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ASSOCIATIONS OF MACRO- AND MICROVASCULAR ENDOTHELIAL DYSFUNCTION WITH SUBCLINICAL VENTRICULAR DYSFUNCTION IN END-STAGE RENAL DISEASE

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Abstract

Patients with end-stage renal disease (ESRD) suffer high rates of heart failure and cardiovascular mortality, and we lack a thorough understanding of what, if any, modifiable factors contribute to cardiac dysfunction in these high-risk patients. In order to evaluate endothelial function as a potentially modifiable cause of cardiac dysfunction in ESRD, we investigated cross-sectional associations of macro- and microvascular dysfunction with left and right ventricular dysfunction in a well-controlled ESRD cohort. We performed comprehensive echocardiography, including tissue Doppler imaging and speckle tracking echocardiography of the left and right ventricle, in 149 ESRD patients enrolled in an ongoing prospective, observational study. Of these participants, 123 also underwent endothelium-dependent flow-mediated dilation (FMD) of the brachial artery (macrovascular function). Microvascular function was measured as the velocity time integral (VTI) of hyperemic blood flow following cuff deflation. Impaired FMD was associated with higher LV mass, independently of age and blood pressure: per two-fold lower FMD, LV mass was 4.1% higher (95%CI [0.49, 7.7], p=0.03). After adjustment for demographics, blood pressure, comorbidities and medications, a two-fold lower VTI was associated with 9.5% higher E/e' ratio (95% CI [1.0, 16], p=0.03) and 6.7% lower absolute RV longitudinal strain (95% CI [2.0, 12], p=0.003). Endothelial dysfunction is a major correlate of cardiac dysfunction in ESRD, particularly diastolic and right ventricular dysfunction, in patients whose volume status is well-controlled. Future investigations are needed to determine whether therapies targeting the vascular endothelium could improve cardiac outcomes in ESRD.

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Keywords

end-stage renal disease; endothelial dysfunction; echocardiography; heart failure; cardiac dysfunction

Introduction

Cardiovascular disease (CVD) accounts for nearly half of the high mortality rate among patients with end-stage renal disease (ESRD); the prevalence of atherosclerotic disease and heart failure are 70% and 45%, respectively, for patients on hemodialysis.[1] Unfortunately, we lack effective cardiovascular therapies for these patients, in part due to an incomplete understanding of the cardiovascular physiology afflicting this population. Aside from volume overload, we do not know whether modifiable factors, such as endothelial dysfunction, contribute to cardiac dysfunction in these patients. Among patients with CKD, endothelial dysfunction is common[2, 3] and predicts adverse outcomes.[4, 5] A prior study did not find an association between endothelial dysfunction and cardiac mechanics in patients with ESRD,[6] but we hypothesized that such an association could be found with more sensitive measures of cardiovascular dysfunction and consistent timing of cardiovascular measurements with respect to dialysis. The Cardiac, Endothelial Function and Arterial Stiffness in ESRD (CERES) study is an ongoing, prospective observational study designed to provide in-depth measures of vascular and cardiac function and determine the utility of these measures in predicting heart failure and overall mortality in ESRD.

Endothelial-dependent flow-mediated dilation (FMD) of the brachial artery is a gold-standard, non-invasive method of quantifying endothelial NO bioavailability[7] that correlates with coronary endothelial function.[8] FMD, the percent change in diameter of the brachial artery during hyperemic blood flow, represents macrovascular endothelial function, and velocity time integral (VTI) of hyperemic blood flow is considered a marker of microvascular endothelial function.[9] Speckle tracking echocardiography (STE) is becoming a widely accepted state-of-the-art research tool.[10, 11] Systolic function, measured using STE as global longitudinal strain (GLS), is associated with adverse outcomes in patients with [12, 13] and without CKD.[14] Tissue Doppler imaging, summarized by E/e' as a measure of diastolic dysfunction and loading conditions, predicts adverse outcomes in ESRD.[15, 16] We sought to delineate associations between endothelial function and cardiac mechanics in ESRD, using baseline FMD and cardiac measures in CERES participants. We hypothesized that advanced methods, consistently timed with respect to dialysis, would demonstrate associations between endothelial function and cardiac mechanics in ESRD patients without symptoms of heart failure, supporting future research into endothelial health-promoting therapies to prevent heart failure and other adverse cardiovascular outcomes in these patients.

