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Factors associated with increased pulse wave velocity in peritoneal dialysis patients

Research Article

Paweł Stróżecki[1], Rafał Donderski[1], Magdalena Grajewska[1], Elżbieta Marcinkowska[1], Michał Kozłowski[1], Joanna Pollak[2], Grażyna Odrowąż-Sypniewska[2], Jacek Manitius[2]

[1] *Department of Nephrology, Hypertension and Internal Diseases, Nicolaus Copernicus University, