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Original Article

Association of segmental wall motion abnormalities occurring during hemodialysis with post-dialysis fatigue

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ABSTRACT

Background. Post-dialysis fatigue (PDF) is a common, debilitating symptom that remains poorly understood. Cardiac wall motion abnormalities (WMAs) may worsen during dialysis, but it is unknown whether WMA are associated with PDF.

Methods. Forty patients were recruited from University of California San Francisco-affiliated dialysis units between January 2010 and February 2011. Participants underwent echocardiograms before and during the last hour of 79 dialysis sessions. Myocardial segments were graded 1–4 by a blinded reviewer, with four representing the worst WMA, and the segmental scores were summed for each echocardiogram. Patients completed questionnaires about their symptoms. Severe PDF (defined as lasting >2 h after dialysis) was analysed using a generalized linear model with candidate predictors including anemia, intradialytic hemodynamics and cardiac function.

Results. Forty-four percent of patients with worsened WMA ($n = 9$) had severe PDF, compared with 13% of patients with improved or unchanged WMA ($P = 0.04$). A one-point increase in the WMA score during dialysis was associated with a 10% higher RR of severe PDF [RR: 1.1, 95% CI (1.1, 1.2), $P < 0.001$]. After multivariable adjustment, every point increase in the WMA score was associated with a 2-fold higher risk of severe PDF [RR: 1.9, 95% CI (1.4, 2.6), $P < 0.001$]. History of depression was associated with severe PDF after adjustment for demographics and comorbidities [RR: 3.4, 95% CI (1.3, 9), $P = 0.01$], but anemia, hemodynamics and other parameters of cardiac function were not.

Conclusions. Although cross-sectional, these results suggest that some patients may experience severe PDF as a symptom of cardiac ischemia occurring during dialysis.

INTRODUCTION

Post-dialysis fatigue (PDF) is common and potentially debilitating [1], affecting up to 50% of patients with end-stage renal disease (ESRD) on hemodialysis [2]. Patients with PDF may need >5 h of sleep to recover from dialysis [2], causing some to skip treatments or withdraw from dialysis entirely. Generalized fatigue (not specified as post-dialysis) independently predicts cardiovascular events [3] and overall mortality [4] in this population. Despite the high burden of morbidity and mortality associated with fatigue in patients with ESRD, risk factors or therapies for PDF remain elusive. Specifically, the presence and severity of PDF is not consistently related to dialysis treatment-related factors such as fluid removal or hemodynamic changes [2, 5].

Prior studies have shown that myocardial stunning, seen as regional wall motion abnormalities (WMAs) on

echocardiogram, can occur during dialysis and persist for at least 30 minutes after dialysis. These WMAs are in turn associated with deterioration in ejection fraction [6] and higher overall mortality [6, 7]. However, the association of these WMA with symptoms has not been investigated. Our objectives were to determine whether worsened intradialytic WMAs were associated with symptoms during or after dialysis.

SUBJECTS AND METHODS

Participants

We recruited and studied 40 patients on chronic hemodialysis from the San Francisco Veterans Affairs Medical Center (SFVAMC), San Francisco General Hospital and University of California San Francisco (UCSF)-Mt. Zion Hospital between February 2010 and February 2011. To be included, patients had to be on a stable chronic hemodialysis regimen. Exclusion criteria were as follows: current treatment for infection, major surgery within 1 month, newly diagnosed or metastatic cancer, myocardial infarction within the last 6 months, active angina, current cocaine or i.v. drug use, current chemotherapy or cognitive deficit limiting ability to give informed consent. Thirty-five eligible patients declined to participate, usually citing the difficulty of traveling to the SFVAMC for dialysis sessions. Patients gave written informed consent, and our protocol was approved by the UCSF Committee for Human Research and the SFVAMC Research and Development Committee.

Protocol

Each participant consented to echocardiograms before and during dialysis. Twenty-nine participants underwent echocardiograms during two dialysis sessions; 11 had fewer or more sessions. Although patients were recruited from several dialysis centers, all patients underwent study-related dialysis sessions at the SFVAMC Hemodialysis Unit, using their routine dialysis prescription, either 3 or 3.5 h dialysis at standard temperature (37°C). No patients were prescribed midodrine. Patients were studied during the second or third dialysis session of the week; we avoided the first dialysis session of the week that follows a 2-day break between dialysis sessions.

