Effects of Arterial Stiffness In Patients With End-Stage Renal Disease On Hemodialysis

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THESIS

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This thesis is dedicated to my husband Sundar Kannabiran and my daughters Veena and Savita without whom it would never have been accomplished. Their endless support and enthusiasm made me continue this endeavor with great zest and reach my goal.

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LIST OF ABBREVIATIONS

CKD	Chronic Kidney Disease
GFR	Glomerular Filtration Rate
HTN	Hypertension
CVD	Cardiovascular Disease
ESRD	End Stage Renal Disease
LV	Left Ventricle
PWV	Pulse Wave Velocity
AIx	Augmentation Index
EBCT	Electron beam computed tomography
SBP	Systolic blood pressure
DBP	Diastolic blood pressure
RPP	Radial Pulse pressure
MAP	Mean arterial pressure
URR	Urea reduction ratio
PTH	Parathyroid hormone
ECG	Electrocardiogram
APP	Aortic pulse pressure
CAD	Coronary artery disease
PVD	Peripheral vascular disease
CVA	Cerebrovascular accident

SUMMARY

Cardiovascular disease is the leading cause of morbidity and mortality in patients with end stage renal disease (ESRD). Although arterial stiffness is now recognized as an independent predictor of cardiovascular mortality in ESRD in Caucasian population, it is unknown if increased arterial stiffness is a risk factor for adverse cardiovascular outcomes in minorities. We therefore conducted a prospective study to study the measures of arterial stiffness (pulse wave velocity, PWV) and reflected wave (augmentation index, Aix) in a predominantly minority cohort of 77 patients with ESRD on hemodialysis and investigate the role of arterial stiffness in cardiovascular morbidity and all- cause mortality.

PWV and AIx were determined from arterial waveforms recorded by SphygmoCor® device. 90% of measurements were taken immediately prior to dialysis sessions. Cardiovascular events were defined as either new onset myocardial infarction/congestive heart failure, arrhythmia related to ischemic cardiomyopathy/acute cerebrovascular event/peripheral vascular disease requiring medical or surgical intervention and this information was gathered from patient interviews and medical chart review. In this cohort, 72% were African Americans (AA), 24% Hispanics, and 4% were non-Hispanic whites. Mean age was 55 yrs; 61 % were male. Major causes of ESRD were diabetes (58 %) and hypertension was present in 91 %. Mean duration of dialysis was 41 mos. Mean PWV was 11 m/sec and mean AIx (corrected for heart rate ***75*** beats/min) was 24% in this cohort. All patients were followed for a mean of 36 months. A total of 4 fatal and 24 non-fatal cardiovascular events which included 15 cardiovascular events and 9 cerebrovascular events were recorded in 19 patients. PWV was elevated in this group (13.8 vs. 10.4m/s) in the group as compared to the group who did not have composite outcome. P< 0.047) On the basis of cox analysis, PWV emerged as significant predictor of composite outcome- cardiovascular event and/ or all- cause mortality.

I. INTRODUCTION

A. Background

Chronic kidney disease (CKD) has become a global pandemic affecting millions of individuals worldwide. According to USRDS 2012 annual report, the prevalence of CKD has increased 30% between 2000 and 2007 and is expected to increase in the coming years. This increasing prevalence of ESRD imposes incalculable human suffering and causes significant burden to the health care costs. Studies have shown that patients with end stage renal disease are 8 times more likely to die within the first 3 years of initiation of dialysis as compared to their normal counterparts.

Cardiovascular disease is the leading cause of death among patients on dialysis. Recent USRDS data reported approximately 40% of deaths in dialysis patients were due to cardiovascular diseases. Foley et al in his cross sectional study of hemodialysis patients showed that about 74% had evidence of left ventricular hypertrophy, 32% had left ventricular dilatation and 15% had evidence of systolic dysfunction at the time of initiation of hemodialysis. He also reported that the incidence of new onset congestive heart failure was about 11% per year and new onset ischemic heart disease was about 5% per year in these patients. It is apparent from these studies that these patients are at high risk for acute cardiovascular events at the time of initiation of dialysis. This heightened risk of new cardiovascular event is increased several fold, when initiated on dialysis. Although patients with ESRD develop traditional atherosclerotic disease (i.e. plaque formation and calcification of the arterial intima leading to vascular occlusion), many develop cardiovascular complications without any clinically significant atherosclerotic disease. In recent years, several studies have shown that medial calcification of the vessel walls contributes to increased cardiovascular risk. It is postulated that several factors unique to this population, such as secondary hyperparathyroidism, chronic inflammation and oxidative stress contribute to increased vascular stiffness. It is possible that these factors along with their underlying co - morbid conditions e.g. diabetes increases the cardiovascular risk several fold. Large arteries that are compliant