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Materials and Methods

Study Population

The CERES study is an ongoing, prospective observational study designed to obtain high quality echocardiography and vascular measures performed at consistent intervals with dialysis and to follow longitudinal outcomes in a cohort of well-controlled hemo- and peritoneal dialysis patients. Patients were recruited by mail and phone from the San Francisco Bay Area kidney transplant waitlist, the San Francisco General Hospital (SFGH) Chronic Dialysis Unit and three local Fresenius dialysis units. To be included, patients had to be on hemodialysis or peritoneal dialysis. Any of the following led to exclusion: more than moderate valvular disease, recent myocardial infarction or major surgery, current infection, newly diagnosed or metastatic cancer, cocaine or intravenous drug use. Patients who had undergone surgical procedures in both arms were excluded from having vascular studies. Study visits took place at the SFGH Clinical Research Center. Medical history, such as cardiovascular disease, cause of renal disease, pack-years of smoking tobacco, were obtained by self-report. Information such as medications and monthly labs was obtained from the participants' dialysis units. The study was carried out according to the principles of the Declaration of Helsinki. Patients gave written informed consent, and the study protocol was approved by the UCSF Committee for Human Research.

Methods for endothelium-dependent FMD and echocardiography are located in the online supplement

Statistical analysis

First, we analyzed demographic and clinical characteristics of all participants whose echocardiograms were included in the analyses. We also examined differences in demographics and comorbidities between subgroups (e.g., those that could or could not undergo FMD, and those above or below median FMD and VTI.) Next, we used Spearman correlations to examine unadjusted associations of FMD and VTI with parameters of LV and RV mechanics. For LV systolic function we relied primarily on longitudinal strain[12, 13] and for LV diastolic function primarily on E/e' based on the prognostic utility of these parameters in the ESRD population.[15, 16] We then performed multivariable linear regression, with the goal to construct parsimonious models using hemodynamic parameters and comorbidities likely to confound either LV or RV associations. We log-transformed the outcomes LV mass, E/e' ratio, RV freewall systolic strain, and RV early diastolic strain rate, and then back-transformed beta coefficients so that estimates would represent percent change in outcome per doubling of FMD or VTI. In Model 1 we adjusted for age, and in Model 2 we adjusted for age and peripheral SBP measured prior to the echocardiogram. Model 3 included covariates that were associated with FMD or VTI at a significance of $p<0.05$ (age, race, cause of renal failure, and body mass index) as well as known cardiovascular risk factors (gender, tobacco use) and months since started dialysis (a surrogate for disease duration). For RV associations, Model 3 included pulmonary artery systolic pressure assessed by echocardiography, in addition to the covariates listed above. Model 4 included prior models and added use of angiotensin converting enzyme inhibitor or

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angiotension receptor blocker, statin, beta-blocker. All statistical analyses were performed with STATA statistical analysis software version 11.0 (College Station, TX).

Results

Characteristics of the cohort are displayed in **Table 1**. The mean±SD age was 55±13 years, 114 (77%) were of non-white race. Patients were relatively healthy for an ESRD cohort: 29% were actively listed for transplant at the time of recruitment (by review of the Bay Area Transplant Waitlist); 32% self-reported atherosclerotic disease (defined as myocardial infarction, stroke, peripheral artery disease, percutaneous coronary intervention or coronary artery bypass graft). SBP was well-controlled and hemoglobin levels measured on the day of study visit (the day after dialysis) were higher than those taken from patients' monthly labs (normally drawn immediately pre-dialysis): 11.4±1.3 g/dL *vs.* 10.8±1.1 g/dL ($p<0.001$). Since fluid removal during dialysis results in an increase in hemoglobin, higher hemoglobin at study visit supports that most patients were euvolemic. Mean LV mass index was 118(±31)g/m^2, and the majority had ejection fraction>50%. **(Table 2)** The median FMD was 4.3% (IQR 2.5, 6.9) and median VTI was 67cm (IQR 47, 81). Participants with VTI below the median tended to be older, of African American race, and to have a history of atherosclerotic disease. Those with FMD below the median tended to self-report diabetes as the cause of their renal disease, to be of African American race, and to have higher SBP and body mass index. **(online supplement)**. Patients who did not undergo FMD testing due to having had bilateral upper extremity surgical interventions (N=20) tended to have been on dialysis longer (median 79 vs. 46 months, p=0.003), and were less likely to be actively listed for kidney transplant (33% vs. 55%, p=0.006).

