Research Article

Aortic-Brachial Stiffness Mismatch and Mortality in Peritoneal Dialysis Patients

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Key Words

Arteries stiffness • PWV ratio • Arterial stiffness mismatch • Peritoneal dialysis

Abstract

Background/Aims: Possible predictive value of aortic-brachial arterial stiffness mismatch assessed by pulse wave velocity PWV ratio in peritoneal dialysis patients' outcomes need to be further elucidated. The aim of this study is to investigate the predictor value of PWV ratio on peritoneal dialysis (PD) patients' outcomes in China. **Methods:** In this longitudinal cohort study, patients who started PD during September 20, 2005, to February 05, 2008, were included. All the patients were followed until January 31, 2018. Aortic-brachial arterial stiffness mismatch was assessed using carotid-femoral pulse wave velocity divided by carotid-radial pulse wave velocity (PWV ratio). **Results:** A total of 181 incident PD patients were included. The median survival of patients in PWV ratio above median group (4.03 years, 95% CI 4.64–7.99 years) was shorter than that of PWV ratio below median group (10.43 years, 95% CI 9.74–11.12 years, $p < 0.001$). The cardiovascular mortality rate in PWV ratio above median group were significantly higher than that of PWV below median group (log rank test, $p < 0.001$). Univariate Cox regression analysis showed that both PWV ratio (HR 2.42, 95% CI 1.80–3.25, $p < 0.001$) and CF-PWV (HR 1.27, 95% CI 1.16–1.38, $p < 0.001$) were associated with high patients' all-cause mortality. Multivariable Cox regression analysis showed that the PWV ratio was a strong and significantly predictor of cardiovascular mortality (HR 2.08 95% CI 1.16–3.71, $p = 0.014$) after adjusting for coronary heart disease history (HR 2.39, 95% CI 1.20–4.76, $p = 0.013$), diabetes mellitus history (HR 2.84, 95% CI 1.51–5.33, $p = 0.001$). However, the CF-PWV was failed to be included as a significant predictor for both all-cause and CVD mortality in the multivariable Cox regression model. **Conclusion:** Aortic-brachial arterial stiffness mismatch as assessed by PWV ratio, a new arteries stiffness risk parameter, is a significant prognostic indicator of CVD mortality in PD patients. We demonstrated that the discriminative power of the PWV ratio for both all-cause and CVD mortality was better than that CF-PWV.

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Introduction

Chronic kidney disease (CKD) is an important global public health problem [1, 2]. End-Stage Renal Disease (ESRD) increases the risk of death by approximately 10 to 20 times compared to the general population [3] mainly because of Cardiovascular disease (CVD) [4]. Arterial stiffness, defined as a decreased ability of the conductive arteries to absorb the pulse pressure has been reported to be a strong independent predictor of overall cardiovascular mortality in the general population and CKD patients [5-8]. Our previous studies also demonstrated that arterial stiffness was associated with many CVD risk factors in peritoneal dialysis (PD) patients [9-16].

Pulse wave velocity (PWV) is an indirect measure of stiffness and is the accepted standard for non-invasive assessment of aortic stiffness [8]. Carotid-femoral PWV has been used in the epidemiological studies demonstrating the predictive value of aortic stiffness for cardiovascular events [7, 8]. Although the CF-PWV is used as the “gold standard” for measuring aortic stiffness, some recently studies indicated that PWV ratio could be a better indicator than CF-PWV [17-19].

The PWV ratio (carotid-femoral pulse wave velocity divided by carotid-radial pulse wave velocity) is a relatively new concept in arterial research [17, 19-22]. Under physiological conditions, the arterial vasculature is characterized by a progressive increase in stiffness from the aorta and large elastic arteries toward the peripheral muscular conduit arteries, often labeled as the arterial stiffness gradient [19, 21]. This reversal of the normal arterial stiffness gradient, named stiffness mismatch assessed by PWV ratio, enhance the transmission of pulsatile energy into the periphery and microcirculation and, theoretically, increase the risk for damage to microvascular beds in highly perfused organs [17, 19]. Fortier et al. demonstrated that PWV ratio was a better prognostic predictor of all-cause mortality than CF-PWV per se in a prevalent dialysis cohort (245 hemodialysis and 65 PD patients) with a median follow-up of 29 months [18]. However, findings from a recent study do not support the notion that PWV ratio provides additional prognostic value over conventional CF-PWV in the community [21]. Thus, the prognostic value of PWV ratio need to be confirmed by further study. It should be noted that the study from Fortier included only 65 (21%) PD patients. Given that different dialysis modality may have distinct impact on arterial stiffness [23-25], the possible predictive value of PWV ratio in patients underwent PD or HD need to be further elucidated separately.