Measurements

Predictors. Data on demographics, comorbidities and medications were collected from the medical record. Patients were considered as having depression if the diagnosis of depression, mood disorder, bipolar disorder or anxiety disorder was listed in the medical chart or if they were prescribed antidepressants. Intradialytic hemodynamics and ultrafiltration were abstracted from dialysis treatment records and averaged over the 30 days prior to administering the symptom questionnaire. Pre-dialysis systolic blood pressure (SBP) was taken with the patient seated, directly before dialysis. Increase in SBP was defined as (highest intradialytic SBP)—(pre-dialysis SBP). Decrease in SBP was defined as (pre-dialysis SBP)—(lowest intradialytic SBP). For all patients, routine monthly laboratory work processed at the patients' regular dialysis units were utilized for values of plasma calcium, phosphorus, parathyroid hormone, albumin and *Kt/v*.

WMAs were measured on formal echocardiograms performed by a trained sonographer, directly before dialysis and then during the last hour of dialysis using a Siemens Sequoia Model C512 with a 3.5 MHz transducer. Date, time and patient identification were removed from echocardiograms, which were then submitted in random order to a single-blinded reader (D.A.) at an established reading center (Cardiocore Labs, Daly City, CA, USA). D.A. is a certified sonographer with over 10 years of experience previously documented as having >90% intra-reader concordance for measurements used in the current study. Each of the 16 myocardial segments was scored as 1 for normal, 2 for hypokinetic, 3 for akinetic and 4 for dyskinetic. The sum score of all 16 segments represented the WMA score for each echocardiogram. Pre- and post-dialysis echocardiograms were then matched by code and the pre-dialysis WMA score was subtracted from the intra-dialysis WMA score. From this, we calculated change in the WMA score, a continuous variable; positive values represent worsened WMA, and negative values represent improved WMA.

Outcomes. Patients' symptoms associated with dialysis were surveyed by questionnaire administered after the dialysis session. The person administering the questionnaire asked, 'Did you feel worse during dialysis today?' Patients who answered yes were asked to specify whether they experienced 'tiredness, shortness of breath, dizziness, chest pain, muscle cramps, or nausea'. Patients were asked to give yes or no answers to 'After most dialysis sessions, do you have fatigue of two hours or less?' and 'After most dialysis sessions, do you have fatigue for more than 2 h?' Severe PDF was defined as a 'yes' answer to the latter question.

Statistical analysis

First, we described the characteristics of the cohort and evaluated the echocardiographic data. After excluding two echocardiograms for poor image quality, we scored the 79 remaining pairs of echocardiograms (representing 79 dialysis sessions/40 patients) for change in WMAs. To account for participants having different numbers of dialysis sessions, we calculated an average WMA score per patient for initial analyses, and, subsequently, we used a clustering variable when using linear regression to calculate relative risk. For initial analyses, the continuous variable, 'change in WMA' was averaged over each patient's dialysis sessions to arrive at the average change in WMA for each patient. Patients with average change in the WMA score >0 were considered to have 'worsened WMA', those with average change in WMA score = 0 to have 'unchanged WMA', those with average change in WMA <0 to have 'improved WMA'. In univariate analysis, patients with worsened WMA were compared with those with unchanged or improved WMA using Chi^2. For univariate and multivariate analyses of relative risk, we used average change in WMA as a continuous variable. We tested the relative risk of potential covariates with severe PDF using

Table 1. Cohort characteristics and univariate relative risks for PDF

	Absent or mild fatigue[a] ($n = 32$)	Severe fatigue[a] ($n = 8$)	Univariate relative risk for severe PDF		
			RR	95% CI	P-value
Demographics					
Age (years)	61 (±15)	61 (±15)	0.99	(0.97, 1.0)	0.9
Dialysis vintage (years)	5 (±6)	3.3 (±2)	0.92	(0.8, 1.0)	0.16
Male gender	25 (78%)	8 (100%)	1.3	(0.4, 5.1)	0.7
Caucasian race	6 (19%)	3 (38%)	2.5	(0.95, 6.6)	0.06
Clinical factors					
History of depression	5 (18%)	3 (30%)	4.6	(1.8, 12)	0.002
Diabetes	15 (47%)	3 (38%)	0.6	(0.2, 1.9)	0.4
Atherosclerosis[b]	14 (44%)	4 (50%)	1.6	(0.5, 4.7)	0.4
Myocardial infarction	8 (26%)	1 (13%)	0.7	(0.2, 1.9)	0.4
Congestive heart failure	6 (19%)	0 (0%)	0.3	(0.05, 1.4)	0.1
Pre-dialysis SBP (mmHg)[c,d]	140 (±18)	143 (±7)	1.1	(0.9, 1.5)	0.4
Hemoglobin (g/dL)	11 (±1)	11 (±2)	0.9	(0.6, 1.2)	0.4
Albumin (g/dL)	3.7 (±0.4)	3.6 (±0.5)	0.6	(0.2, 1.3)	0.19
Phosphorus (mg/dL)	5.3 (±2)	5.6 (±1)	1.1	(0.9, 1.4)	0.5
Parathyroid hormone (mg/dL)	286 (7, 2800)	331 (97, 2800)	1.0	(0.99, 1.0)	0.4
Dialysis-related factors					
Symptomatic hypotension[e]	6 (19%)	2 (25%)	1.5	(0.7, 3.6)	0.3
Decrease in SBP during dialysis (mmHg)[c,d]	25 (±15)	32 (±8)	1.3	(0.96, 1.8)	0.09
Increase in SBP during dialysis (mmHg)[c,d]	13 (±9)	9 (±5)	0.5	(0.3, 1.1)	0.1
Ultrafiltration[c] (l)	2.5 (±1)	3 (±1)	1.4	(0.9, 2.1)	0.19
Kt/v	1.6 (±0.3)	1.6 (±0.3)	0.8	(0.18, 3.4)	0.8
Echocardiographic factors					
Left ventricular mass index (g/m^2)	99 (59, 172)	87 (61, 170)	0.3	(0.07, 1.3)	0.1
Baseline abnormal diastolic function	22 (69%)	5 (63%)	0.7	(0.3, 1.5)	0.4
Baseline ejection fraction[d]	57% (±7%)	56% (±5%)	<0.001	(<0.001, >1000)	0.5
Baseline WMA	8 (25%)	2 (25%)	0.6	(0.13, 2.4)	0.4
Worsened WMA (dichotomous)	5 (16%)	4 (50%)	1.7	(1.1, 1.9)	0.04
Average change in the WMA score (point)	0 (−1.5, 2.7)	0 (0, 8)	1.1	(1.1, 1.2)	<0.001

[a]Mean (±SD), *n* (%) or median (range).
[b]History of myocardial infarction, peripheral arterial disease or cerebral vascular attack.
[c]30-day average.
[d]RR is per 10-unit increase.
[e]Decrease in SBP >20 mmHg accompanied by cramps, dizziness or other symptoms.
WMA, wall motion abnormality.

generalized linear models, with a Poisson working model to account for clustering from participants with more than one dialysis session. Multivariable regression was carried out using staged models. The first model included demographic and clinical factors associated with severe PDF at $P < 0.2$ (dialysis vintage, white race, depression, heart failure and albumin). Model 2 included these covariates and added 30-day averaged hemodynamics (decrease and increase in SBP during dialysis, ultrafiltration). Collinearity appeared to be minimal in the final model. All analyses were performed using STATA 11 (StataCorp, College Station, TX, USA).