in the young, undergoes various histological changes with passage of time resulting in stiffening of these vessels. This causes early return of the reflected wave from the peripheral reflecting sites to the heart during systole when the ventricle is still ejecting blood. This mechanism augments ascending aortic systolic pressure and pulse pressures, an effect that increases arterial wall stress, potentiates development of atherosclerosis, elevates left ventricular (LV) afterload, thereby increasing LV oxygen demand and decreasing coronary perfusion. The potential consequences are increased LV mass, subendocardial infarctions and ultimately serious cardiovascular events.

Pulse Wave Velocity and Augmentation Index are two measures of arterial stiffness that have been investigated in various diseases and are shown to be independent predictors of cardiovascular and all- cause mortality. London et al in their cohort of 241 dialysis patients, showed a strong positive association between increased pulse wave velocity / augmentation index and mortality, particularly cardiovascular mortality. After adjustment for all confounding factors, the risk ratio for each 10% increase in augmentation index was 1.51 for all- cause mortality and 1.48 for CV mortality. Similarly, the odds ratio for PWV> 12 versus < 9.4 m/s was 5.4 for all- cause mortality, and 5.9 for CV mortality. This study provided the first direct evidence, that in patients with ESRD, increased aortic stiffness determined by pulse wave velocity and augmentation index was a strong predictor of all- cause, particularly CV mortality. Similar results were reported by Shoji et al who showed increased pulse wave velocity as an important predictor of cardiovascular mortality. However, many of the published studies were done in predominantly in Caucasian and Asian patients in low risk population where the incidence of diabetes was very low. In US, diabetes is the leading cause of end stage renal disease, followed by hypertension. Among US population, racial and ethnic disparities continue to exist and prevalent rate of ESRD is 4.2 times higher in African –Americans compared to Caucasians. Though the prognostic value of PWV velocity has been determined, much is still unknown regarding the risk factors for development of arterial stiffness in patients with ESRD, and kidney disease in general. Several factors have been implicated in the development of vascular stiffness. In addition to traditional risk factors like diabetes, hypertension and

hypercholesterolemia, others like vascular calcification, chronic inflammation and endothelial dysfunction have been postulated to play a role in the development of vascular stiffness. Haydar et al showed significant correlation between increased pulse wave velocity and EBCT generated calcification scores in a group of 55 patients who had varying degrees of renal insufficiency ($r = 0.65$, $p - 0.0001$) Studies have shown that young healthy African Americans have decreased arterial compliance compared to young Caucasians suggesting that certain genetic traits and inherent vascular abnormalities may influence arterial compliance. Given the high prevalence of end stage renal disease in African Americans, it is possible that this altered arterial compliance may play a vital causative role in the development of cardiovascular disease in this population.

To date, no study to our knowledge has investigated non-traditional risk factors for arterial stiffness in ESRD patients on dialysis in the United States. This study intends to look at the relationship between various clinical parameters and measures of arterial stiffness –pulse wave velocity PWV, augmentation index AIx in a cohort of patients on hemodialysis. The study will also investigate the role of arterial stiffness in predicting cardiovascular morbidity and all-cause mortality.

II. METHODS

A. Study Design

Patients who were 18 years of age and above and on hemodialysis for at least 3 months at the University of Illinois dialysis center were eligible for participating in the study. Patients with a history of a cardiovascular event in the preceding 6 months - acute myocardial infarction, acute congestive failure, acute arrhythmia related to acute coronary event or coronary revascularization in the preceding 6 months, patients who had end stage renal disease secondary to failed kidney transplant, patients who had femoral arteriovenous access for dialysis, patients who had atrial fibrillation, patients who had severe peripheral vascular disease, or had history of femoral- popliteal bypass surgery or limb amputation, patients who were unable to consent for the study, and patients who were of age 85 years and above were excluded from the study. Out of 110 patients were eligible, 77 patients consented for the study.

This is a prospective longitudinal study with baseline measurements and follow up for minimum of 3 years. The study protocol was approved by the University of Illinois at Chicago Institutional Review Board and the research was conducted in accordance with the ethical principles of the Declaration of Helsinki.

B. Study Measurements

1. Clinical Data

Clinical data was obtained by questionnaires administered to the subjects at the time of study entry. Further clinical data was collected from their computerized medical records in the system.

Blood pressure and anthropometric measurements were obtained prior to performing the study measurements. Study measurements include pulse wave velocity and augmentation index which are validated measures of arterial stiffness. These measurements were obtained using Sphygmocor® tonometer. After brief physical exam, the study measurements were obtained with the patients in supine position. These

measurements and data collection were yearly for 3 years and all subjects were followed up for a period of 3 years.

2. Monitoring of Outcomes

The events of interest include mortality, cardiovascular or cerebrovascular events, and peripheral vascular event. Information regarding these events were gathered from the patient and medical records. They were monitored for occurrence of these events at 6-month intervals by examining the patient's medical record in the computer and gathering information from the patient.

3. Mortality

Cause of death was obtained from review of medical records of the patient and were classified as either cardiovascular, cerebrovascular, peripheral vascular, or other depending on the cause.

4. Cardiovascular and Cerebrovascular Events

Determination of these events were based on the diagnosis given in the subject's medical record. Cardiovascular events include acute myocardial infarction, new-onset congestive heart failure, new-onset cardiac arrhythmia, new-onset valvular disease (not including endocarditis). Cerbrovascular events include cerebrovascular accident and transient ischemic attack. Peripheral vascular disease events include worsening limb claudication, loss of tissue from ischemia, and amputation.

5. Description of Study Measurements

a. Brief Physical Exam and Blood Pressure

After a brief physican exam, blood pressure readings were taken after 15 minutes of recumbency in the arm contralateral to the subject's arteriovenous shunt using an appropriate cuff size. Phase 1 and phase 5 of the Korotkoff sounds was used to measure systolic and diastolic blood pressures,

respectively. The mean arterial pressure (MAP) was calculated as follows:

$$MAP = DBP + (SBP - DBP)/3$$

Three blood pressure determinations was measured at 2 minute intervals and average of 3 readings was used for the study. Similarly heart rate was also determined 3 times at 2 minutes intervals, with the average reading taken for the study.

b. Measurements of Arterial Stiffness: Aortic Pulse wave velocity (PWV), Augmentation Index (AIx)

Next, the two measures of arterial stiffness were determined at the baseline visit. These measures namely pulse wave velocity and augmentation index are described in the following section

Pulse wave velocity – Aortic pulse wave velocity (PWV) was calculated from carotid artery pressure waveform and the femoral artery pressure waveform. A 3-lead orthogonal ECG was used for this exam. The heart rate was determined from this ECG. Distance from neck to navel, and from navel to groin was measured. Aortic PWV was determined using transcutaneous Doppler flow recordings and foot to foot method using the Sphygmocor Pulse-Wave Velocity device (Atacor Medical, Westmead, Sydney, Australia). Two simultaneous Doppler flow tracings were taken at two different sites – the aortic arch and the femoral artery in the groin – using a non directional Doppler unit with a hand held probe. The recording speed was set at 100-200 mm/s. For aortic flow, the transducer was placed in the suprasternal notch. If a high frequency signal cannot be recorded at this location, it was recorded from the common carotid artery on the contralateral side of the arteriovenous fistula or graft. The time delay (t) was measured between the feet of the flow waves recorded at these different points and was averaged over 10 beats. The distance (D) traveled by the pulse wave as measured over the body surface as the distance between the two recording sites. When distance (D) was measured from the carotid artery, the distance from the suprasternal notch to the carotid was subtracted. PWV was calculated from the following formula:

$$PWV = D/t.$$

Augmentation index (AIx)– Radial artery pressure waveforms were attained in the supine position using applanation tonometry. Using generalized validated transfer function, a central aortic pressure waveform was created using aforementaioned radial artery waveform. Augmentation index provides a measure of the contribution of wave reflection pressure (i.e augmented pressure) to systolic BP relative to total pulse pressure.It was calculated as the ratio of amplitude of the pressure wave above its systolic shoulder (i.e. the difference between early and late systolic peaks of the arterial waveform), to the total pulse pressure expressed as a percentage (P2-P1/Pulse Pressure*100). Because augmentation index is influenced by HR, their values were standardized to heart rate of 75 bpm by correction factor inbuilt within the system.

C. Statistical Methods

The outcomes events studied were cardiovascular events and all- cause mortality. Continuous variables were expressed as means +/- SD and categorical variables were described using the frequency method. Univariate linear regression analysis was used to identify significant predictors of pulse wave velocity and augmentation index. Multivariate linear regression analysis was used to identify the significant clinical predictors after adjustments of confounding factors. Student –T test was used to find the differences in the means of pulse wave velocity and augmentation index between the group who had composite outcome and the group who did not have outcome. Survival curves were studied by Kaplan-Meier analysis and compared by log rank test. Prognostic factors of survival were identified using Cox proportional hazards analysis. The cohort was divided into 3 groups according to PWV < 8 m/s in the lower tertile, between 8 and 12 in the second tertile and > 12 in the upper tertile. All analyses were performed using SAS version 9.1.3 and were considered statistically significant at $p<0.05$.

III. RESULTS

A. Participant Characteristics

The mean age was 55 years and most (61%) participants were males. 72% were African –Americans, 24% were Hispanics and 4% were Caucasians. 58% were diabetic and 91% had hypertension. 27% had history of cardiovascular disease i.e. acute myocardial infarction, acute congestive heart failure or history of coronary revascularization. Mean number of months on dialysis was 41 months. 70% were on antihypertensive meds that included ACE-I, angiotensin receptor blockers, diuretics, beta blockers, alpha blockers, calcium channel blockers. The mean [standard deviation (SD)] systolic and diastolic blood pressure (BP) was 138 (24) and 76 (14) mmHg, respectively. Mean body mass index (BMI) was 28 (7) kg/m^2. 70% were receiving erythropoietin analogs and 94% were either on active vitamin D analogs -calcitriol or paracalcitol. The average calcium – phosphorus product was 46 and average Hemoglobin A1C was 6.2 in this cohort. All patients were dialyzed using the standard hemodialysis technique, including the same high flux dialyzers, bicarbonate dialysate and the duration of hemodialysis session was individually tailored to achieve adequate volume control and attain urea reduction ratio > 65%. 77% achieved URR > 65%. (Table I) All subjects provided informed written consent to participate in the study, approved by University of Illinois Institutional review board.

TABLE I

BASELINE CHARACTERISTICS

Characteristic	N - 77	Characteristic	N - 77
Age (yrs)	55 ± 14	Cholesterol(mg/dl)	147 ± 40.02
Male Gender (%)	61	LDL(mg/dl)	79 ± 31.59
Race (%) AA Hispanics Whites Others	 72 23 4 1	Smoking (%) (Former/Current)	43
BMI (kg/m^2)	28 ± 7	Statin use (%)	43
Diabetes (%)	58	RAAS agent use (%)	68
Hypertension (%)	91	Beta blockers (%)	78
Known CVD (%) (CVD= MI or CHF)	27	PWV (m/sec)	11.1 ± 4.60
SBP(mm Hg)	138 ± 24	Aix (adjusted for HR)	24 ±11.53
DBP(mm Hg)	76± 14	ESA use (%)	70
PP(mm Hg)	62 ± 21	Active Vitamin D use (%)	94
Dialysis Vintage (mon)	41± 48		
Calcium(mg/dl)	8.5 ± 8.52		
Phosphorus(mg/dl)	5.5± 5.49		
Ca x Phos	46 ± 12.31		
Hemoglobin A_1C	5.8± 1.62		
Hb (g/dl)	11.7± 1.19		
S.Albumin (g/dl)	3.5± 0.37		
URR > 65 (%)	77± 8.39		

a. Continuous variables are expressed as means with SD and the categorical variables are measured as %.

B. Predictors of Pulse Wave Velocity and Augmentation Index

Table II shows the results of simple linear regression analysis of various clinical parameters with measures of arterial stiffness- PWV and Aix determined at the time of study entry. According to simple regression analysis, pulse wave velocity was significantly associated with age ($p < 0.0001$), diabetes ($p < 0.0001$), smoking ($p < 0.05$), systolic blood pressure ($p < 0.005$), radial pulse pressure ($p < 0.0001$), aortic pulse pressure ($p < 0.0001$), URR ($p < 0.05$), hemoglobin A1C ($p < 0.05$), and prior history of cerebro-cardiovascular disease ($p < 0.05$). However serum phosphorus was negatively associated with pulse wave velocity suggesting that low serum phosphorus may signal malnutrition, a known independent predictor of morbidity and mortality in kidney disease. Multivariate linear regression analysis was performed with clinical variables as independent covariates and PWV as dependent variable. (Table III) Only age ($p < 0.05$) and diabetes ($p < 0.05$) remained significantly associated with pulse wave velocity in this model. Similar analysis was done to identify the relationship between clinical parameters and the augmentation index. In the simple regression model, age, gender, presence of diabetes, systolic blood pressure, diastolic blood pressure, pulse pressure, aortic pulse pressure, smoking and URR –measure of dialysis adequacy were all significantly associated with augmentation index ($p < 0.05$). However, in the multivariate regression model, augmentation index when corrected for heart rate was significantly associated with gender, with women having greater augmentation index than men. (Table IV, Table V, Figure 1, Figure 2)

TABLE II

UNIVARIATE REGRESSION ANALYSIS OF PULSE WAVE VELOCITY

Variable	β estimate	Std Error	P value
Age (years)	0.15	0.03	<0.0001
Race(whites vs. AA)	-1.4	1.17	0.2
Body Mass Index (kg/m^2)	0.06	0.07	0.41
Gender (M/F)	1.03	1.07	0.3
Diabetes	4.09	0.96	<0.0001
HTN	0.69	1.8	0.7
S.Albumin (g/dl)	-0.6	1.4	0.6
S.Calcium (mg/dl)	0.13	0.6	0.8
S.Phosphorus (mg/dl)	-0.64	0.03	0.05
Ca x Phos	-0.09	0.04	0.04
Hemoglobin(g/dl)	-0.64	0.44	0.1
Smoking	1.79	1.1	0.02
PTH (pg/mL)	-0.001	0.001	0.3
S.Cholesterol (mg/dl)	-0.02	0.01	0.07
SBP	0.06	0.02	0.005
DBP	-0.06	0.03	0.09
RPP	0.11	0.02	<0.0001
APP	0.12	0.02	<0.0001
A1C	0.83	0.3	< 0.05
URR	0.12	0.06	0.04
Prior CVD(CAD or CVA or PVD)	2.56	1.05	0.03

a. P value <0.05 is considered statistically significant.

TABLE III

MULTIVARIATE REGRESSION ANALYSIS OF PULSE WAVE VELOCITY

Variable	β estimate	Std Error	P value
Age	0.08	0.04	0.04
Diabetes	2.53	1.07	0.02
Smoking	0.63	0.73	0.40
Albumin	0.41	1.43	0.77
Phosphorus	-0.22	0.32	0.49
URR	0.04	0.06	0.48
MAP	0.02	0.03	0.46

a. P value < 0.05 is considered statistically significant.

TABLE IV

UNIVARIATE REGRESSION ANALYSIS OF AUGMENTATION INDEX

Variable	β estimate	SE	P value	Variable	β estimate	SE	P value
Age (years)	0.03	0.09	0.001	SBP	0.14	0.02	0.01
Race	-2.65	3.07	0.4	DBP	0.06	0.04	0.5
BMI (kg/m^2)	-0.02	0.07	0.9	RPP	0.16	0.02	0.01
Gender (M/F)	9.7	1.1	0.0002	APP	0.01	0.05	<0.001
Diabetes	5.3	1.04	0.05	A1C	-0.06	1.2	0.9
HTN	3.64	4.6	0.42	URR	0.44	0.1	0.004
S.Albumin (g/dl)	0.19	1.5	0.9	PTH (pg/mL)	-0.001	0.001	0.6
S.Calcium (mg/dl)	-0.65	0.7	0.7	Cholestrol (mg/dl)	0.02	0.01	0.6
S.Phosphorus (mg/dl)	-0.53	0.3	0.5	Smoking	1.03	1.1	0.02
Hemoglobin(g/dl)	-1.2	0.4	0.3				

a. P value < 0.05 is considered statistically significant.

TABLE V

MULTIVARIATE REGRESSION ANALYSIS OF AUGMENTATION INDEX

Variable	β estimate	Std Error	P value
Age	0.2	0.09	0.3
Gender	8.09	2.8	0.006
Diabetes	1.9	2.6	0.5

a. Model included age, gender, race, diabetes, HTN, s. albumin, s. phosphorus, hemoglobin, smoking, parathyroid hormone levels, dialysis adequacy and pulse pressure.

b. P value < 0.05 is considered statistically significant.

