidemiologically with invasive pressure monitoring. Those that do are often small in size. Some analyses from the ESCAPE trial have suggested no association between renal failure and any pulmonary artery catherization hemodynamic value [8, 13], whilst other observational series suggest weak associations between renal failure and cardiac congestion [7, 9, 10, 14, 15]. Damman et al. [15] demonstrated in the largest series on this topic by far (n = 2,557 patients) an inverse relationship in terms of cardiac filling pressures, predominantly renal artery pressure, with renal function. However, this study utilized a single-center Dutch population of unclear generalizability, and included patients who may not have had clinical heart failure and also demonstrated an unexpected inverse relationship in terms of CI and renal function. Finally, this study did not address concerns regarding the difficulty in the literature of establishing pulmonary capillary wedge pressure (PCWP) as having a prominent role in cardiorenal syndromes, despite the clinical foundation of the CVP hypothesis theory revolving around left-sided cardiac filling pressures being the driving factor for an elevated CVP.

Thus, we have a limited understanding of the relationship of hemodynamic changes and renal dysfunction in heart failure, especially in relation to nonhemodynamic processes. The United Network of Organ Sharing (UNOS) is a private, nonprofit organization that manages the US organ transplant system under contract with the federal government. It collects pretransplant data on all patients listed for heart transplantation in the USA and possesses one of the largest right heart catherization (RHC) databases in the world. This dataset has recently been utilized to question the absence of a relationship between CI and baseline renal dysfunction [16] in a powerful fashion. We chose to utilize this data to investigate whether a biological gradient between cardiac filling pressures and renal dysfunction exists in the advanced heart failure population.

Methods

Using the UNOS heart transplant database, all patients over the age of 18 years listed for heart transplantation and who underwent RHC between April 1987 and May 2016 were identified. We chose to exclude patients with a history of any use of extracorporeal membranous oxygenation, intra-aortic balloon pumps, previous transplantation, listing for dual organ transplantation (i.e., heart/kidney listing), any use of renal replacement therapy pre- or posttransplantation, prior history of malignancy, and prior history of cardiac surgery. Patients with incomplete RHC data were also excluded. Data in regard to age, sex, weight, ethnicity, diabetes mellitus, cerebrovascular disease, listing status, pretransplant diagnosis, implantable cardioverter defibrillator implantation, and inotropic use were collected. Hemodynamic variables assessed during RHC at the time of listing were CI (L/min/m^2) as assessed by the Fick or thermodilution method as per physician preference, PCWP, pulmonary artery diastolic pressure (PADP), and pulmonary artery systolic pressure (PASP). Serum creatinine (SCr) was assessed at the time of listing (mg/dL).

Data are presented as a mean value with standard deviation (SD) for continuous data, and frequency statistics are provided for categorical data. Outliers and potentially erroneous values were evaluated by Cook's distances and observations with Cook's distances greater than $4/n$ were eliminated from the sample set. Significant differences between continuous variables and categorical variables were assessed by ANOVA methods and χ^2 tests, respectively. Pearson correlation coefficients (a value ranging between 0 and 1 which is reflective of the strength of association between two variables) were used to describe relationships between each primary hemodynamic variable and SCr. A simple linear univariate regression analysis was also performed for all hemodynamic values versus SCr. Finally, we used scatterplots with fitted Lowess smoothing lines to evaluate for potential nonlinear relationships between the described hemodynamic values and SCr. Statistical significance was set at a two-tailed probability level <0.05 for all analyses. Statistical analyses were performed using STATA 14.2 software. The authors had full access to the data and take responsibility for its integrity. All authors read and agreed to the paper as written.

Results

A total of 13,381 patients were initially identified with utilization of exclusion criteria and, after elimination of outliers and potential erroneous values (n = 259), 13,122 patients were included in the final analysis. These patients were divided into quartiles by mean PCWP (Table 1).

The overall population captured was 70% male and had a mean age of 51 years. This overall population was 65% white, 23% African-American, 8% Hispanic, and 3% Asian in ethnicity. A total of 66% of patients had implantable cardioverter defibrillators, suggestive of a high degree of chronic severe systolic dysfunction. Whilst our exclusion criteria precluded patients requiring mechanical support, 34% of the captured population was receiving an inotrope at the time of listing and 54% of these were status 2. The mean SCr in the overall population was 1.2 ± 0.35 mg/dL. The mean PCWP was 19.6 ± 8.4 mm Hg, mean PASP was 42.98 ± 13.7 mm Hg, mean PADP was 20.95 ± 8.39 mm Hg, and mean CI was 2.1 ± 0.63 L/min/m^2.

