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Original Paper

Arterial Stiffness and Walk Time in Patients with End-Stage Renal Disease

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Key Words
Arterial stiffness • Shuttle walk • ESRD

Abstract
Background: End-stage renal disease patients experience increased prevalence of cardiovascular disease. Heart-artery interaction may be shifted, impacting blood pressure lability, and exercise tolerance. The coupling ratio consists of the ratio of indexed arterial elastance (EaI, arterial load) to ElvI, a measure of cardiac contractility or stiffness. Our purpose was to explore the relationship between elastances and functional capacity. We hypothesized that arterial stiffness (central pulse wave velocity, PWV) and elastances would be correlated to shuttle walk time. ***Methods****:* We used applanation tonometry, ultrasonography, and a shuttle walk test to evaluate our hypothesis. Spearman's correlations were used to assess relationships between variables. Block regression was also performed. ***Results:*** Forty-two subjects on maintenance hemodialysis participated. Average age=44±5 years, body surface area=2.01 kg/m^2. Mean EaI=4.45 and mean ElvI=6.89; the coupling ratio=0.82. Mean aortic pulse pressure=51 mmHg and PWV=9.6 m/s. PWV(r=-0.385) and EaI (r=-0.424) were significantly and inversely related to walking time while stroke volume index (SVI) was positively correlated to shuttle walk time (r=0.337), p<0.05 for all. ***Conclusions:*** We conclude that, like other clinical populations, both arterial and heart function predict walking ability and represent potential targets for intervention; arterial stiffness and SVI are strongly related to shuttle walk time in patients with ESRD.

Introduction

The incidence of cardiovascular disease (CVD) and mortality is increased in patients with chronic kidney disease (CKD) [1] and end-stage renal disease (ESRD) [1-3]. This patient

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population also has a high prevalence of hypertension and augmented left ventricular work compared to healthy adults of the same age [1]. The hypertension-induced stiffening of both the heart and arteries in ESRD increases the workload imposed on the heart and consequently alters cardiac performance [2]. This may also alter the coupling of the left ventricle and vascular system, an important consideration as the ventricular-vascular interaction is associated with mortality [4] and can provide important information on cardiac load and energetics [5], but this outcome has not been fully explored in this population.

Ventricular-vascular coupling [6] quantifies the workload imposed on the ventricle by the entire arterial tree [7], and can be expressed as the ratio of arterial elastance (Ea) to left ventricular elastance (Elv). Increased Ea/Elv can be physically attributed to stiffer arteries and reduced cardiac compliance or decreased systolic function [8, 9]. Changes in Ea are also a consequence of physiological factors affecting the arterial load, including: total peripheral resistance, characteristic impedance, total arterial compliance, and diastolic time [10]. Likewise, changes in left ventricular (LV) elastance occur not only because of changes in structure, but also because of altered contractility and metabolic factors affecting cardiac energetics [11]. This interaction may be of particular importance to individuals with ESRD as the coupling ratio is pivotal for maintaining blood pressure homeostasis and reducing pressure lability in response to fluid and volume shifts, a hallmark of ESRD [5].

Appropriate ventricular and vascular matching is crucial in preventing exacerbated myocardial ischemia in response to reduced perfusion due to blood volume changes [5] and has been linked to survival post-infarction in patients with CVD [4]. Importantly, coronary flow reserve has already been shown to be compromised in ESRD, and functional capacity is also limited in other clinical populations by elevated Ea/Elv [12-14]. Thus, there may be a relationship between Ea/Elv and measures of physical capability in patients with ESRD. This could be important in understanding potential hemodynamic mechanisms involved in the manifestation of functional limitations as well as CVD mortality in these patients. This is of particular importance to this population, as only 13.2% of patients with ESRD report reaching recommended levels of physical activity [15]. Additionally, low levels of exercise and physical activity may further contribute to the prevalence of CVD in patients with ESRD.