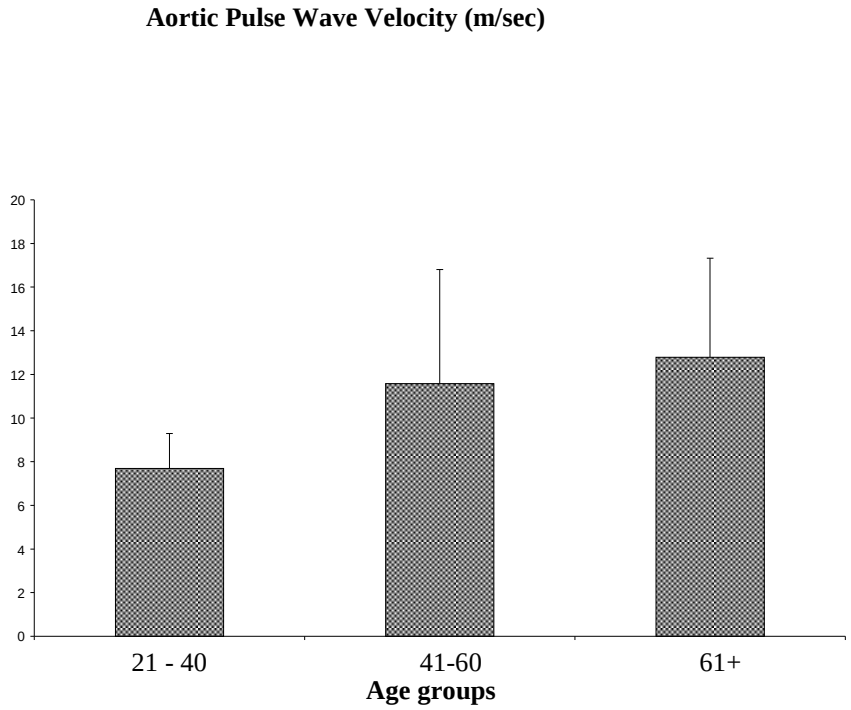

Figure 1. Relationship between age and the pulse wave velocity.

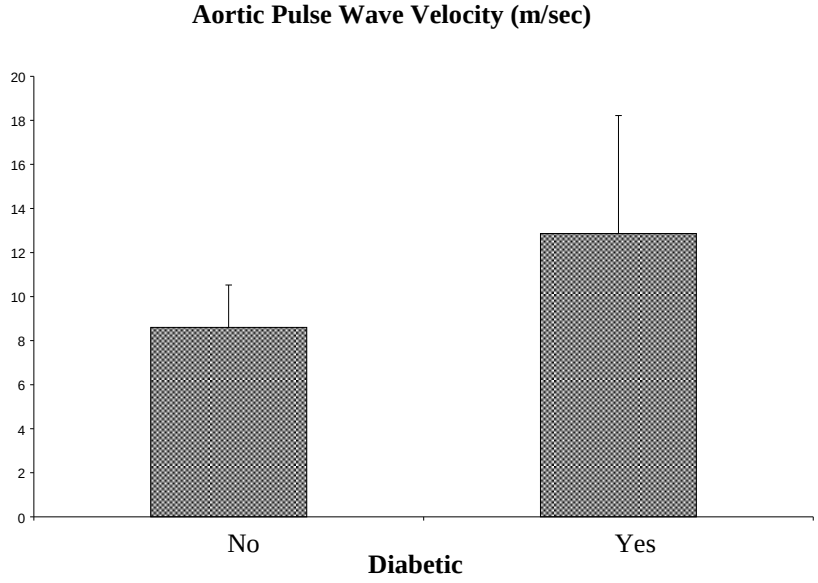

Figure 2. Relationship between diabetes and the pulse wave velocity.

C. Cardiovascular Outcomes

All subjects were followed for a mean of 36± 9 months. In our cohort, 19 subjects had a total of 4 fatal events and 24 non-fatal cardiovascular events. T-test procedure was used to find if there is statistically significant difference between the means of PWV in 2 groups- subjects who had composite outcome- non fatal cardiovascular event and/ or all- cause mortality and subjects who did not have composite outcome (Table VI). Similar T test analysis was used to find if there is significant difference in augmentation index between the two groups (Table VII). Although there were fewer cardiovascular events in our study cohort, aortic PWV was significantly elevated in patients who had either non- fatal cardiovascular event and / or all- cause mortality, compared to the patients who did not suffer from any of these events. There was no difference in augmentation index between the two groups. Logistic regression analysis was performed using presence or absence of cardiovascular event as dependent variable. In this model which included age, PWV, diabetes, history of CVD, race, gender and Aix, PWV was independently predictive of cardiovascular event (Table VIII).Kaplan – Meier survival cures (Figure 3) showed that the group in lowest tertile of PWV had better event free rate as compared to the other groups. Comparisons between survival curves using log rank test was statistically significant. Univariate cox analysis identified age, diabetes, history of cardiovascular disease, pulse wave velocity, serum phosphorus and hemoglobin as significant variables. In multivariate Cox analysis, (Table IX) the significant covariate retained in the model was pulse wave velocity after stepwise regression. Age, diabetes, serum phosphorus and hemoglobin were not significant in the model. Prior history of cardiovascular disease was significant in the model, which after step wise regression, did not reach statistical significance.

TABLE VI
PULSE WAVE VELOCITY IN SUBJECTS WITH AND WITHOUT COMPOSITE OUTCOME

Outcomes	No of participants	PWV (mean)	P value
Yes	19	13.7	0.003
No	58	10.2	

a. P value < 0.05 is considered statistically significant.