Reproducibility

Eleven patients returned for repeat studies performed 7 days following the initial visit, on the day after dialysis. Mean(SD) absolute difference in FMD and VTI between study visits were as follows: FMD 1.6% (±1.4), VTI 15cm (±13). Reproducibility of strain parameters were as follows: LV GLS, intraclass correlation (ICC) 0.97 [0.93, 1.0], coefficient of variation (CoV) 3%; LV early diastolic strain rate, ICC 0.96 [0.91, 1.0], CoV 5%; right ventricle (RV) free wall systolic strain, ICC 0.90 [0.79, 1.0], CoV 5%.

Associations of Vascular and Cardiac Parameters

In unadjusted analyses, we found that higher FMD (better endothelial function) correlated with lower LV mass and lower E/e' ratio (better diastolic function), and with higher RV early diastolic strain rate (better diastolic function). By comparison, higher VTI (better endothelial function) correlated with lower E/e' and with higher RV freewall systolic strain (better systolic function). Correlations of FMD and VTI with other left and right ventricular parameters were weaker and did not reach statistical significance. **(Figure 1; Table 3)**

We then performed multivariable linear regression analysis to determine whether the associations of FMD and VTI with LV parameters were independent of demographic factors, comorbidities and cardiovascular medication use. Higher FMD remained associated with lower LV mass after adjustment for age and SBP, but addition of demographics (particularly

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gender) rendered the association statistically non-significant. Higher VTI remained significantly associated with lower E/e' ratio, even after adjusting for medications (−9.5% per per doubling of VTI, 95%CI(−16, −1.0). **(Table 4)**

We performed similar multivariable linear regression analysis of the associations of endothelial and RV parameters. Higher VTI remained associated with higher RV systolic free wall strain after multivariable adjustment (6.7% per VTI doubling, 95%CI 2.0, 11.6). Likewise, higher VTI remained associated with higher RV early diastolic strain rate (11.6% per VTI doubling, 95%CI 3.0, 21). (**Table 5**)

We compared endothelial function among patients with diastolic dysfunction categorized as normal, mild, moderate and severe diastolic dysfunction. Mean(SD) FMD were 5.7(±3.9), 4.8(±3.3), 4.4(±2.9), 3.5(±1.6) (ANOVA p=0.34, p for trend=0.14); VTI were 72(±28), 68(±35), 53(±27), 48(±30) (ANOVA p=0.08, p for trend=0.03). These results are in agreement with the correlation of VTI and diastolic dysfunction, measured as E/e'. In a sensitivity analysis of a subset of 83 patients who did not self-report atherosclerotic disease, the only correlation that remained significant ($p<0.05$) was VTI and RV freewall systolic strain (R=0.23, p=0.04). The correlation of FMD and LV mass became less significant (R=-0.22, p=0.05); the correlation of VTI and LV mass remained statistically insignificant, but became a trend (R=0.19, p=0.09).

Discussion

We present several salient findings that, to our knowledge, have not been previously demonstrated in the setting of ESRD or other populations. Namely, microvascular endothelial dysfunction (VTI) has an independent association with LV diastolic dysfunction, RV systolic dysfunction and RV diastolic dysfunction. Macrovascular function was associated with LV mass, but after full adjustment the association was not significant. For this discussion, it is important to note that brachial FMD and VTI are considered important correlates of cardiac endothelial function.[8]