We examined ventricular-vascular coupling, arterial stiffness and functional walking ability in patients with end-stage renal disease. Our purpose was to evaluate the relationship of these physiologic variables to measured functional performance. We hypothesized that ESRD patients will exhibit increased Ea/Elv ratios and central stiffness, and that these changes will be related to functional performance in this patient population.

Materials and Methods

Subjects

Forty-two patients on maintenance hemodialysis (16 females, 26 males) were recruited from the Champaign-Urbana Dialysis Clinic and the University of Illinois at Chicago dialysis clinic (Champaign, IL and Chicago, IL). Patients were screened for eligibility with a health and medical history questionnaire. All participants gave written informed consent and this study was approved by the University of Illinois Institutional Review Board, and the protocol complied with Declaration of Helinski. Inclusion criteria for participation in this study included the following: 1) End stage renal disease and on dialysis; 2) an age of 30-70 years; 3) a BMI less than 35 kg/m^2 ; 4) medical clearance from a primary care physician. Subjects were excluded if they had chronic obstructive pulmonary disease (COPD), coronary heart failure (CHF), or cardiovascular surgery (e.g., coronary bypass, valve replacement, or angioplasty) in the past 6 months.

Anthropometrics

Standing height and weight measurements were completed with participants wearing light-weight clothing using a stadiometer and balance-beam scale.

Brachial artery blood pressure assessment

Resting systolic BP (SBP) and diastolic BP (DBP) were measured at the brachial artery using an automated oscillometric cuff (HEM-907 XL; Omron, Shimane, Japan). Brachial BP was taken in duplicate. If the two values were not within 5 mm Hg, another measurement was taken until 2 values within 5 mmHg of each other were obtained. Values within 5 mm Hg of each other were averaged and used for analysis. End-systolic pressure (ESP) was calculated from the equation 0.9 x SBP [7] .

Pulse contour analysis

Radial artery pressure waveforms were obtained in the supine position from a 10-s epoch using applanation tonometry (Millar Instruments, Houston, TX) and calibrated with brachial blood pressure (BP) obtained from a standard sphygmamonometer. Using a generalized validated transfer function [16], a central aortic pressure waveform was reconstructed from the radial artery pressure waveform (SphygmoCor; AtCor Medical, Sydney, Australia) to obtain central BP. Aortic mean arterial pressure and aortic pulse pressure [4] were determined from the integration of the reconstructed aortic pressure waveform using the SphygmoCor software. This technique has been validated for use in obtaining central pressure [16]. The sub-endocardial viability index (SEVR) was derived from the reconstructed waveform and is defined as the ratio of the area under the diastolic portion of the curve to the systolic area under the curve in the recreated central pulse waveform [17]. Both aortic pulse pressure (aPP) and SEVR are determined, at least in part, by heart and large artery interaction.

Pulse Wave Velocity

Central pulse wave velocity was calculated from the waveform at the carotid and femoral (central) site. All waveforms were found on the right side of the body using applanation tonometry (except when the presence of a fistula required acquisition of waveforms from the opposite side of the body) (SphygmoCor; AtCor Medical, Sydney, Australia) and described in detail elsewhere [18].

Echocardiography

Cardiac output (CO), stroke volume, and end systolic volume (ESV) were assessed by two-dimensional echocardiography using an Aloka alpha-10 system (Tokyo, Japan). With subjects in the left lateral position, measurements were obtained using the four-chamber apical view. The interior of the left ventricle was traced manually during both end systole and end diastole. Volumes were measured using Simpson's rule. Stroke volume (SV) was calculated by subtracting end-diastolic volume (EDV) from ESV. CO was calculated as heart rate (HR) multiplied by SV. Three beats were measured and the average of the measurement was used in the analysis. All analyzed values were normalized for body surface area (BSA) using DuBois's formula [19]. Ejection fraction was calculated from the ventricular volumes and expressed as a percentage of ESV to EDV. Left ventricular mass (LVM) was determined using the Penn convention from M-mode images taken at the parasternal long-axis using methodology described in detail elsewhere [20].