TABLE VII
AUGMENTATION INDEX IN SUBJECTS WITH AND WITHOUT COMPOSITE OUTCOME

Outcomes	No of participants	AIx (mean)	P value
Yes	19	25.5	0.4
No	58	23.5	

a. P value < 0.05 is considered statistically significant.

TABLE VIII

LOGISTIC REGRESSION ANALYSIS FOR CARDIOVASCULAR EVENTS AND /OR ALL CAUSE MORTALITY

Variable	Estimate	SE	P value
age	0.0220	0.0317	0.4875
race	0.4945	0.7807	0.5264
Diabetic	0.3040	0.8263	0.7129
Gender	-0.0859	0.7615	0.9102
History of CVD	0.7658	0.7582	0.3124
PWV	0.6915	0.3380	0.0408
Aix__at_HR75	0.2083	0.1176	0.0765

a. P value < 0.05 is considered statistically significant.

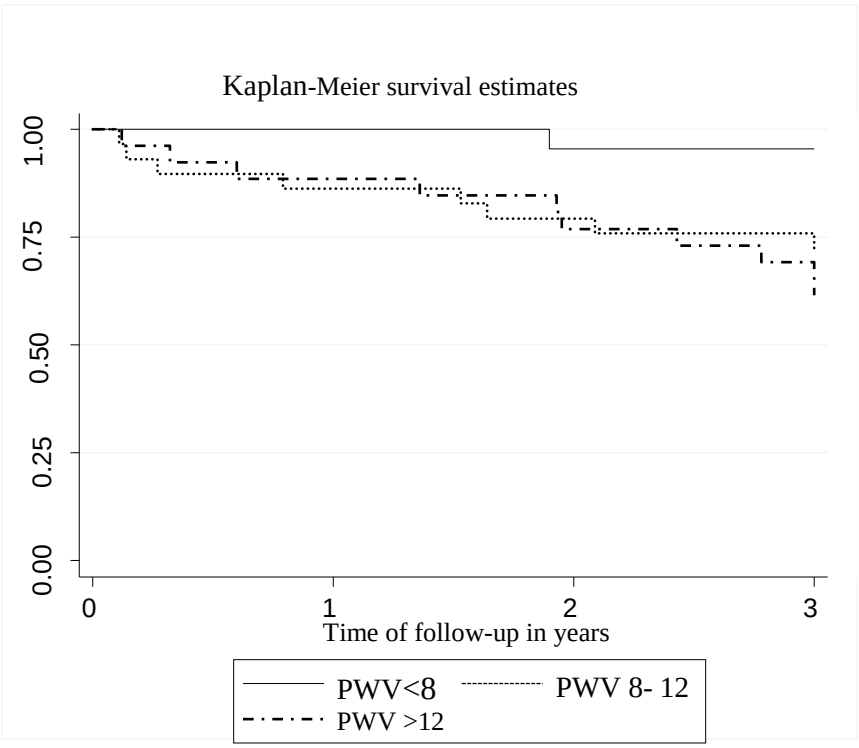

Figure 3. Kaplan Meier Survival Curves.
a. Probablitites of overall survival without cardiovascular event and/or all cause mortality according to pulse wave velocty(PWV) divided into tertiles.

TABLE IX

MULTIVARIATE COX REGRESSION ANALYSIS OF CARDIOVASCULR EVENTS AND/OR ALL-CAUSE MORTALITY

Variable	Hazard Ratio	95% CI limits	P value
Age (y)	1.02	1.00 - 1.1	0.35
Diabetes	1.55	0.5 -- 5.3	0.50
Prior CV D	1.53	0.5 ---4.8	0.50
PWV (m/s)	1.10	1.00 – 1.2	0.15

a. CVD- Cardiovascular disease, PWV- Pulse wave velocity.