When this overall population was stratified by quartiles of PCWP (Table 1), significant differences were noted between the groups. Most notably, in comparing the patients with the lowest PCWP (group 1) at listing to those with the highest PCWP (group 4), patients with higher PCWP were more likely to have lower CIs and higher PASPs and PADPs, to be status 1a or 1b, to be of nonwhite race, and overall had slightly worse renal function (mean SCr, 1.15 vs. 1.23 mg/dL). They were also less likely to be diabetic.

Scatter plots of hemodynamic variables versus SCr are presented with linear regression and Lowess smoothing lines (Fig. 1). For the overall population, the Pearson correlation coefficients (Table 2) for PCWP, PASP, PADP, and CI versus SCr were 0.102, 0.0754, 0.08, and –0.0435, respectively (p < 0.0001). The linear regression correlation coefficients (Table 3) for

Table 1. Patient demographics (as stratified by quartiles of PCWP)

	Group 1 (<13 mm Hg)	Group 2 (13–19 mm Hg)	Group 3 (19–25 mm Hg)	Group 4 (>25 mm Hg)	*p* value
Patients, *n*	2,894	3,701	2,771	3,756	
Age, years	51.9±11.4	51.7±12.0	50.8±12.4	50.6±12.9	<0.001
BMI	27.2±4.9	27.2±4.9	27.45±14.7	27.6±5.1	0.287
Gender					
Female	35.38	31.18	29.27	23.14	<0.001
Male	64.62	68.82	70.73	76.86	<0.001
Diagnosis					
Ischemic	30.9	29.13	27.79	27.98	0.028
Nonischemic	69	70.87	72.21	72.02	0.028
Diabetes					
Yes	21.2	23.21	24.65	25.05	<0.001
No	78.8	76.8	75.35	74.95	<0.001
CVA					
Yes	4	3.32	4.44	4.02	0.132
No	96	96.68	95.56	95.98	0.132
ICD present					
Yes	66.7	68.12	67.38	65.31	0.069
No	33.3	31.88	32.62	34.69	0.069
Inotrope use					
Yes	24.40	31.50	38.65	41.29	<0.001
No	75.60	68.50	61.35	58.71	<0.001
Initial status					
1a	6.39	8.65	11.98	13.39	<0.001
1b	25.47	32.10	35.58	40.76	<0.001
2	66.28	57.55	50.81	44.12	<0.001
Other	1.87	1.7	1.62	1.73	<0.001
Days waiting, *n*	455±655	385±625	310±520	310±516	<0.001
Race					
White	67.45	67.6	65.25	61.61	<0.001
Black	21.11	20.4	22.84	25.56	<0.001
Hispanic	7.74	7.94	7.65	9.08	<0.001
Asian	2.63	2.84	3.25	2.42	<0.001
Other	1.07	1.22	1.01	1.33	<0.001
PCWP, mm Hg	8.67±2.77	16.11±1.91	21.82±1.48	29.9±4.61	<0.001
PASP, mm Hg	28.99±8.68	38.61±9.3	46.46±9.3	55.53±10.9	<0.001
PADP, mm Hg	12.06±5.03	18.08±5.02	22.92±5.18	29.18±6.5	<0.001
CI, L/min/m^2	2.3±0.63	2.24±0.64	2.09±0.6	1.89±0.58	<0.001
SCr, mg/dL	1.15±0.32	1.19±0.35	1.23±0.39	1.23±0.36	<0.001

Data are presented as mean ± SD or %, unless otherwise indicated. BMI, body mass index; CVA, cerebrovascular accident; ICD, implantable cardioverter defibrillator; PASP, pulmonary artery systolic pressure; PADP, pulmonary artery diastolic pressure; PCWP, pulmonary capillary wedge pressure; CI, cardiac index; SCr, serum creatinine. *p* value reflects ANOVA or χ^2 test for differences between PCWP groups 1–4.

