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Estimated pulmonary artery systolic pressure and self-reported physical function in patients on hemodialysis

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Abstract

Background/Aims—Patients on chronic hemodialysis have a high prevalence of heart disease and poor self-reported physical function. The association between structural heart disease and self-reported physical function in patients on hemodialysis is unknown.

Methods—We studied the association between elevated pulmonary artery systolic pressure (PASP) and self-reported physical function in ESRD in 253 patients in the USRDS ACTIVE/ADIPOSE study between 2009 and 2011. We used multivariate linear regression with PASP obtained from clinical echocardiogram reports as the primary predictor and the Physical Function (PF) subscale of the SF-36 as the primary outcome. To determine whether associations between PASP and PF were driven by fluid overload or left ventricular hypertrophy, we assessed whether PASP was associated with bioimpedance spectroscopy (BIS)-derived extracellular water (ECW) and with left ventricular posterior wall thickness.

Results—In a multivariable model, each 10 mmHg higher PASP was associated with 3.32-point lower PF score (95% CI: -5.95, -0.68). In a multivariable model that included BIS estimates, both

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left ventricular posterior wall thickness (LVPW, per 5 mm) and ECW were associated with higher PASP (left ventricular posterior wall thickness 4.21 mmHg, 95% 0.38-8.04; ECW 1.12 mmHg per liter, 95% CI 0.07-2.18). Higher LVPW and higher ECW were independently associated with lower PF score.

Conclusion—Left ventricular hypertrophy and elevated pulmonary pressure are associated with worse self-reported physical function in patients on hemodialysis. The role of chronic volume overload on PASP and PF score should be evaluated in a prospective manner.

Keywords

physical function; end-stage renal disease; echocardiography; volume status

Introduction

The heavy burden of cardiovascular disease among patients with ESRD has long been appreciated [1], but there is increasing recognition of the potential contribution of the uremic milieu to heart disease by various mechanism including myocardial wall stress from hypertension and volume overload, subclinical ischemia, cardiac remodeling, and fibrosis [2]. Approximately 80% of patients with ESRD have at least one form of heart disease [3], and approximately 40% have pulmonary hypertension based on echocardiographic parameters (elevated pulmonary artery systolic pressure [PASP]) [4-7].

Previous studies have suggested a relationship between volume overload and elevated PASP [8]. Using continuous hemodynamic monitoring, one study described a decrease in right ventricular systolic pressure of 39% during dialysis, highlighting the important contribution of excess volume to right-sided pressures. In fact, a recently-proposed classification system recognizes the potentially additive contribution of volume overload and structural heart disease to patients' functional status, and its authors highlight the need for studies to further elucidate the role of cardiac disease on function in the ESRD population [9].

The widely utilized heart failure staging system, the New York Heart Association classification [10], categorizes patients primarily according to their functional limitations during daily activities. Patients on chronic hemodialysis report extremely poor physical function [11,12]. Perhaps because of the many possible causes of poor self-reported physical function in patients with ESRD, including uremic myopathy [13], deconditioning from sedentary lifestyle [14], anemia, comorbid conditions, and others, the contribution of cardiopulmonary abnormalities seems to have been underappreciated. Because elevated PASP is potentially a result of structural heart disease and volume overload in patients with ESRD, we hypothesized that higher PASP would be associated with worse self-reported physical function in patients with ESRD.

We used data from the United States Renal Data System (USRDS) ACTIVE/ADIPOSE (A Cohort study To Investigate the Value of Exercise/Analyses Designed to Investigate the Paradox of Obesity and Survival in ESRD), which includes echocardiogram reports, bioimpedance spectroscopy (BIS) measurements, and patient-reported physical function, to evaluate the association between elevated PASP and self-reported physical function in

ESRD. In addition, we assessed the potential contributions of fluid overload and structural heart disease to high PASP and poor physical function.

Methods

ACTIVE/ADIPOSE is a cohort study of the United States Renal Data System (USRDS) Nutrition and Rehabilitation/Quality of Life Special Studies Centers that enrolled prevalent hemodialysis patients from the Atlanta metropolitan area and the San Francisco Bay Area between July, 2009 and August, 2011. There were 771 patients who were enrolled and linked to USRDS. A description of the ACTIVE/ADIPOSE study and methods has been published elsewhere [15]. English or Spanish-speaking patients who had been receiving dialysis for at least 3 months in 14 dialysis facilities in the San Francisco Bay Area and Atlanta metropolitan area were included. Study participants provided informed consent, and the study was approved by the Institutional Review Boards at Emory University and the University of California, San Francisco.