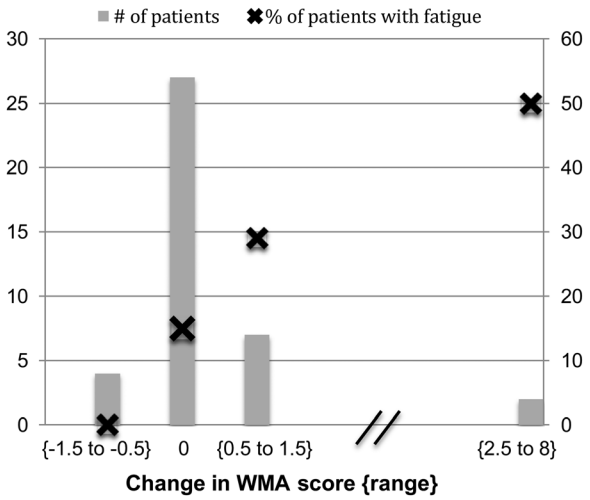

FIGURE 1: Distribution of average change in the WMA score and fatigue among 40 dialysis patients (79 dialysis sessions). The change in the WMA score for each patient was averaged over each patient's dialysis sessions. Data were collected from 79 dialysis sessions. Negative values for change in the WMA score indicate that the score decreased and WMA improved during dialysis. Positive values indicate that the score increased and WMA worsened.

RESULTS

The majority of the cohort were non-white male veterans (38% were African American, 15% Hispanic and 10% Filipino), and almost half had diabetes or atherosclerosis. Twenty percent experienced symptoms such as cramping or dizziness associated with a decrease in blood pressure of >20 mmHg, and 20% experienced severe PDF. Only two had both symptomatic hypotension and severe PDF (Table 1). Using the average change in the score for each patient's dialysis sessions, 9 participants (23%) had worsened WMA, 27 (67%) had unchanged WMA and 4 (10%) had improved WMA (Fig. 1).

The prevalence of severe PDF in participants with worsened WMA was 50%, compared with 16% in those with unchanged or improved WMA ($P = 0.04$). Each one-point increase in the WMA score during dialysis was associated with a 10% higher relative risk of severe PDF [RR: 1.1, 95% CI (1.1, 1.2), $P < 0.001$]. To explore whether this association was driven by the one case of globally worsened WMA (average change in score 8 and severe PDF), we excluded this case and found a similar RR of severe PDF associated with one-point increase in the WMA score [RR: 1.2, 95% CI (1.1, 1.4), $P = 0.001$]. The only other covariate significantly associated with severe PDF was depression (Table 1). Interestingly, worsened WMAs were not associated with symptoms occurring during dialysis (for one-point worsened WMA, RR of intradialytic symptoms was 0.95, 95% CI: 0.9, 1.0, $P = 0.3$).

After adjustment for demographics, comorbidities and hemodynamics, every point increase in the WMA score was associated with a nearly doubled relative risk of severe PDF [RR: 1.9, 95% CI (1.4, 2.6), $P < 0.001$]. Excluding the case of globally worsened WMA (the patient with the highest average change in WMA) did not change this result. Depression remained associated with severe PDF after adjustment for demographics and comorbidities (Table 2).

Table 2. Adjusted relative risk for severe PDF

	Model 1			Model 2		
	RR	(95% CI)	P-value	RR	(95% CI)	P-value
Change in the wall motion abnormality score (point)	1.2	(1.1, 1.3)	<0.001	1.9	(1.4, 2.6)	<0.001
Depression	3.4	(1.3, 9.0)	0.01	2.0	(0.6, 6.8)	0.3
Decrease in SBP during dialysis (mmHg)[a,b]	—	—	—	1.6	(0.8, 3.1)	0.15
Increase in SBP during dialysis (mmHg)[a,b]	—	—	—	1.1	(0.6, 2.2)	0.7
Ultrafiltration (L)[b]	—	—	—	1.0	(0.7, 1.4)	0.9

When estimating relative risk for each predictor, that predictor is removed from the model. For example, for predictor 'depression', Model 1 and Model 2 do not include depression.
Model 1: dialysis vintage, white race, depression, heart failure and albumin.
Model 2: Model 1 + 30-day average decrease in SBP during dialysis, 30-day average increase in SBP and 30-day average ultrafiltration.
[a]30-day average.

DISCUSSION

We report the novel finding of an association between worsened intradialytic WMA and severe PDF. This association was independent of age, depression and hemodynamics. Symptoms occurring during dialysis, intradialytic hemodynamics, ultrafiltration or anemia were not associated with severe PDF.