PCWP, PASP, PADP, and CI versus SCr were 0.003, 0.003, 0.003, and –0.024, respectively ($p < 0.0001$). Pearson correlation coefficients were then assessed for all identified demographics subgroups as well as the subgroup of patients between the ages of 18 and 24 years ($n = 529$). These values are presented in Table 2. Collectively, no identified subgroup showed Pearson correlation scores that markedly deviated from those of the overall population. Furthermore, all analyses were repeated with the inclusion of the eliminated outliers without a significant alteration in outcome.

Table 2. Correlation coefficients between measured hemodynamic variables and SCr

	Pearson correlation	*p* value
Total population		
SCr vs. PCWP	0.1028	<0.0001
SCr vs. PASP	0.0754	<0.001
SCr vs. PADP	0.0802	<0.001
SCr vs. CI	–0.0435	<0.001
PCWP group 1		
SCr vs. PCWP	0.0006	<0.0001
SCr vs. PASP	0.1104	<0.001
SCr vs. PADP	0.005	<0.001
SCr vs. CI	0.006	<0.001
PCWP group 2		
SCr vs. PCWP	0.0442	0.0072
SCr vs. PASP	0.1012	<0.0001
SCr vs. PADP	0.0546	0.0009
SCr vs. CI	–0.0401	0.0148
PCWP group 3		
SCr vs. PCWP	0.0172	0.3651
SCr vs. PASP	0.0395	0.0374
SCr vs. PADP	0.0201	0.2893
SCr vs. CI	–0.0213	0.2619
PCWP group 4		
SCr vs. PCWP	0.0058	0.724
SCr vs. PASP	0.0362	0.0263
SCr vs. PADP	–0.0114	0.4848
SCr vs. CI	0.0131	0.4232
Ischemic		
SCr vs. PCWP	0.0834	<0.0001
SCr vs. PASP	0.1018	<0.001
SCr vs. PADP	0.0813	<0.001
SCr vs. CI	–0.0262	<0.001
Nonischemic		
SCr vs. PCWP	0.0804	<0.001
SCr vs. PASP	0.1001	<0.001
SCr vs. PADP	0.0761	<0.001
SCr vs. CI	–0.0537	<0.001
Female		
SCr vs. PCWP	0.0608	0.0002
SCr vs. PASP	0.0938	<0.001
SCr vs. PADP	0.0581	0.0003
SCr vs. CI	–0.0482	0.0028
Male		
SCr vs. PCWP	0.0491	<0.001
SCr vs. PASP	0.0774	<0.001
SCr vs. PADP	0.0515	<0.001
SCr vs. CI	0.0349	0.0008
Race		
White		
SCr vs. PCWP	0.0789	<0.001
SCr vs. PASP	0.0974	<0.001
SCr vs. PADP	0.0708	<0.001
SCr vs. CI	–0.0476	<0.001
Black		
SCr vs. PCWP	0.084	<0.001
SCr vs. PASP	0.0998	<0.001
SCr vs. PADP	0.0803	<0.001
SCr vs. CI	–0.0293	0.1105
Hispanic		
SCr vs. PCWP	0.0716	0.0191
SCr vs. PASP	0.123	0.0001
SCr vs. PADP	0.0838	0.0061
SCr vs. CI	–0.0425	0.1651
Asian		
SCr vs. PCWP	0.0524	0.3199
SCr vs. PASP	0.0421	0.4246
SCr vs. PADP	0.0327	0.5348
SCr vs. CI	0.0004	0.9932
Inotropes (+)		
SCr vs. PCWP	0.0785	<0.001
SCr vs. PASP	0.1023	<0.001
SCr vs. PADP	0.0724	<0.001
SCr vs. CI	–0.0551	0.1753
Inotropes (–)		
SCr vs. PCWP	0.0718	<0.001
SCr vs. PASP	0.0923	<0.001
SCr vs. PADP	0.0675	<0.001
SCr vs. CI	–0.0202	<0.001
Listing status		
Status 1a		
SCr vs. PCWP	0.0434	0.1123
SCr vs. PASP	0.0795	0.0036
SCr vs. PADP	0.0259	0.3442
SCr vs. CI	–0.026	0.3413
Status 1b		
SCr vs. PCWP	0.0661	<0.001
SCr vs. PASP	0.0823	<0.001
SCr vs. PADP	0.0672	<0.001
SCr vs. CI	–0.0053	0.7246
Status 2		
SCr vs. PCWP	0.0894	<0.001
SCr vs. PASP	0.1118	<0.001
SCr vs. PADP	0.0802	<0.001
SCr vs. CI	–0.0695	<0.001
Diabetes		
SCr vs. PCWP	0.0728	<0.001
SCr vs. PASP	0.1134	<0.001
SCr vs. PADP	0.0791	<0.001
SCr vs. CI	–0.055	0.0022
Nondiabetic		
SCr vs. PCWP	0.0793	<0.001
SCr vs. PASP	0.0892	<0.001
SCr vs. PADP	0.0685	<0.001
SCr vs. CI	–0.0424	<0.001
ICD present		
SCr vs. PCWP	0.0827	<0.001
SCr vs. PASP	0.1035	<0.001
SCr vs. PADP	0.0812	<0.001
SCr vs. CI	–0.0484	<0.001
ICD absent		
SCr vs. PCWP	0.0788	<0.001
SCr vs. PASP	0.102	<0.001
SCr vs. PADP	0.0707	<0.001
SCr vs. CI	–0.0269	0.0757
Age 18–24 years		
SCr vs. PCWP	0.1091	0.0118
SCr vs. PASP	0.028	0.5195
SCr vs. PADP	0.0627	0.149
SCr vs. CI	–0.053	0.222