We performed a cross-sectional analysis to examine the association between PASP and self-reported physical function among 253 patients (33%) who had PASP recorded on reports from echocardiograms that were obtained as part of clinical care.

Clinical Echocardiogram Reports

We reviewed patient charts for clinical echocardiogram reports, and we selected the echocardiogram report with the date closest to the time of administration of the study questionnaire if the patient had multiple echocardiogram reports. Each echocardiogram report was reviewed to abstract the left ventricular posterior wall thickness (LVPW), and estimated PASP. Left ventricular hypertrophy (LVH) is common in patients on hemodialysis and has been attributed to anemia, volume overload, heart failure, and hypertension [16]. LVH can cause cardiac stiffness leading to high left-sided filling pressures which have been associated with elevated PASP [17,18]. Left ventricular posterior wall thickness is a measure used to estimate LVH that has been associated with outcomes in a previous study of LVH in patients on hemodialysis [19]. We standardized the assumed right atrial pressure to 10 mmHg when calculating the PASP.

Physical Function Scale

The SF-36 is an instrument that uses 36 questions to assess health-related quality of life (HRQoL) that has previously been used in patients with ESRD [20,21]. The Physical Function scale (PF) is a subscale of the SF-36 that uses ten items that are hierarchically ordered to assess physical function. Each item is scored based on the degree of physical limitation, and the total score is scaled to a 100-point total with higher scores indicating better function [22]. The PF scale of the SF-36 was administered to patients before a mid-week or end-of-week dialysis session by a research assistant.

Bioimpedance Spectroscopy

We performed whole-body BIS prior to a mid-week or end-of-week dialysis session using a device that scans 256 frequencies between 4 and 1000 kHz

(SFB7;ImpediMed,SanDiego,CA) as previously described [23]. We placed electrodes on patients in a tetrapolar configuration on the hand and foot opposite the side of dialysis access after patients were supine for at least 10 minutes. The proximal and distal electrodes were placed 5 centimeters apart, and ten measurements were performed within one minute. We estimated total body water (TBW) by extrapolating resistance to infinite frequency and extracellular water (ECW) by extrapolating resistance to zero frequency.

Covariates

We included covariates based on a clinical conceptual model and included age, sex, African-American race, hemoglobin, diabetes mellitus, peripheral vascular disease, serum albumin, ESRD vintage (time since first ESRD treatment), heart failure, coronary artery disease, and arteriovenous (AV) fistula hemodialysis access. We obtained data on coronary artery disease, heart failure, diabetes, and peripheral vascular disease from the Centers for Medicare and Medicaid Services (CMS) Medical Evidence Form 2728. We measured serum albumin concentration with nephelometry. We used the most recent clinical hemoglobin level documented in the chart. Information about use of an AV fistula was obtained from review of the hemodialysis prescription. These data were included because previous reports have linked AV fistula creation with elevated pulmonary artery pressures [24]; however, this association remains controversial [25].

Statistical Analysis

We summarized data as mean (standard deviation) for normally distributed variables, median (25th, 75th percentile) for non-normally distributed variables, and proportions for dichotomous variables. We compared characteristics of patients with a PASP \geq 35 mmHg and those with a lower PASP using chi squared tests, t-tests, and linear regression as appropriate because a PASP of \geq 35 mmHg has been used as a cutoff for pulmonary hypertension in previous studies in the ESRD population [4-6]. We examined the time between the echocardiogram and PF testing. We used multivariate linear regression with PASP as the primary predictor and the PF score as the primary outcome.

To determine whether associations between PASP and PF were driven by fluid overload or left ventricular hypertrophy, we first assessed whether PASP was associated with ECW and with left ventricular posterior wall thickness. We then added BIS results and left ventricular posterior wall thickness into a multivariable model separately and then jointly. We performed a sensitivity analysis excluding echocardiograms that were done more than two years from the time of PF testing. We conducted all analyses using Stata 13 (StataCorp LP).