In the present study, we respectively analyzed an incident cohort of PD patients with long follow-up and tried to investigate the predictor value of PWV ratio on all-cause as well as CVD mortality in this cohort.

Materials and Methods

In this longitudinal cohort study, all the incident PD patients who initiated PD from 20-Sep-2005 to 05-Feb-2008 were included. Patients' the first time PWV were performed within three months after PD initiation. Patients who had following situation were exclude for data analysis (1) persistent hypotension blood pressure (SBP) < 90 mmHg, (2) paralytic or cognitive impairment following cerebrovascular event, (3) absence of femoral or radial pulse, (4) an unwillingness to participate, (5) clinical unstable like peritonitis, acute heart failure, (6) had malignant disease. This study was approved by the Peking University Third Hospital Medical Science Research Ethics Committee on human research. All procedures performed in studies involving human participants were in accordance with the 1964 Helsinki declaration.

The primary outcomes examined were all-cause mortality on peritoneal dialysis (censored for loss to follow-up, renal transplantation, recovery of renal function, and transfer to hemodialysis and end of study) and cardiovascular mortality (censored for loss to follow-up, renal transplantation, transfer to

hemodialysis, other causes of death and end of study). Cardiovascular death was defined as death from cardiovascular disease, such as acute myocardial infarction, sudden death, heart failure, aortic aneurysm rupture, cerebrovascular accident, and other cardiovascular reasons.

Measurement of PWV

All the PWV measurements were performed by one doctor and the intra-observer CV was about 5% as previous reported [9]. Aortic PWV was determined using an automatic device, the Complior (Colson, Gargesles Gonesse, France) [26], which allows online pulse-wave recording and automatic calculation of PWV. Common carotid artery and femoral artery pressure waveforms were recorded non-invasively using a TY-306 Fukuda pressure-sensitive transducer (Fukuda, Tokyo, Japan) while the patient was in the supine position. Measurement was repeated over 10 different cardiac cycles, and the mean value was used for the final analysis. The distance traveled by the pulse wave was measured over the body surface as the distance between the two recording sites (D), while pulse transit time (t) was automatically determined by the Complior. PWV was automatically calculated as $PWV = D/t$. carotid-femoral pulse wave velocity (CF-PWV) and carotid-radial pulse wave velocity (CR-PWV) were calculated accordingly. Aortic-brachial arterial stiffness mismatch (pulse wave velocity ratio) was assessed using CF-PWV divided by CR-PWV.

Measurement of biochemical parameters

Serum albumin was determined by the bromocresol green method. Other biochemical indices, such as blood urea nitrogen, serum creatinine were determined using standard methods. Patients' estimated glomerular filtration rate (eGFR) was estimated by Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation [27].

Measurement of blood pressure

To insure the accuracy of measurements, a dedicated renal nurse was in charge of all BP measurements, and the mercury sphygmomanometer used was calibrated regularly. All measurements were performed in a quiet room. Brachial BP was measured twice in sitting position after patients had rested more than ten minutes. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were averaged from values of the two measurements.

Statistical Analysis

Results were expressed as frequencies and percentages for categorical variables, mean $\pm$ standard deviation for continuous normally distributed variables, and median [interquartile range; IQR] for continuous variables that were not normally distributed. Comparison for patients in different groups was performed using chi-square tests, two tailed unpaired t-tests or Mann-Whitney tests, depending on data distribution. Time to event analyses was evaluated by Kaplan-Meier and multivariable Cox proportional hazards survival analyses. Multivariate Cox's proportional hazard model included all the significant variables ($p < 0.1$) from the univariate analysis. Variables in the final model were selected by a forward (conditional) manner.

Statistical analysis was performed using IBM SPSS Statistics software (version 22.0). P values less than 0.05 were considered statistically significant.

Results

All the patients were followed until January 31, 2018. A total of 181 incident PD patients with a median follow-up of 3.82 (inter-quarter range 2.31, 7.50) years were included in the present study. Death occurred in 102 (56.4 %) patients. A total of 31 patients (17.1%) transferred to hemodialysis. 10 patients (5.5%) underwent renal transplantation and 3 patients (1.7%) had recovery of renal function during follow-up. Loss to follow-up occurred in 15 patients (8.3%) and 3 patients (1.7%) transferred to other dialysis centers.

Patients were divided into two groups by median of PWV ratio. That is below median (n=91) and above median (n=90). The baseline comparison between the two groups were depicted in Table 1. Patients with PWV ratio above median had significantly higher CF-PWV but lower CR-PWV compared with patients with PWV ratio lower than median. Patients in the group of PWV above median were relatively older (p<0.001), diabetic (p<0.001), with more coronary heart disease (p=0.001) and cerebral vascular disease (p<0.001). The levels of serum creatinine, urea, albumin and phosphorous were significantly higher in PWV below median Group than that of the above median Group, while the levels of hemoglobin, calcium and eGFR is lower in the in PWV below median Group compared to PWV above median Group.

Death occurred in 33 patents (36.26%) in PWV ratio below median Group and 69 patients (76.67%) in PWV ratio above median group. There were no significant difference in the causes of death between the groups (p= 0.428; Table 2). The median survival of patients in PWV ratio above median group (4.03 years, 95% CI 4.64-7.99 years) was shorter than that of PWV ratio below median group (10.43 years, 95% CI 9.74-11.12 years, p<0.001) (Fig. 1). The cardiovascular mortality rate in PWV ratio above median group were significantly higher than that of PWV below median group (log rank test, p<0.001; Fig. 2). Univariate Cox regression analysis showed that both PWV ratio (HR 2.42, 95% CI 1.80-3.25, p<0.001) and CF-PWV (HR 1.27, 95% CI 1.16-1.38, p<0.001) were associated with patients' all-cause

Table 1. Clinical Parameters at Baseline for all patients According to Median of Pulse Wave Velocity Ratio. Abbreviations: PWV, pulse wave velocity; CF-PWV, carotid-femoral pulse wave velocity; CR-PWV, carotid-radial pulse wave velocity; PWV ratio, carotid-femoral pulse wave velocity divided by carotid-radial pulse wave velocity; SBP, systolic blood pressure; DBP, diastolic blood pressure; DKD, diabetic kidney disease; CGN, chronic glomerulonephritis; HBP, hypertension; ADPKD, autosomal dominant polycystic kidney disease; CIN, chronic interstitial nephritis; BMI, body mass index; CHD, coronary heart disease; eGFR, estimated glomerular filtration rate

Variables	below Median (n=91)	PWV Ratio above Median (n=90)	P value
Pulse wave velocity			
CF-PWV	9.94±1.35	12.83±1.97	<0.001
CR-PWV	10.35±1.49	8.94±1.86	<0.001
PWV ratio	0.97±0.14	1.51±0.48	<0.001
SBP (mmHg)	143±22	149±22	0.041
DBP (mmHg)	88±14	80±13	<0.001
Primary disease			<0.001
DKD	13 (14.3%)	52 (5.87%)	
CGN	40 (44.0%)	13 (14.4%)	
HBP	7 (7.7%)	7 (7.8%)	
ADPKD	5 (5.5%)	1 (1.1%)	
CIN	15 (16.5%)	7 (7.8%)	
Unknown	4 (4.4%)	8 (8.9%)	
Others	7 (7.7%)	2 (2.2%)	
Dialysis vintage (months)	1.36 ± 0.90	1.39 ± 0.97	0.836
Age (years)	49.3±14.8	65.9±10.8	<0.001
Gender (male,%)	50 (4.95%)	44 (8.94%)	0.415
BMI (kg/m ²)	23.3±4.0	23.5±3.9	0.702
Medical History			
Diabetes mellitus	13 (14.3%)	52 (57.8%)	<0.001
CHD	9 (9.9%)	27 (30.3%)	=0.001
Cerebral infraction	1 (2.2%)	14 (14.6%)	<0.001
Cerebral hemorrhage	1 (1.1%)	2 (2.2%)	0.554
Creatinine (umol/L)	964±385	713±271	<0.001
Urea (mmol/L)	31.8±11.1	26.7±9.5	0.001
Albumin (mmol/L)	36.1±5.5	34.4±4.8	0.026
Hemoglobin (g/L)	77.2±19.1	83.9±17.7	0.017
Calcium (mmol/L)	1.80±0.31	1.91±0.30	0.011
Phosphorous (mmol/L)	2.14±0.67	1.85±0.51	0.001
eGFR (ml/min/1.73m ²)	5.02±2.01	6.67±3.47	<0.001
Heart rate (beats per minutes)	71.8±13.9	68.8±17.6	0.21

Table 2. Causes of death between patients with PWV ratio higher or lower than median. The difference between the two groups was not significant (p=0.428)

Causes of death	Total (n=102)	below Median (n=33)	above Median (n=69)
Cardiovascular disease	42 (41.2%)	12 (36.4%)	30 (43.5%)
Peritonitis	6 (5.9%)	3 (9.1%)	3 (4.3%)
Infection	12 (11.8%)	4 (12.1%)	8 (11.6%)
Gastrointestinal disease	11 (10.8%)	6 (18.2%)	5 (7.2%)
Malignancy	4 (3.9%)	1 (3.0%)	3 (4.3%)
Withdrawal	2 (2.0%)	1 (3.0%)	1 (1.4%)
Multiple organ failure	7 (6.9%)	2 (6.1%)	5 (7.2%)
Unknown	12 (11.8%)	1 (3%)	11 (15.9%)
Respiratory failure	6 (5.9%)	3 (9.1%)	3 (4.3%)

Fig. 1. Kaplan–Meier peritoneal patients' survival curves of all-cause mortality for patients with different pulse wave velocity (PWV) ratio groups.

Fig. 2. Kaplan–Meier peritoneal patients' survival curves of cardiovascular mortality for patients with different pulse wave velocity (PWV) ratio groups.

Table 3. Cox proportional Hazards model for all-cause mortality related to PWV Ratio. Multivariate Cox's proportional hazard model included all the significant variables ($p < 0.1$) from the univariate analysis. Variables in the final model were selected by a forward (conditional) manner. Abbreviations: PWV, pulse wave velocity; CF-PWV, carotid-femoral pulse wave velocity; CR-PWV, carotid-radial pulse wave velocity; PWV ratio, carotid-femoral pulse wave velocity divided by carotid-radial pulse wave velocity; PP, pulse pressure; BMI, body mass index; CHD, coronary heart disease; eGFR, estimated glomerular filtration rate

Variable	Univariate Cox regression		Multivariate Cox regression	
	HR [95% CI]	P value	HR [95% CI]	P value
PWV ratio	2.42 [1.80-3.25]	<0.001	1.52 [0.97-2.36]	0.067
CF-PWV	1.27 [1.16-1.38]	<0.001		
CR-PWV	0.92 [0.82-1.03]	0.918		
SBP	1.00 [1.99-1.01]	0.694		
DBP	0.98 [0.96-0.99]	0.003		
PP	1.01 [1.00-1.02]	0.011		
CHD history (yes)	2.22 [1.43-3.45]	<0.001		
Dialysis vintage				
	1.00 [0.81-1.25]	0.971		
Age (per 1-year increase)	1.05 [1.03-1.06]	<0.001	1.04 [1.02-1.06]	<0.001
Gender (female)	0.90 [0.61-1.33]	0.590		
BMI (per 1-kg/m ² increase)	1.00 [0.95-1.05]	0.981		
Diabetes (yes)	2.42 [1.63-3.60]	<0.001	1.66 [1.08-2.56]	0.021
Cerebral infraction (yes)	2.51 [1.32-4.77]	0.005		
eGFR(per1-ml/min.1.73m ² increase)	1.09 [1.03-1.13]	0.001		
Creatinine (per 1-umol/L increase)	0.999 [0.998-0.999]	0.001	0.999 [0.998-1.00]	0.020
Urea (per 1-mmol/L increase)	0.97 [0.95-0.99]	<0.001		
Albumin (per 1-mmol/L increase)	0.96 [0.92-0.99]	0.022		
Hemoglobin (per 1-g/L increase)	1.01 [1.00-1.02]	0.177		
Calcium (per 1-mmol/L increase)	2.98 [1.52-5.87]	0.002		
Phosphorus(per1-mmol/L increase)	0.78 [0.55-1.10]	0.156		

mortality. However, CR-PWV were not significantly associated with all-cause mortality even in univariate analysis. Other factors associated with patients all-cause mortality were diastolic blood pressure ($p = 0.003$), pulse pressure ($p = 0.011$), coronary heart disease history ($p < 0.001$), age ($p < 0.001$), with diabetes mellitus ($p < 0.001$), with history of cerebral vascular disease ($p < 0.001$), eGFR ($p < 0.001$), serum creatinine ($p = 0.001$), urea ($p < 0.001$), serum albumin ($p = 0.022$) and calcium ($p = 0.002$). Multivariable Cox regression analysis showed that increased age ($p < 0.001$), with diabetes mellitus ($p = 0.021$) and increased blood creatinine levels ($p = 0.020$) were significantly associated with higher all-cause mortality on PD. However, the CF-PWV were failed to be included as a predictor for all-cause mortality in the multivariable Cox regression model. (Table 3). Most importantly, the PWV ratio was a strong and significantly predictor of cardiovascular mortality (HR 2.08, 95% CI 1.16-3.71, $p = 0.014$) after adjusting for coronary heart disease history (HR 2.39, 95% CI 1.20-4.76, $p = 0.013$), diabetes mellitus history (HR 2.84, 95% CI 1.51-5.33, $p = 0.001$) (Table 4). However, both the CF-PWV and CR-PWV were failed to be included as a predictor for CVD mortality in the multivariable Cox regression model.

Discussion

In our investigation, we demonstrated that the aortic-brachial arterial stiffness mismatch, defined as the ratio between CF-PWV and CR-PWV, is significantly related to both cardiovascular and all-cause mortalities in this Chinese incident PD cohort. Most importantly, we showed that the discriminative power of the PWV ratio for both all-cause and CVD mortality was better than that CF-PWV.

Table 4. Cox proportional Hazards model for cardiovascular mortality related to PWV Ratio. Multivariate Cox's proportional hazard model included all the significant variables ($p < 0.1$) from the univariate analysis. Variables in the final model were selected by a forward (conditional) manner. Abbreviations: PWV, pulse wave velocity; CF-PWV, carotid-femoral pulse wave velocity; CR-PWV, carotid-radial pulse wave velocity; PWV ratio, carotid-femoral pulse wave velocity divided by carotid-radial pulse wave velocity; PP, pulse pressure; BMI, body mass index; CHD, coronary heart disease; eGFR, estimated glomerular filtration rate

Variable	Univariate Cox regression		Multivariate Cox regression	
	HR [95% CI]	P value	HR [95% CI]	P value
PWV ratio	2.83 [1.83-4.37]	<0.001	2.08 [1.16-3.71]	0.014
CF-PWV	1.24 [1.08-1.42]	0.002		
CR-PWV	0.77 [0.65-0.90]	0.001		
SBP	1.00 [1.99-1.01]	0.694		
DBP	0.98 [0.96-0.99]	0.003		
PP	1.02 [1.00-1.03]	0.027		
CHD history (yes)	3.07 [1.61-5.87]	0.001	2.39 [1.20-4.76]	0.013
Dialysis vintage	0.88 [0.62-1.25]	0.479		
Age (per 1-year increase)	1.04 [1.02-1.07]	0.001		
Gender (female)	1.17 [0.64-2.16]	0.606		
BMI (per 1-kg/m ² increase)	1.02 [0.94-1.10]	0.687		
Diabetes (yes)	2.48 [1.87-6.46]	<0.001	2.84 [1.51-5.33]	0.001
Cerebral infraction (yes)	2.31 [0.81-6.62]	0.118		
eGFR(per1-ml/min.1.73m ² increase)	1.10 [1.02-1.18]	0.012		
Creatinine (per 1-umol/L increase)	0.998 [0.997-0.999]	0.001		
Urea (per 1-mmol/L increase)	0.96 [0.93-0.99]	0.008		
Albumin (per 1-mmol/L increase)	0.96 [0.91-1.02]	0.183		
Hemoglobin (per 1-g/L increase)	1.01 [0.99-1.02]	0.554		
Calcium (per 1-mmol/L increase)	2.27 [0.81-6.38]	0.121		
Phosphorus(per1-mmol/L increase)	0.60 [0.34-1.06]	0.080		

Aortic stiffness is an established predictor for cardiovascular morbidity and mortality [7, 11, 21, 28]. The carotid-femoral pulse wave velocity (CF-PWV) is used as the “gold standard” for measuring aortic stiffness, the carotid-femoral pulse wave velocity (CF-PWV) has the most evidence for association with cardiovascular outcomes in the general population. However, in dialysis population, the studies evaluate the predict value of CF-PWV generate conflict results. In a prospective study, Szeto found that a high baseline CF-PWV was associated with a lower overall survival of PD patients but the prognostic value of CF-PWV disappeared after adjusting for clinical confounding factor [29]. In recent years, the PWV ratio is a relatively new concept in arterial research [19, 20, 22]. Fortier et al. proved that the PWV ratio could be a better prognostic predictor of mortality than CF-PWV in dialysis patients [18, 19]. But other findings suggested that the prognostic significance of PWV ratio may vary based on baseline CVD risk, and CF-PWV should remain the criterion standard for assessing vascular stiffness [21]. Our study, by performed in an incident PD cohort with long follow-up, strengthened the powerful predict value of PWV ratio than CF-PWV along in PD patients.

Besides, although the predict value of PWV ratio have been elucidated by previous study in ESRD patients [18]. This study only included 65 (21%) PD patients. Give that the different dialysis modality may have distinct impact on arterial stiffness [24, 25], the possible distinct predictor value of PWV ratio in patients underwent PD or HD need to be further elucidated separately. By including only PD patients, we could eliminate dialysis modality effect on PWV ratio. The present study, to our knowledge, is the first study evaluated the PWV ratio in only incident PD patients. Besides, different from the previous study that only all-cause mortality were evaluated, we observe both all-cause and CVD mortality. We demonstrated that the predictor value of PWV ratio for both all-cause and CVD mortality was better than that CF-PWV along. We believe that our finding could expand the knowledge in the role of PWV ratio for PD patients' outcomes.

It should be noted that the PWV below median group had higher mean serum creatinine, urea, albumin and phosphorus level, this may indicate higher nutrition in this group. The lower all-cause and cardiovascular mortalities in the PWV below median group in the present study may be consistent with a reverse epidemiology phenomena [30] that reverse or paradoxical relationships between nutritional markers and outcome in end-stage renal disease.

The strengths of this study include its relative long-term follow-up, only PD participations, use PWV ratio as a new biomarker and compared it with CF-PWV, use of multivariable analyses to adjust for potentially confounding factors. Weighed against these strengths, the study had several limitations. First, patients included in this study were recruited from a single tertiary academic hospital in China, thereby raising the possibility of ascertainment bias. Second, although we carefully defined the CVD outcomes, the possibility of misclassification bias cannot be excluded. Finally, although we attempted to adjust for a range of demographic, clinical and laboratory characteristics, residual confounding remains possible.

Conclusion

In conclusion, we proved PWV ratio, a new arteries stiffness parameter, is a significant prognostic indicator of CVD mortality in PD patients. Most importantly, we demonstrated that the discriminative power of the PWV ratio for both all-cause and CVD mortality was better than that CF-PWV.

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WenHan Bao was involved in the data collection, interpretation the results and wrote part of the draft. FangYu Wang were involved in data analysis and wrote part of the draft. Wen Tang conceptualized the idea, involved in data analysis and drafting the manuscript.

The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. The study protocol has been approved by the Peking University Third Hospital Medical Science Research Ethics Committee on human research.

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Disclosure Statement

The authors have no conflicts of interest to declare.

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