Factors that contribute to generalized fatigue in ESRD patients include anemia, malnutrition and cytokine activation [1], but with the possible exception of erythropoietin stimulating agents [8], we lack effective therapies. Only a few investigations have focused specifically on PDF, and these have suggested that while ultrafiltration and osmotic shifts may contribute [9], intradialytic blood pressure variation does not [2]. To our knowledge, ours is the first report of an association between worsened intradialytic WMA and severe PDF. While causality cannot be assumed from this cross-sectional study, our data raise the possibility that, in some cases, severe PDF may be a sequela of intradialytic ischemia. Prior studies showed that 50% of intradialytic WMAs persist 30 minutes after dialysis [10]. By inference, some patients may experience severe PDF as a symptom of myocardial ischemia. Given the association of intradialytic WMA with higher mortality [6, 7], this could explain why fatigue is an independent predictor of cardiovascular events in patients with ESRD [3]. Alternatively, an unmeasured phenomenon could cause both WMA and fatigue. Vascular refilling, in which extravascular fluid replenishes the vascular blood volume, occurs during and after dialysis. One may speculate that slow vascular refilling causes reduced perfusion to both the brain and heart for hours following dialysis, causing both centrally mediated fatigue and reduced myocardial perfusion.

Depression remained significantly associated with severe PDF after adjustment for demographics and comorbidities, in accordance with prior studies [2, 11]. Numerous recent studies indicate that depression is common [12] and is independently associated with higher mortality in the ESRD population [13, 14]. Depression may render patients more apt to become fatigued with any stressor, including dialysis. Alternatively, in the context of our study, patients with worsened WMA during dialysis may experience severe PDF as a sequela of cardiac ischemia, and this thrice weekly cycle of exhaustion may cause or exacerbate depression. Lower rates of cardiac WMA have been observed with frequent dialysis than with thrice weekly dialysis [15]. Compared with thrice weekly dialysis, daily dialysis has been shown to reduce rates of depression and time to recovery [16]. Further longitudinal studies may delineate whether intradialytic WMA, depression and fatigue are causally related and whether therapies aimed at WMA could reduce rates of depression and PDF.

It is worth noting important differences between our results and prior studies of intradialytic WMA. We observed a 26% incidence of WMA compared with 64% incidence of previously reported [6]. Our cohort was more racially diverse, having 38% African Americans versus the prior cohort having 3% Afro-Caribbean [6]. In our study, WMAs were manually measured, as opposed to using automatic border detection, which may be more sensitive. While this may account for the lower prevalence of WMA in our study participants, it is also possible that myocardial stunning during dialysis is less common among non-white patients; this could contribute to the survival advantage of African Americans in the USA who are on hemodialysis [17]. Although we are underpowered to compare WMA among races, we did observe that white race was associated with higher likelihood of PDF.

Strengths of our study include the blinded, graded scoring system for WMA. In regard to age, the prevalence of diabetes or atherosclerosis, and high proportion of African Americans, our study cohort reflects the United States Renal Disease System ESRD population [17]. Our observed prevalence of intradialytic WMA and symptomatic hypotension were consistent with prior literature [7, 18]. Thus, we have no reason to believe our results would not generalize to other ESRD cohorts. Important limitations of our study include its cross-sectional nature, the predominantly male cohort, and the modest sample size. We had limited assessments of depression, which was extracted from the medical record. PDF was assessed on questionnaire relating to the last 30 days, instead of after each dialysis session, and was defined solely on the basis of duration rather than intensity; additional information such as whether patients required sleep or bed rest would have increased our ability to detect associations between WMA and severity of fatigue. Several subjects had only one dialysis session, but none of these subjects had a high change in the WMA score, so these patients are unlikely to have skewed our results.

In conclusion, we found that worsened intradialytic WMAs were associated with severe PDF independently of demographics, comorbidities and hemodynamics. Of other covariates tested (including intradialytic hemodynamics), only depression was associated with severe PDF. In some patients, intradialytic cardiac ischemia may be a contributing factor to severe PDF.

CONFLICT OF INTEREST STATEMENT

N.B.S. is a consultant to Cardiocore for projects unrelated to the current manuscript. The other authors have no financial conflicts of interest to declare. The results presented in this paper have not been published previously in whole or part, except in abstract format.

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