Association of Macrovascular Function (FMD) with LV mass

In animal knockout models, mice deficient in endothelial or neuronal nitric oxide synthases (NOS) rapidly develop LV hypertrophy.[17] In ESRD, high levels of asymmetric dimethylarginine inhibit NOS, mimicking the knockout state.[18] There have been two large studies showing associations between FMD and LV mass in community dwelling populations,[19, 20] and smaller studies have demonstrated this association in hypertensive patients.[21-23] There have been relatively few studies in patients with CKD. Our findings are in accordance with a prior study by Pannier et al. showing that forearm reactive hyperemia, measured by venous plethysmography, correlated with LV mass index and common carotid media-intima thickness.[24] However, a prior study by Fathi et al. did not find correlations between FMD and cardiac structure and function.[6] In the subgroup without self-reported cardiovascular disease, the microvascular function - LV mass association gained statistical significance. As a potential explanation for this observation, microvascular dysfunction may precede macrovascular dysfunction, as it does in diabetics.[25] Capillary rarefaction in the LV is a common finding in CKD.[26, 27] In advanced stages of CKD, microvascular structure

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or function may be obliterated by the time LV hypertrophy occurs, accounting for why VTI did not correlate with hypertrophy in patients with advanced disease. It is also notable that the FMD – LV mass association was attenuated by adjustment for gender. We are currently investigating the influence of gender on cardiovascular function in the cohort.

Association of Endothelial Dysfunction With Subclinical LV Diastolic Dysfunction

We show that in asymptomatic ESRD patients, both macrovascular (FMD) and microvascular function (VTI) are highly correlated with E/e' ratio, a parameter that reflects LV diastolic function and preload. Given that patients were studied the morning after dialysis, that most patients were <0.5 kg over dry weight, and that hemoglobin on the study day was higher than on monthly labs, we conclude that participants were close to euvolemic. In this context, E/e' ratio is less likely a marker of generalized fluid overload and more likely an indicator of intrinsic LV diastolic function. We also controlled for SBP in multivariate analyses. Thus, while we cannot determine the extent of confounding due to volume status, we conclude that the associations observed reflect correlations between endothelial and intrinsic LV diastolic function. These findings support current views [28, 29] on the importance of endothelial dysfunction as a pathophysiologic factor in LV diastolic dysfunction. As others have elegantly described, endothelial dysfunction and inflammation are likely synergistic precursors to diastolic dysfunction. [28, 29] CKD exemplifies a disease state of endothelial dysfunction[30] and inflammation[31] and thus CKD may be an especially appropriate population to study associations between endothelial dysfunction, inflammation, and abnormal systolic and diastolic cardiac mechanics. Further studies of inflammatory mediators in these patients might clarify the role of inflammation in the associations that we observed. Additional mediators known to correlate with endothelial dysfunction and left ventricular hypertrophy, including asymmetric dimethylarginine[32, 33] and phosphorus[34, 35] could also play an important role; we plan further analyses of our data to examine associations between these factors and macro- and microvascular dysfunction. It is notable that, in contrast to the finding that both FMD and VTI were associated with LV diastolic dysfunction, neither was associated with systolic function as measured by GLS or ejection fraction (EF). Several possible explanations exist, including type II error due to modest sample size; however, we note that the effect sizes observed are not consistent with a clinically meaningful association, and thus we would not expect greatly different results with a larger sample size. This cohort sampled relatively healthy ESRD patients with mostly normal EF, which could have affected our ability to detect correlations with EF. Alternatively, our findings could be interpreted as showing that endothelial function is a contributor to diastolic dysfunction, but that other factors (for example, volume status or anemia) are more important determinants of systolic function in ESRD.

Association of Microvascular Function (VTI) with RV function

Animal studies have suggested that pulmonary microvascular remodeling may lead to increased RV afterload[36] and influence RV function.[37] Epidemiological studies in non-CKD populations have shown that RV dysfunction is particularly common in the setting of heart failure with preserved ejection fraction (HFpEF).[38, 39] Recent work by Shah and colleagues has shown that RV remodeling is an independent prognostic factor in HFpEF;[40] in the same cohort, microalbuminuria (a marker of endothelial dysfunction) was associated

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with RV remodeling independent of comorbidities and LV mass.[41] To our knowledge, the association of VTI with RV function that we observed has not been demonstrated previously in CKD or non-CKD populations. Notably, the association between VTI and RV dysfunction persists even in the smaller subgroup without self-reported atherosclerotic disease and in the whole group after adjustment for medications. These findings suggest there is a particularly robust association between microvascular dysfunction and RV dysfunction. In light of current literature indicating RV dysfunction precedes LV dysfunction, and assuming that microvascular disease occurs before macrovascular disease, as in diabetes,[25] it is possible that microvascular disease mediates RV dysfunction in early pre-clinical stages of heart failure.