IV. CONCLUSIONS

Cardiovascular disease remains one of the most important causes of morbidity and mortality among patients with end stage renal disease on dialysis. Many of these patients are at risk of cardiovascular disease due to the underlying disease – diabetes, hyperlipidemia and hypertension. However when they develop chronic kidney disease, they are exposed to an array of metabolic disturbances unique to chronic kidney disease. Many studies have shown increased uremic toxins, accelerated arterial calcification, dyslipidemia, chronic inflammation, activation of renin angiotensin axis and disordered bone metabolism hasten the decrease in arterial compliance, hence result in increased arterial stiffness. There is ample evidence to show that increased arterial stiffness is an independent predictor of all cause and cardiovascular mortality in patients with chronic kidney disease, including dialysis. Pulse wave velocity is one simple measure that can be used to measure arterial stiffness in routine clinical settings. Carotid-femoral pulse wave velocity has been shown to be a better measure of arterial stiffness than brachial ankle velocity as it tends to accurately reflect central aortic pressures which are clinically more significant in understanding the cardiovascular stress imposed by increased arterial stiffness. Earlier studies have investigated the role of various clinical parameters in predicting increased arterial stiffness and have consistently shown age and pulse pressure are significantly associated with pulse wave velocity. In our study, pulse pressure was not included as predictor in our multivariate analysis, as many studies have shown elevated pulse pressure results from increased arterial stiffness. In our multivariate analysis, age and diabetes were significant predictors of pulse wave velocity which is consistent with previously published literature. With advancing age, arteries undergo various histological changes like increase in collagen content and decrease in elastin content. With upsurge in the prevalence of ESRD population, our dialysis patients tend to be older and live longer. This places them at increased risk of cardiovascular disease. Similarly, with recent epidemic rise in the incidence of diabetes, this is becoming an increasingly important risk factor of cardiovascular disease. Hyperglycemia per se causes structural changes in vessels by cross linking of collagen and glycation of elastin and collagen which leads to

decreased vascular compliance. Other important clinical parameters like serum calcium levels, calcium-phosphorus product, and time on dialysis did not show any significant association with pulse wave velocity or augmentation index. Serum albumin, phosphorus and hemoglobin showed inverse association with pulse wave velocity. Lower serum albumin has been shown to be associated with increased mortality in ESRD population. Similarly low phosphorus may also indicate malnutrition. In our study, a higher hemoglobin level was associated with lower pulse wave velocity. However there is adequate data to show that high hemoglobin levels portend increased cardiovascular risk. Similarly lower hemoglobin is also associated with increased mortality. It is possible that hemoglobin alters the viscosity and induces changes in endothelial function which may influence the pulse wave velocity. It was interesting to note that augmentation index was not influenced by age, hypertension or diabetes. Females tend to have higher augmentation index due to the influence of height on the augmentation index. This has been validated in many studies. During follow up for 3 years, patients who had high pulse wave velocity at baseline had recurrent cardiovascular events including fatal events. Our results also confirmed PWV as an independent predictor of cardiovascular event and/or all-cause mortality. This strongly suggests that, when patients with significant cardiovascular disease exhibit increased pulse wave velocity, they are at increased risk of recurrent cardiovascular events. Arterial stiffening as measured by increased pulse wave velocity was independently associated with significant cardiovascular disease and /or all- cause mortality independent of age, diabetes and prior cardiovascular disease. Our study cohort experienced fewer cardiovascular events than previous studies which may be related to easy access to cardiovascular imaging and early intervention at the tertiary medical center. In spite of low event rates, our group with composite outcome had higher pulse wave velocity at baseline. This highlights the role of arterial stiffness in risk stratification of cardiovascular disease in addition to being an independent predictor of cardiovascular morbidity and mortality in dialysis patients.

In conclusion, pulse wave velocity is easily measurable using a small bedside device. This measure provides a composite measure of arterial stiffness which results from several clinical and metabolic factors in chronic kidney disease. Age and diabetes are very important determinants of pulse wave velocity and increased pulse wave velocities at baseline portend increased cardiovascular risk in dialysis patients. This measure of arterial stiffness is an important prognostic indicator of cardiovascular disease and may provide better risk stratification and early intervention in these high risk patients.

V. LIMITATIONS

There are some limitations to this study. We were not able to find significant racial differences between pulse wave velocities as our study cohort were primarily African- Americans and Hispanics. Similarly we could not analyze the differences in the influence of arterial stiffness on cardiovascular disease among different racial groups. Given the short follow up and small sample, our study was underpowered due to fewer composite endpoints of cardiovascular event and /or all-cause mortality. However one can extrapolate from other earlier studies, that pulse wave velocity is an independent predictor of cardiovascular disease in all racial groups.

VI. IMPLICATIONS FOR FUTURE RESEARCH

These measures of arterial stiffness are easy to measure and reproducible in routine clinical practice. There are several studies showing the association between these measures at baseline and its impact on cardiovascular and all-cause mortality. However there are very few studies investigating the progression of arterial stiffness over the years and its impact on clinical outcomes. More importantly, there is some data suggesting that RAAS blockers may attenuate arterial stiffness in these patients. This should be studied in a prospective manner and its role in modifying the arterial compliance evaluated. Similarly, other medications including statins, vitamin D analogs on arterial stiffness should be investigated as these are routinely used in this population. Larger studies must be conducted to evaluate the racial differences in arterial compliance which may give valuable insight into the predominance of ESRD in African Americans.

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