Calculation of Arterial and Ventricular Elastances and Ea/Elv

Arterial elastance (EaI) was calculated as end-systolic pressure (ESP), determined from the SphygmoCor, divided by stroke volume index (SVI, SVI=SV/BSA). Left ventricular elastance (ElvI) was calculated as ESP/end-systolic volume index (ESVI, ESVI=ESV/BSA). The indexed volumes were used because body size affects these measures [10]. The ratio of EaI/ElvI represents indexed ventricular-vascular coupling.

Shuttle Walk Test

Physical performance was measured by distance walked during an incremental shuttle walk test (ISWT). The ISWT is a progressive test in which patients walk back and forth continuously over a 10 meter course. The walking speed is paced by a series of beeps that signal when the subject should have completed the 10 meter walk. The pace is progressively increased so that the walking speed at the end of each successive minute is ≥ to: 1.12, 1.54, 1.88, 2.26, 2.64, 3.02, 3.4, 3.78 miles per hour. The test was terminated when the subject was unable to complete the 10m course before the subsequent beep. The ISWT was performed on non-dialysis days, 18 to 30 hours after a previous dialysis session.

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Table 1. Subject Characteristics

	(n)
Smoking	
Current	12
Previous	18
Never	12
Hypertension	
Controlled	39
Uncontrolled	1
Normotensive	2
Reason for Terminating Walk Test	
Fatigue	8
Leg Pain	2
Inability to Maintain Pace	32
Diabetes	
Type I	1
Type II	13
None	28

Table 2. Cardiac Characteristics

Variable	Mean	Standard Deviation
SVI (ml/m^2)*	35.2	2.3
ESVI (ml/m^2)	24.1	1.7
COI (l/min/m^2)*	2.6	1.5
LVMI (g/m^2)	225	87
SEVR (%)	131.54	5
EaI (mmHg*m^2/ml)*	4.45	2.5
ElvI (mmHg*m^2/ml)	6.89	4.1
EaI/ElvI	0.82	0.7
Shuttle walk time (s)	251	120

SVI = stroke volume indexed to body size, **ESVI** = end-systolic volume indexed to body size, **COI** = cardiac output indexed to body size, **LVMI** = left ventricular mass indexed to body size, **SEVR** = sub-endocardial viability ratio, **EaI** = arterial elastance indexed to body size, **ElvI** = ventricular elastance indexed to body size, **EaI/ElvI** =the indexed coupling ratio, **Shuttle walk time** = amount of time walked during shuttle test, *denotes a significant correlation to shuttle walk time, $p<0.05$.

Statistical Analysis

Descriptive statistics are presented as mean ± standard error. Normality of distribution was assessed by using Shapiro-Wilk tests, and extreme outliers were removed before further analysis. Pearson's and Spearman's correlations were used to assess relationships between normally and non-normally distributed variables, respectively. Block regression was performed to examine the significance of individual arterial and cardiac variables to walking time; block 1 consisted of arterial variables (Ea, aPP, MAP, PWV) while block 2 contained ventricular variables (ElvI, SVI, COI, HR). We then performed the same block regression as previously described but added a third block for age in order to account for independent effects of aging upon walk time. Significance was set a $p<0.05$. Analysis was performed using Statistical Package for the Social Sciences (SPSS) version 19.0 (Chicago, IL).

Results

Subject Characteristics

This study includes a total of 42 subjects. Mean age was 44±5 yrs, and average BSA was 2.01±0.04 kg/m^2. The average vintage was 51±42 months (range = 1-177 months). Other subject characteristics are presented in Table 1.

Blood Pressures and Arterial Stiffness

Average brachial MAP was 95±15 mmHg, SBP was 137±3 mmHg and DBP was 75±2 mmHg. Mean aortic MAP, SBP and DBP were 93±2, 127±4 and 75±4 mmHg respectively. The mean central PWV was 9.6±0.6 m/s.

Cardiac Variables and Elastances

Cardiac variables and elastances are shown in Table 2.