Results

The mean age of the cohort was 55.8 years. Clinical characteristics did not differ significantly between patients with PASP \geq 35 and those with lower PASP (Table 1). The median interval between the PF test and echocardiogram was 19 days (302 days before PF testing, 407 days after PF testing). Patients included in the study were more likely to have a longer ESRD vintage and were less likely to have an AV fistula when compared to patients who were excluded (Supplemental Table 1).

Association between PASP and PF

In univariate analysis, every 10 mmHg higher PASP was associated with a 5.7-point lower PF score (95% CI: -8.4,-2.9). In the multivariable model, each 10 mmHg higher PASP was associated with 3.32-point lower PF score (95% CI: -5.95, -0.68; Table 2). Diabetes mellitus, older age, lower serum albumin concentration, and female sex were also associated with significantly lower PF.

Etiology of Elevated PASP

In a subset of 194 patients with recorded left ventricular posterior wall thickness, higher left ventricular posterior wall thickness was associated with higher PASP (4.87 mmHg per 5 mm, 95% CI 1.37-8.38) in a univariate model. In a multivariable model that included BIS estimates, both left ventricular posterior wall thickness (per 5 mm) and ECW were associated with higher PASP (left ventricular posterior wall thickness 4.21 mmHg, 95% 0.38-8.04; ECW 1.12 mmHg per liter, 95% CI 0.07-2.18; Table 3). There was no statistically significant association between AV fistula use and PASP.

Volume Status, Echocardiogram Measures, and PF

Higher left ventricular posterior wall thickness was associated with lower PF score (-7.13 points per 5 mm, 95% CI -14.07, -0.19; Table 4, Model 1) in a multivariable model including age, sex, African-American race, hemoglobin, diabetic status, serum albumin, peripheral vascular disease, and ESRD vintage. In a multivariable model adjusted for the same covariates, each liter of extracellular water was associated with a 2.6-point lower PF score (95% CI -4.48, -0.73; Table 4, Model 2). When both left ventricular posterior wall thickness and BIS estimates were included in the same multivariable model, left ventricular posterior wall thickness was associated with a 7-point lower PF per 5 mm (95% CI -14.12, 1.02) and each liter of ECF was associated with a 2-point lower PF score (95% CI -4.09, 0.05).

Sensitivity Analysis

We performed a sensitivity analysis excluding participants with echocardiogram reports that were done more than two years from the completion of the SF-36 (n=35). The associations between PASP and PF score (-3.10 per 10 mmHg; 95% CI -5.89, -0.32), left ventricular posterior wall thickness (4.84 per 5 mm, 95% CI 0.77, 8.92), and ECW and self-reported PF score (-2.26 per liter, 95% CI -4.28, -0.24) remained similar in multivariate analysis. LVPW was similarly associated with lower PF score (-7.12 per 5 mm, 95% CI -14.69, 0.45), but this association did not reach statistical significance.

Discussion

We demonstrated that higher pulmonary artery systolic pressures were associated with worse self-reported physical function after adjustment for age, sex, diabetes, peripheral vascular disease, serum albumin, and hemoglobin. Both left ventricular posterior wall thickness and ECW when adjusted for body size by including FM and ICW were independently associated with higher PASP. ECW was associated with lower PF score, suggesting that volume overload may be a detrimental factor in the physical function of

patients on hemodialysis. Similarly, left ventricular posterior wall thickness was associated with lower PF score in a multivariable model.

The causes of pulmonary hypertension in ESRD patients have been recently reviewed [4], and chronic volume overload is a likely contributor [26]. The linear association between BIS measures of volume overload, PASP, and PF score highlights the importance of close monitoring of volume status in patients on hemodialysis and suggests that volume overload could be one factor contributing to poor physical function in this population. Because intravascular volume is influenced by ECW, we expected that ECW would be related to PASP. The potential adverse effect of volume overload on physical function was also highlighted by a recent study that showed lower PF scores in patients with asymptomatic pulmonary congestion [27].