Strengths

Our study has several strengths. The cohort is well-characterized and is diverse with regard to age, gender and race. We captured a broad range of subclinical CVD by including participants actively waitlisted for kidney transplant, who by definition do not have severe CVD, as well as participants with more severe disease. There are several potential reasons why we found these associations between endothelial function and cardiac function, while a prior ESRD study did not.[6] Study visits for hemodialysis patients were systematically planned for the day after the first dialysis day of the week dialysis week (Tuesday or Wednesday morning), a study design that may have minimized variations in volume status. FMD poses numerous technical difficulties in ESRD, and we were fortunate to have one specially trained technician perform all FMD and VTI studies. Additionally, we used upper arm cuff occlusion, an accepted site of cuff occlusion that typically results in FMD values twice as large as the more distal placement;[7] this method detected a broad range of endothelial function among our participants.

Limitations

In addition to these strengths, our study has several limitations. Indices of cardiac function, and in particular RV mechanics, are load dependent.[42] Invasively measured central pressures are not available for these analyses, and thus we cannot determine whether the observed associations are independent of volume status. However, we did adjust for peripheral and pulmonary SBP. Similarly, invasively measured coronary endothelial function was not measured; however, the correlation between peripheral FMD and coronary endothelial function in prior studies[8] supports our analyses. Since we did not include a control group, our results are specific to ESRD, and further studies would be required to find out if these associations hold true in populations with less advanced or no kidney disease. Participants are likely to represent the most medically compliant patients, judging by their euvolemic status and well-controlled blood pressure, and results may not generalize to patients with greater disease burden or higher rates of non-compliance. There were 11 participants with current tobacco use, and although we did adjust for smoking pack-years and asked patients to abstain from smoking for 12 hours prior to the study, the effects of smoking probably influenced these patients' endothelial dysfunction. Additional factors likely to affect endothelial function, that were not available for these analyses, include onset of hypertension and dosage of erythropoietin stimulating agents. Our cross-sectional results show associations, but cannot establish a causal relationship between endothelial function

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and cardiac function; longitudinal studies are needed to demonstrate whether endothelial function predicts decline in cardiac function in these patients.

Perspectives

Our data show that among asymptomatic, well-controlled patients on dialysis, macrovascular endothelial dysfunction (FMD) is independently associated with LV mass. Microvascular endothelial dysfunction (VTI) is independently associated with LV diastolic dysfunction and RV systolic dysfunction. Studies of HFpEF or patients with less advanced CKD might elucidate whether the VTI correlations with RV dysfunction and LV diastolic dysfunction apply to other populations. Our study provides a foundation for future interventional trials to determine whether novel endothelial therapies could slow the progression of LV hypertrophy or prevent heart failure in the ESRD population. Of particular interest are novel therapies that act downstream of nitric oxide synthase and could potentially obviate the issue of nitrate tolerance.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Novelty and Significance

What Is New To our knowledge, this is the first study in ESRD in which both macro- and microvascular endothelial function have been measured simultaneously with modern echocardiographic measures of systolic and diastolic cardiac function. We show that microvascular function is associated with diastolic LV and systolic RV dysfunction independently of comorbidities and hemodynamics.

What Is Relevant Diastolic and right ventricular dysfunction are increasingly recognized as integral to the development of HFpEF, which is itself a common, highly morbid condition that is especially in CKD and ESRD. Our results provide a foundation for trials of endothelial-promoting therapeutics to prevent heart failure in CKD, for which short-term surrogate outcomes might include endothelial function or speckle tracking echocardiography.

Summary In this ongoing prospective study of patients with ESRD, baseline studies show strong correlations between microvascular function and both LV and RV dysfunction. Our results yield insight into the range and reproducibility of endothelial and cardiac function in this population and provide rationale for investigations of endothelial-promoting therapies that could prevent heart failure in this population.