Correlations

Shuttle walk time was inversely correlated to EaI (r=-0.424), central PWV (r=-0.385) and positively related to both indexed cardiac output (r=0.442) and indexed stroke volume (r=0.337, Figure 1 C), $p<0.05$ for all. The relationships between EaI and PWV and shuttle walk time are illustrated in Figure 1 A and B. The relationships between shuttle walk time and PWV/MAP (r=-0.297) and aortic pulse pressure (aPP, r=-0.276) did not reach significance, $p=0.06$ for both. There were no significant relationships between shuttle walk time and HR (r=-0.061), SEVR (r=-0.298), ElvI (r=-0.218), or the coupling ratio (r=-0.041), $p>0.05$.

Regression

Our block regression revealed that SVI (β=3.114, p=0.013) and PWV (β=-11.187, p=0.036) were significant determinants of shuttle walk time. When we controlled for age in our block regression, PWV remained a significant predictor of walk time, β=-14.68 and p<0.012.

Discussion

Our study generated several new and novel findings. Patients with ESRD in this cohort have an average Ea/ELV of 0.82. This value is not different from the 0.5 to 1.0 range found in a healthy population, suggesting ventricular-arterial coupling is maintained in a normal range [7]. However, the individual components, EaI and ElvI, were much higher than values observed in a healthy population, most likely due to the prevalence of hypertension and resultant increased end-systolic stiffness and reduction in cardiac performance observed in patients with ESRD [21]. In support of this notion, our group's average ejection fraction was 49%, which is above the clinical cut-off for heart failure (40%) but less than the mean ejection fraction of 60-70% of a young, healthy heart.

We also found a significant and inverse relationship between shuttle walk time and EaI,as well as shuttle walk time and central PWV, and a positive correlation of both COI and SVI with shuttle walk time. This suggests that higher levels of arterial load and stiffness negatively affect functional shuttle walk ability whereas higher stroke volume positively affects shuttle walk ability in this population. The age of the patient did affect our correlations, but the relationship between central arterial stiffness and walking time remained. This suggests that although age of the patient may impact some measures of arterial stiffness, and thus, affect walking ability, arterial stiffness itself is a predictor of walk time independent of age.