Left ventricular hypertrophy is common in ESRD patients, with approximately 75% of patients starting hemodialysis meeting criteria for LVH [28]. Left ventricular posterior wall thickness is an echocardiographic measure of left ventricular hypertrophy, which leads to left ventricular stiffness and diastolic dysfunction [18]. The finding that worse LVH was associated with lower PF score suggests that ventricular stiffness related to left ventricular hypertrophy is also potentially a contributor to poor self-reported physical function in patients on hemodialysis.

In a recently published proposed functional classification of heart failure in patients with ESRD, the three major mechanisms described to induce cardiomyopathy were volume overload, pressure overload, and nonhemodynamic factors including renin-angiotensin system activation [9]. This proposed classification from the Acute Dialysis Quality Initiative Workgroup uses echocardiogram abnormalities and dyspnea assessment before and after renal replacement therapy to classify severity of heart failure. Our study draws attention to the relationships between self-reported functional status, volume overload, pulmonary artery systolic pressure, and left ventricular hypertrophy that underlie this proposed classification. KDOQI guidelines recommend performing echocardiograms at the initiation of hemodialysis and at regular intervals [29], an approach that could direct clinicians to possible strategies, such as additional ultrafiltration or treatment aimed at underlying cardiac disease, to improve physical function.

For example, previous studies have evaluated strategies for managing LVH in ESRD. The authors of a meta-analysis of frequent or extended hemodialysis concluded that frequent or extended hemodialysis was associated with a significant reduction of left ventricular mass index and mean blood pressure and an improvement in ejection fraction [30]. Similarly, a secondary analysis of the Frequent Hemodialysis Network (FHN) trial found that frequent in-center hemodialysis reduced left and right ventricular end systolic and diastolic ventricular volumes along with left ventricular mass [31]. Although these data support left ventricular hypertrophy being addressable with hemodialysis, we cannot be certain of the effect of reduced left ventricular mass on physical function until prospective studies are conducted.

To put our population in context, 51% of our cohort had a PASP of 35 mmHg or higher, a proportion similar to previous cohorts of hemodialysis patients [5-7]. The mean PF score was 51.9, slightly higher than the mean PF score of 44 for multiple ESRD cohorts reported in a previous review [32]. Comparing our results to the results of the FHN population, age and diabetes were similarly associated with lower PF scores, and higher albumin and male sex were associated with higher PF scores [33]. In contrast to findings from the FHN, peripheral vascular disease was not significantly associated with lower PF scores in our population.

The minimal clinically important difference (MCID) has been described as the “smallest benefit of value to patients [34].” Previous studies have determined the MCID for the SF-36 to be 3-5 points [35,36]. Using this cutoff, both 5 mm higher left ventricular posterior wall thickness and 10 mm higher PASP were associated with clinically significant impairment of PF. Another way to put these results into context is to compare to the association of age with PF. We found coefficients for higher PASP, ECW, and LVPW in our study that were comparable to the difference associated with 10 years of age [37].

Strengths of our study included careful measurement of body composition and use of the PF, which allows for comparison with other populations. However, several limitations of our study should be addressed. First, only patients who had echocardiograms were included in the study which might limit the generalizability of the findings. Second, echocardiograms in the study were obtained as part of routine clinical practice rather than according to a standardized study protocol. As a result, the reporting of echocardiographic parameters was not uniform. In addition, the time between echocardiograms and BIS and PF measures was variable, and we do not know when echocardiograms were performed relative to hemodialysis procedures. These limitations would be expected to bias the results to the null (that is, to potentially obscure an association between echocardiographic parameters and physical function). Only patients with a clinical indication for an echocardiogram were included in the study, which could lead to spectrum bias, however, we used continuous predictors of PASP, ECW, and LVPW that were not categorized and found a linear association with PF score. Third, we did not specifically ask patients about dyspnea on exertion, a major criterion in the NYHA classification, but we did ask if their health limited them in daily activities, and we believe that dyspnea would usually be reported as a health-related limitation. Fourth, we did not have longitudinal data on use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARB) use that could have influenced the relationship between left ventricular mass and physical function.

In summary, higher PASP was associated with lower self-reported physical function in patients on hemodialysis. The role of chronic volume overload on PASP and PF score should be evaluated in a prospective manner. Future studies should examine the effect of volume normalization on PASP and PF score.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1

Baseline patient characteristics based on PASP*.