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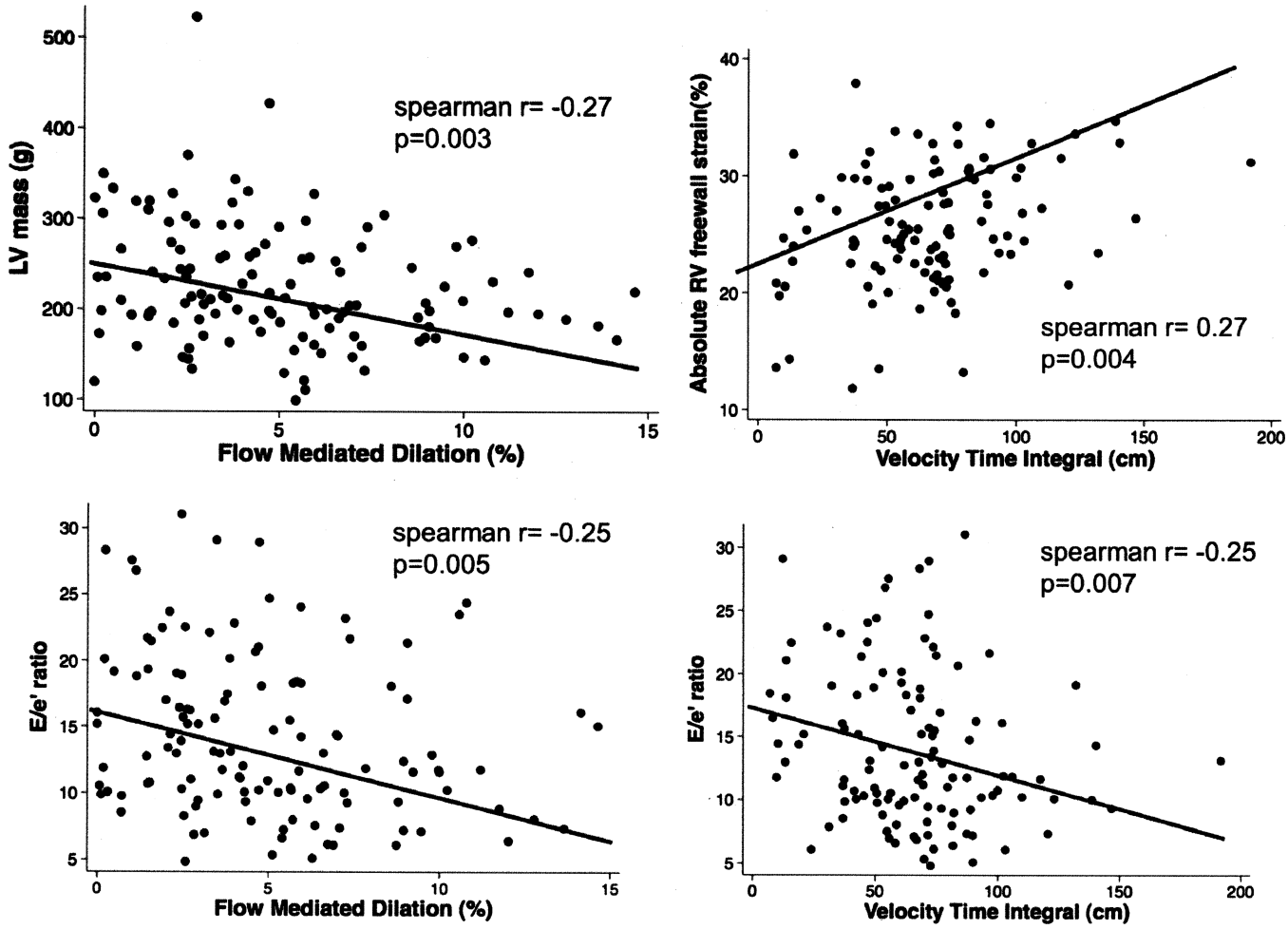

Figure 1. Associations of FMD and VTI with Left and Right Ventricular Mechanics

Figure depicts Spearman correlations of FMD or VTI with echo parameters, with a linear regression fitted line.