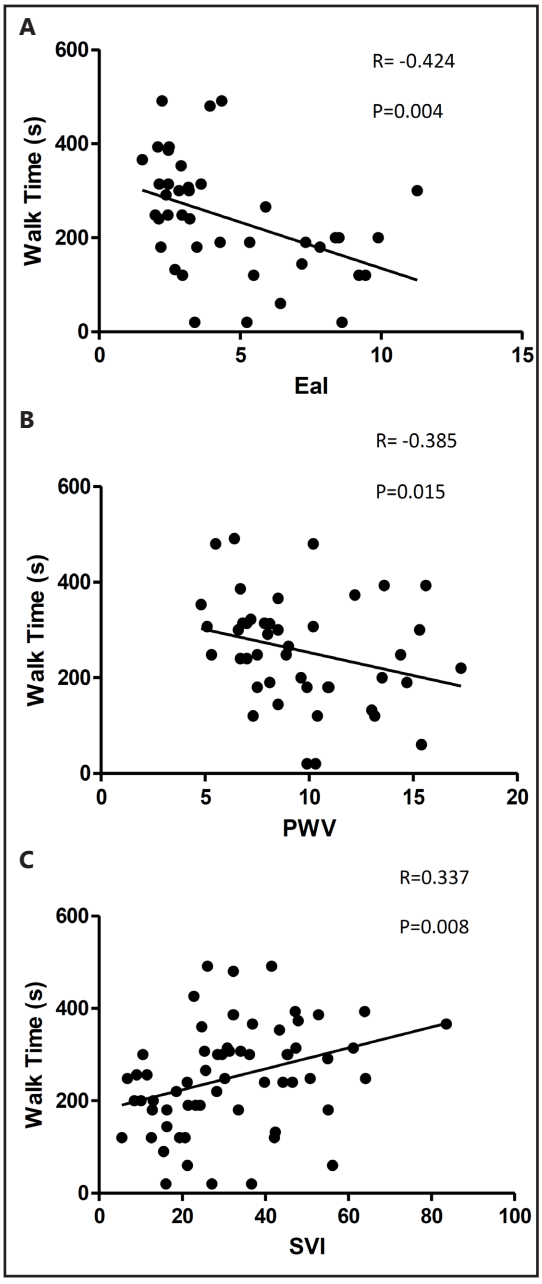

Fig. 1. A, B, and C. EaI and central PWV are inversely related to walking time in ESRD while SVI is directly correlated to shuttle walk time.

Previous work has compared heart function of ESRD patients to that of patients with heart failure [22]. Borlaug, et al. also report upon the importance of global cardiovascular reserve and its impact on ventricular-vascular interaction and exercise performance in heart failure [23]. The heart failure patients in this prior study exhibited impairment in many aspects of cardiovascular performance: chronotropic incompetence, endothelial dysfunction, vasodilation, and impaired contractility all contributed to reduced exercise tolerance [23]. This finding may be extended to understand the constellation of factors also affecting exercise tolerance in patients with ESRD. Our patients had very high resting EaI

and ElvI, themselves integrated measures of total arterial and heart function. Therefore, we may speculate that there is little ability to further augment arterial/ventricular elastance in order to accommodate physical work, i.e., walking. This study reinforces the idea that there is a cardiovascular phenotype common to patients with heart failure and ESRD. Along this line, left ventricular hypertrophy, caused by arterial resistance heightened by hypertension is also common in patients with heart failure with preserved ejection fraction. Left ventricular hypertrophy may reduce myocardial efficiency and compromise exercise tolerance (perhaps by reducing SV) in both populations. Our cohort does suffer from clinical levels of left ventricular hypertrophy [24]; clinical LVH is diagnosed at 106 g/m^2 for women and 114 g/m^2 for men, and our cohort's mean left ventricular mass index was greater than the established cut-off.

Amplified pulse waves caused by arterial stiffness have been found in normotensive patients with CKD [20]. Earlier work has shown that patients with early CKD also exhibit decreased aortic distensibility [22]. Furthermore, the reduction in aortic compliance was correlated to attenuated glomerular filtration rate [22] and increased incidence of vascular calcification in CKD [25]. Our data on patients with ESRD are consistent with these earlier reports showing increased arterial stiffness and arterial load in this patient population. Furthermore, markers of central stiffness and arterial load were predictors of shuttle walk time in this population. This relationship between arterial stiffness and walking ability has also been demonstrated in patients with other cardiovascular diseases, such as peripheral arterial disease [26, 27], and adds to the similarities between ESRD patients and other types of CVD. Our data add to the growing body of literature supporting the inclusion of measures of arterial stiffness in exams and as targets for intervention in order to improve quality of life for individuals with ESRD.

COI and SVI were directly related to shuttle walk time in this study. Because HR was not related to walking time ($p>0.05$), we propose that the ability of a more compliant arterial system may allow generation of a higher SV and this may lead to the ability to increase functional walking ability. The results of the multiple regression analysis support this notion, as SVI and PWV were the only variables retained as significant predictors of walking time, explaining 27% of the variance. Considering that stiff arteries result in increased afterload thus impeding ejection, this may affect the ability of the left ventricle to generate sufficient SV [8] and distribute blood to the periphery. This is a plausible physiologic explanation for the association between SVI, EaI, central PWV and walking time.