SCr, serum creatinine; PCWP, pulmonary capillary wedge pressure; PASP, pulmonary artery systolic pressure; PADP, pulmonary artery diastolic pressure; CI, cardiac index; ICD, implantable cardioverter defibrillator

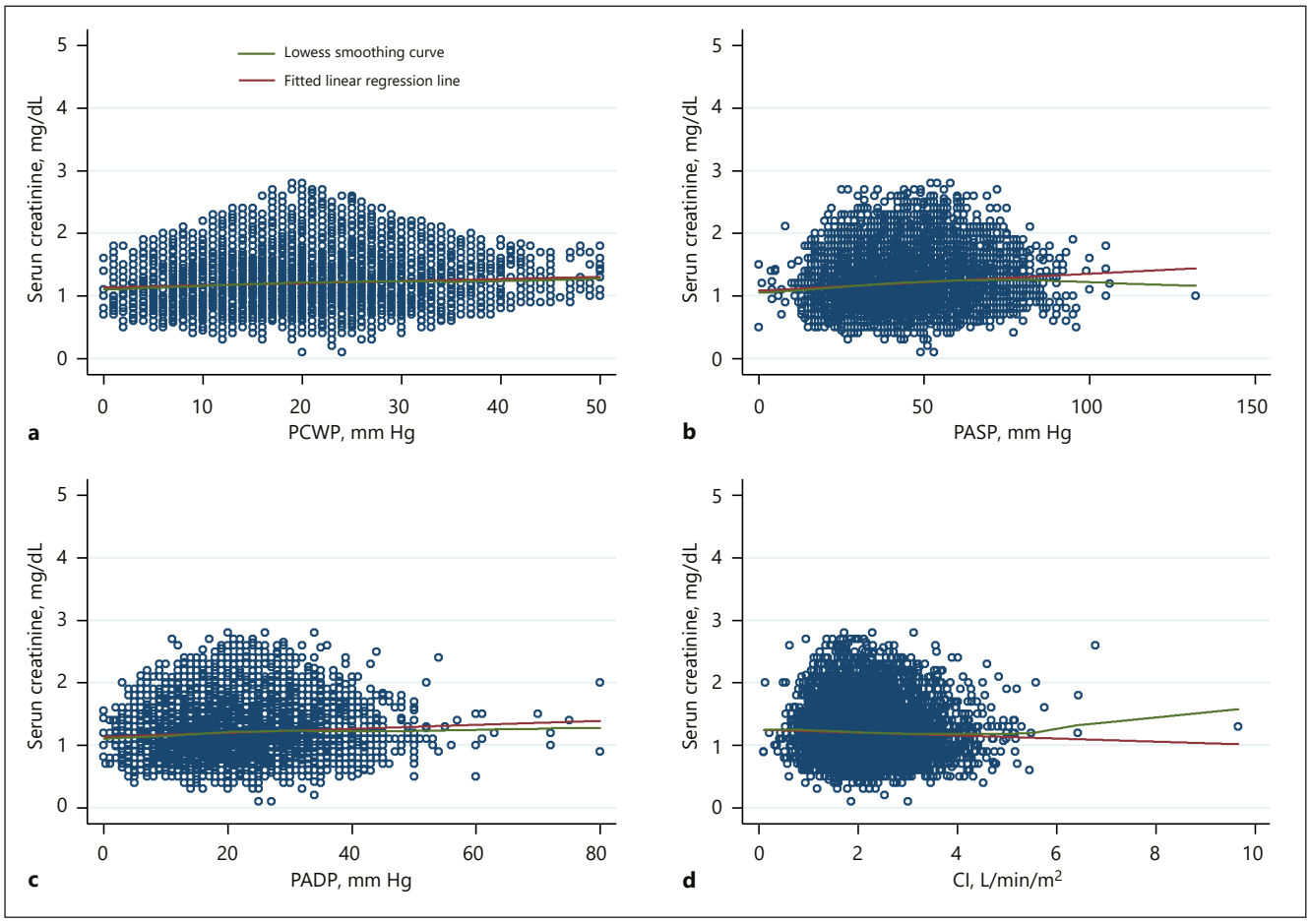

Fig. 1. Scatterplots of PCWP (**a**), PASP (**b**), PADP (**c**), and CI (**d**) versus serum creatinine for the overall population with linear regression and Lowess smoothing lines. PCWP, pulmonary capillary wedge pressure; PASP, pulmonary artery systolic pressure; PADP, pulmonary artery diastolic pressure; CI, cardiac index.

Discussion

Few contemporary studies describe the epidemiologic relationship between cardiac congestion and renal failure with pulmonary arterial catherization. Many of these studies are limited by small size and constrained generalizability, and yield conflicting results. We addressed this topic using the UNOS heart transplantation database which provides RHC data for patients with advanced heart failure across the USA. To gain insight into the mechanisms of cardiorenal syndromes, we chose to invoke the concept of a biological gradient, i.e., the notion that greater exposure to a causative factor should lead to a greater incidence and or measured severity of an effect. In essence, the presence or absence of a robust correlation between cardiac congestion and renal dysfunction epidemiologically supports or undermines the likelihood of a causal relation between the two.

By methodology, this study aims to minimize noncardiac etiologies of severe derangements in renal function (i.e., hemodialysis use) as such processes would prove obvious confounders. Thus, we conservatively excluded patients with such clinical factors. This resulted in a cohort of predominantly ambulatory nonischemic patients (due to exclusion of prior cardiac surgery). We chose the Pearson correlation coefficient to evaluate the

Table 3. Linear regression coefficients between measured hemodynamic variables and SCr (dependent variable)