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Table 1

Patient Characteristics

All patients (N=149)		
Characteristic		**Mean(SD)** **N(%)**
Age (years)		55(±13)
Female gender		52(35%)
Race	**White**	35(23%)
	African American	53(36%)
	Filipino	14(9%)
	Asian	8(5%)
	Pacific Islander	8(5%)
	Multiple race	31(21%)
Hispanic		43(29%)
Time on dialysis (months)		47(19, 79)
History of tobacco		69(46%)
Diabetes		68(46%)
History of atherosclerotic disease *		47 (32%)
History of heart failure		21(14%)
Peritoneal dialysis		15(10%)
Current vascular access is graft or fistula		85(76%)
History of bilateral vascular access attempts, precluding flow mediated dilation		26 (17%)
Cause of renal failure		
Diabetes		48(32%)
Hypertension		40(27%)
Glomerulonephritis		5(3%)
Other cause		20(14%)
Unknown		35(24%)
Active on transplant list		43(29%)
Anuric		41(28%)
History of chronic obstructive pulmonary disease		15(10%)
History of liver disease		10(7%)
Beta blocker		90(60%)
ACE or ARB		50 (34%)
Statin		62 (42%)
Systolic blood pressure prior to echo (mmHg)		133(±23)
Diastolic blood pressure prior to echo (mmHg)		75(±14)
Body mass index (kg/m^2)		22 (±7.4)
Most recent post-dialysis weight – dry weight (kg) †		0.2 (−0.1, 1)
Calcium (mg/dL) ‡		9 (±0.76)
Phosphorus (mg/dL)		5.6 (±1.5)

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All patients (N=149)	
Characteristic	**Mean(SD)** **N(%)**
Parathyroid hormone (pg/mL)	451 (277, 686)
Albumin (g/dL)	4.0 (±0.34)
Kt/V	1.6 (±0.33)
Hemoglobin (g/dL)	10.8 (±1.1)
Hemoglobin (g/dL) (at study visit)	11.4(±1.3)

* atherosclerosis defined as self-report of myocardial infarction, stroke, percutaneous coronary intervention, coronary artery bypass graft, or peripheral artery disease.

† Represents the degree of volume overload after the last dialysis session, which was the day prior to study visit.

‡ Labs are from patients' monthly dialysis unit labs unless otherwise noted.

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Table 2

Baseline Echocardiographic Parameters

Cardiac Parameter		Mean(SD) / N(%)
LV mass(g)		227(±66)
LV mass index (g/m2)		118(±31)
Mitral annular calcification = moderate or worse		10(7%)
IVC collapsibility (%)		60.4 (±7.3)
Pulmonary artery systolic pressure (mmHg)		38(±13)
Ejection fraction(%)		60(±8)
E(cm/s)		100(±34)
E/A		1.2(±0.9)
e'(cm/s)		7.3(±2.2)
E/e' ratio		15(±7.7)
Mitral deceleration (ms)		190(±45)
Diastolic dysfunction category	**Normal**	46(31%)
	Mild	66(44%)
	Moderate	31(21%)
	Severe	6 (4%)
LV global longitudinal strain (%) *		16(±3.2)
LV early diastolic strain rate (s^{-1})		0.95(±0.33)
RV free wall systolic strain (%)		26(±4.9)
RV early diastolic strain rate (s^{-1})		1.0(±0.29)

* All strain measurements are reported as absolute values. Lower values represent worse cardiac mechanics.

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Table 3

Unadjusted Associations of FMD and VTI With Left and Right Ventricular Mechanics

Cardiac Parameter	FMD (N=123)		VTI (N=117)	
	Spearman r	p	Spearman r	p
LV Structure				
Left ventricular mass	**−0.27**	**0.003**	0.02	0.81
LV Function				
Ejection fraction	0.09	0.30	0.04	0.70
Global longitudinal systolic strain *	0.08	0.38	0.07	0.47
Diastolic function assessed by E/e' ratio †	**−0.25**	**0.005**	**−0.25**	**0.007**
LV early diastolic strain rate	0.02	0.82	−0.05	0.6
RV Function				
RV freewall systolic strain	0.15	0.10	**0.27**	**0.004**
RV early diastolic strain rate	**0.23**	**0.01**	0.08	0.38

*All strain measurements are reported as absolute values. Lower values represent worse cardiac mechanics.