Further support for this notion is provided by Chantler et al. [28], who concluded that, in a large and apparently healthy subject population, there is an inverse relationship between EaI and the use of the Frank-Starling mechanism during exercise, such that individuals with the highest EaI also had the lowest SVI and EDVI [28] . In contrast to this study, our cohort was evaluated only at rest. It does appear, though, that patients with ESRD cannot offset reductions in SV by increasing arterial O_2 extraction, as was the case of the group healthy adults in the study by Chantler et al. Consistent with patients with ESRD, patients with heart failure also have peripheral limitations that contribute to reduced capacity during exercise tasks [29], and these are compounded by limited arterial-venous O_2 extraction [30]. Hence, exercise tolerance is low and skeletal muscle atrophy, weakness, and fatigue all contribute to this endpoint. Low exercise tolerance, skeletal muscle atrophy, weakness and fatigue are also prominent features in ESRD, and previous work suggests that patients with ESRD, like those with heart failure, are also limited by peripheral O_2 extraction ability [31].

Central arterial stiffness is a strong prognostic indicator of cardiovascular mortality in renal patients [32]. It also correlates more directly to the load imposed on the left ventricle by arterial stiffness as it represents the immediate impedance to ejection [33]. For this reason, central PWV is a more important mediator of ventricular-vascular coupling than is brachial pressure, and these data support the idea that it can also affect blood delivery and impact exercise tolerance. When controlled for MAP, the relationship between central PWV and walking time lost significance ($p=0.06$), perhaps suggesting that other structural physiological alterations (such as central calcification) are primarily pressure-driven

determinants of walking time in our cohort. This also indicates that there is a pressure-driven shift of load onto the stiffer collagen versus more compliant elastin fibers within the arterial wall [34], opposing ventricular ejection. Not surprisingly, the average central PWV of this group of patients with ESRD is higher than the established norm of 7.2 m/s that one would expect in an otherwise healthy population of similar age [13].

The physiologic and structural arterial stiffening described previously should also cause an augmentation of aortic pulse pressure [4]. Both aPP and PWV have prognostic value in cardiovascular disease, and are recognized as cardiovascular risk factors in hypertensive and CKD patients [13, 25]. Increased PWV is also correlated to compromised renal function in CKD [35, 36] and plays a role in mediating the pulsatile component of EaI through its effect on SV. Though we did not find a significant relationship between aPP and shuttle walk time, we did find predictive value in EaI, an integrated measure of total arterial load that includes time intervals, peripheral resistance, and aortic impedance. However, arterial stiffness and SVI appear to be the most important cardiovascular mediators of walking time in ESRD.

Future Directions and Study Limitations

Both the heart and arteries are functionally affected by ESRD. Because exercise interventions have been successful in improving ventricular capabilities in coronary artery disease populations [37], individuals in heart failure [5], and ESRD patients, [38, 39] further investigation should examine the potential role ventricular and vascular cross-talk may play in mediating both overall cardiovascular morbidity as well as functional improvement in ESRD . Indeed, in other patients whose walking ability is also related to arterial stiffness (patients with peripheral arterial disease), a home-based walking program improved both mobility and quality of life [40], and a 12-week exercise intervention attenuated overall cardiovascular morbidity and mortality [41].

The response of the ERSD patient to endurance exercise has not been completely elucidated. Future studies may explore the role of exercise training in reducing ventricular and vascular stiffness in order to enhance functional abilities, reduce cardiovascular events, and improve quality of life in ESRD.

A few limitations of this study should be noted: we used the equation 0.9 x SBP to estimate end-systolic pressure, an equation that has been validated at rest in other populations but not specifically tested in ESRD [7]. We also estimated V_0 to be equal to zero and non-invasively measured cardiac volumes. It is also important to note that this is a cross-sectional study, and correlation (not causation) is reported.

Conclusion

EaI, and central PWV are inversely related to physical performance (shuttle walk time) in individuals with ESRD, while SVI is positively related to shuttle walk time. This is similar to the cardiovascular phenotype in other clinical populations where augmented arterial stiffness adversely affects exercise and functional performance. This study highlights the importance of managing the mediating influence of arterial stiffening on functional capacity in individuals with ESRD and suggests a role for exercise as therapy in this population as well.

Conflict of Interests

The authors of this study have no conflict of interests to report.

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