	Regression coefficient	Standard deviation	95% confidence interval
SCr vs. PCWP	0.0033945	0.0003684	0.0027 to 0.004
SCr vs. PASP	0.0026515	0.0002241	0.002 to 0.003
SCr vs. PADP	0.0031962	0.0003691	0.0025 to 0.004
SCr vs. CI	–0.0243011	0.0048773	–0.034 to 0.015

SCr, serum creatinine; PCWP, pulmonary capillary wedge pressure; PASP, pulmonary artery systolic pressure; PADP, pulmonary artery diastolic pressure; CI, cardiac index.

relationships between various hemodynamic measures and SCr. Clinical factors that are strongly correlated have values close to 1 and if there is no association measure close to zero. By convention, this coefficient is independent of the scale and units of measurement of the factors evaluated. In general, values less than 0.25 and values greater than 0.75 are suggestive of a weak and strong relationship, respectively. For example, correlation values between all of our hemodynamic pressures (PCWP and PASP, PASP and PADP, etc.) were extremely strong, ranging between 0.74 and 0.88. The interpretation of a weak Pearson correlation coefficient necessitates the acceptance that other factors besides the variables assessed are responsible for the majority of the variations seen. The utilization of a linear regression analysis allows for the assessment of relationships, with the incorporation of units of measurement. Finally, the addition of a Lowess regression curve evaluates for hidden nonlinear relationships that are otherwise poorly characterized. Ideally, the relationships between RHC data and renal function are best assessed longitudinally (i.e., multiple RHC measurements and SCr values assessed over time with the same patients) and this has been performed in some small studies [13, 17]. However, it is often not feasible to serially repeat invasive catherization. We therefore chose to follow the majority of the literature and pursue a cross-sectional study where the utilization of a large number of data points taken from patients at different phases in heart failure can elicit these trends [9, 10, 15].