†E/e' =tissue Doppler evaluation of diastolic function.

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Table 4

Multivariable Associations of FMD and VTI with Left Ventricular Mass and Diastolic Function (E/e')

Endothelial parameter		LV Mass %Estimate (95% CI) *	p	Diastolic function assessed by E/e' %Estimate (95% CI)	p
FMD (per doubling)	Unadjusted	−4.5 (−7.7, −0.99)	0.01	−5.5 (−10.4, −0.29)	0.04
	Model 1 †	−4.6 (−7.7, −0.99)	0.01	−5.6 (−10.4, −0.29)	0.06
	Model 2	−4.1 (−7.7, −0.49)	0.03	−2.7 (−7.7, 3.0)	0.31
	Model 3	−2.4(−5.8, 1.2)	0.19	−3.5(−8.6, 2.0)	0.20
	Model 4	−2.0(−5.8, 1.2)	0.28	−2.0(−6.7, 3.0)	0.40
VTI (per doubling)	Unadjusted	0.30 (−4.9, 6.2)	0.9	−13.1 (−20.5, −5.8)	0.001
	Model 1	0.40 (−4.9, 6.2)	0.9	−12.2 (−20.0, −4.9)	0.003
	Model 2	1.0 (−4.9, 7.3)	0.6	−10.4 (−17.3, −2.0)	0.01
	Model 3	−1.9(−6.7, 4.1)	0.50	−10.4(−18, −2.0)	0.01
	Model 4	−1.0 (−6.7, 5.1)	0.7	−9.5(−16, −1.0)	0.03

*Outcomes analyzed are log-transformed LV Mass and E/e' ratio; beta coefficients are back-transformed so estimates represent percent change in outcome per doubling of FMD or VTI.

†Model 1: Age adjusted. Model 2: 1 + systolic blood pressure. Model 3: 2 + race, gender, months since start of dialysis, tobacco use, cause of renal failure, body mass index, Model 4: 3+ use of angiotensin converting enzyme inhibitor or angiotension receptor blocker, statin, beta-blocker

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Table 5

Multivariable Adjusted Associations of FMD and VTI with Right Ventricular Function

Endothelial parameter		RV free wall systolic longitudinal strain %Estimate (95% CI) *	p	RV early diastolic strain rate %Estimate (95% CI)	p
FMD (per doubling)	Unadjusted	0.30 (−2.0, 3.0)	0.8	2.7 (−0.98, 7.3)	0.18
	Model 1 †	−0.09 (−3.0, 2.0)	0.9	2.0 (−0.98, 6.2)	0.3
	Model 2	−0.29 (−2.0, 2.0)	0.8	2.0 (−1.9, 5.1)	0.4
	Model 3	−0.6(−3.0, 2.0)	0.6	0.30(−3.9, 5.1)	0.9
	Model 4	−0.70(−4.0, 2.0)	0.6	−1.0(−5.8, 4.1)	0.6
VTI (per doubling)	Unadjusted	7.3 (3.0, 11.6)	0.001	8.3 (1.0, 16.1)	0.02
	Model 1	6.2 (2.0, 10.5)	0.004	6.2 (−0.7, 13.8)	0.08
	Model 2	5.1 (2.0, 10.5)	0.007	5.1 (−1.8, 13.9)	0.09
	Model 3	5.1(1.0, 9.4)	0.02	8.2(0.2, 17)	0.04
	Model 4	6.7(2.0, 11.6)	0.003	11.6(3.0, 21)	0.007

*Outcomes analyzed are log-transformed LV Mass and E/e' ratio; beta coefficients are back-transformed so estimates represent percent change in outcome per doubling of FMD or VTI.

†Model 1: Age adjusted. Model 2: 1 + systolic blood pressure. Model 3: 2 + race, gender, months since start of dialysis, tobacco use, cause of renal failure, body mass index, pulmonary artery systolic pressure. Model 4: 3+ use of angiotensin converting enzyme inhibitor or angiotension receptor blocker, statin, beta-blocker