	PASP<35 (n=123)	PASP 35 (n=130)	p-value
Mean PASP (mmHg)	27.8(6.0)	48.7(11.0)	<0.001
Age, yrs	55.0(14.4)	57.7(13.6)	0.14
Male sex, n(%)	73(59)	67(52)	0.21
African American, n(%) [±]	103(84)	100(78)	0.21
Diabetes mellitus, n(%)	49(40)	59(45)	0.37
Peripheral Vascular Disease, n(%)	9(7)	13(10)	0.45
Coronary artery disease, n(%)	6(5)	11(8)	0.26
Heart failure, n(%)	12(10)	23(18)	0.07
ESRD vintage (yrs)	3.1(1.4,7.9)	3.5(1.9,7.9)	0.72
Albumin (g/dl)	4.0(0.37)	3.9(0.33)	0.06
Hemoglobin (g/dl)	11.5(2.7)	12.1(4.4)	0.15
Arterio-venous Fistula, n(%)	68(55)	66(51)	0.47
ICW [†] (L)	22.0(4.9)	21.6(5.3)	0.50
ECW ^σ (L)	19.1(4.2)	19.3(4.6)	0.79
Fat mass (kg)	25.4(13.3)	24.2(13.9)	0.52

[±]Includes 1 missing value

* PASP: pulmonary artery systolic pressure. Values are mean (sd) for normally distributed variables and median (25th, 75th percentile) for non-normally distributed continuous variables.

[†]Intracellular water^σExtracellular water

Table 2

Predictors of PF score.

	Difference in PF score (95% CI)	p-value
PASP (per 10 mmHg)	-3.32(-5.95, -0.68)	0.01
Age (per yr)	-0.34(-0.61,-0.06)	0.02
Male sex	9.27(2.23,16.31)	0.01
African American	5.14(-3.18, 14.09)	0.26
Diabetes mellitus	-12.70 (-20.58, -4.82)	0.002
ESRD vintage (log years)	0.06(-3.24, 3.36)	>0.9
Peripheral Vascular Disease	-7.08(-19.81, 5.66)	0.28
Albumin (per 0.5 g/dl)	7.10 (2.22,11.97)	0.005
Hemoglobin (per g/dl)	-0.24 (-1.17, 0.69)	0.61
Heart failure	0.73(-9.46, 10.93)	0.89
Coronary artery disease	11.67(-3.49, 26.83)	0.13

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Table 3

Predictors of PASP.

	Difference in PASP (95% CI)	p-value
Left ventricular posterior wall thickness (per 5 mm)	4.21(0.38, 8.04)	0.03
Age (per yr)	0.15(-0.02, 0.32)	0.08
Male sex	-9.48(-15.42, -3.54)	0.002
African American	-3.01(-8.46, 2.43)	0.28
Diabetes mellitus	1.79(-3.08, 6.66)	0.47
ESRD vintage (log years)	0.15(-1.90, 2.21)	0.88
Peripheral Vascular Disease	-7.51(-16.78, 1.76)	0.11
Albumin (per 0.5 g/dl)	-1.70(-4.75, 1.35)	0.27
Hemoglobin (per g/dl)	0.43(-0.04, 0.91)	0.07
AV Fistula	0.13(-4.13, 4.39)	0.95
Heart failure	7.21(0.92, 13.50)	0.03
Coronary artery disease	-5.69(-21.55, 10.18)	0.48
<i>BIS estimates</i>		
ICW (per L)	-0.58(-1.45, 0.30)	0.19
ECW (per L)	1.12(0.07, 2.18)	0.04
Fat mass	-0.25(-0.44, -0.06)	0.01

Table 4

Association between left ventricular posterior wall thickness (Model 1) and BIS estimates (Model 2) with PF score.

	Difference in PF score (95% CI)	p-value
MODEL 1* (n=194)		
Left ventricular posterior wall thickness (per 5 mm)	-7.13(-14.07, -0.19)	0.04
MODEL 2* (n=213)		
ECW (per L)	-2.61 (-4.48, -0.73)	0.007
ICW (per L)	1.20(-0.37, 2.78)	0.13
Fat mass (per kg)	-0.005(-0.34, 0.33)	0.98

* Adjusted for age, sex, African-American race, diabetes mellitus, ESRD vintage, peripheral vascular disease, albumin, and hemoglobin