In aggregate, we found that correlations between cardiac filling pressures and cardiac congestion were markedly weak. In the overall population listed for cardiac transplantation that met our exclusion criteria, Pearson correlation coefficients for PCWP and PASP versus SCr were 0.1 and 0.075, respectively, with p values of <0.001. Similarly, the linear regression coefficients between these factors were 0.003 and 0.0026, and for most ranges of the values studied, the Lowess regression curve was identical to the linear regression line. These predicted values are extremely low. Contextually speaking, our analysis suggests that with each 10 mm Hg increase in PCWP between 2 identical patients, the expected increase in SCr is 0.03 g/dL. Given the considerable renal function fluctuations physicians see during the care of heart failure patients, these results are strongly suggestive that the majority of renal function variability in heart failure is explained by factors unrelated to PCWP, PASP, PADP, and CI, though these factors do play a statistically significant, but minute, role. Additionally, we tested our hypothesis across several demographic categories as well as in a young cohort listed for cardiac transplantation without notable differences in results. We felt the young cohort was of particular importance to evaluate. It is estimated that the prevalence of chronic kidney disease in the general US population under 30 years of age is 0.6–0.8% [18]. We hypothesized that this cohort of young patients listed for cardiac transplantation would

generally even further lack common noncardiac etiologies of renal dysfunction such as diabetes, hypertension, renovascular disease, adult polycystic kidney disease, etc. In patients 18–24 years old, who are unlikely to have other etiologies of renal dysfunction, not only were the correlations weak but the *p* values in that subgroup were not significant.

Comprehensively, our results are consistent with findings represented in prior, smaller studies of similar scope and design [7, 8, 17, 19] in both outcome and effect size. Our study is of interest in that it is the largest of its kind by far, captures a population of patients with only advanced heart failure, and represents patients across all major medical centers within the USA. Looking at this cross-section of patients, we find poor epidemiologic evidence to support the notion that alterations in cardiac filling pressures or CI explain the majority of the marked variations in renal function seen in the care of patients with heart failure. Rather, this result suggests that the fluctuating renal function observed in practice is likely due to either mechanisms of hemodynamic injury which are poorly assessed by intermittent RHC or due to predominantly nonhemodynamic mechanisms such as inflammation, hypoxemic renal injury, and neurohormonal impairment. Whilst experts in this field accept that a hemodynamic approach is overly simplistic and does not explain these complex interactions well, these notions remain pervasive in medicine and are commonly taught, despite increasing evidence to the contrary. This study provides additional evidence regarding the unpredictability of renal function in heart failure and how little is truly understood regarding this issue.

In our analysis of the relation between CI and renal dysfunction, we found that as CI increases renal function appears to worsen. This paradoxical result was unexpected and whilst the correlation coefficient was extremely small, it was consistent throughout subgroups within this study. Hanberg et al. [7] and Dammen et al. [15], in similarly designed studies, also found such a paradoxical association. This analysis adds to the literature on this issue, suggesting it may indeed represent in vivo phenomena of unclear significance.

We note several limitations to this work. As the data were collected prospectively, we were unable to control for residual confounders beyond the factors the registry provides, such as medications or physician practice patterns. We also cannot comment on patients who did not meet our exclusion criteria, which includes patients who were not referred for RHC or had incomplete catherization data. However, our conclusions have been supported in prior studies that do not have these limitations. Finally, this data lacks assessment of right atrial pressures and does not directly address the question of the relationship between right atrial pressure and renal dysfunction. Unfortunately at this time, UNOS does not collect CVP data and we would implore the collection of this information so as to maximize the value of the data they are currently gathering. Whilst it appears that cardiac filling pressures are strongly correlated to each other, the specific relationship of renal artery pressure to renal function remains unknown.

In conclusion, as assessed in a large cohort of patients with advanced heart failure pending heart transplantation, our findings suggest that none of the factors – PCWP, PASP, PADP, or CI – appear to have strong correlations with renal dysfunction. These findings challenge some longstanding but poorly supported beliefs regarding cardiorenal syndromes and suggest that further study into the mechanisms of these disorders is needed.

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Disclosure Statement

The authors have no conflicts of interest to disclose.

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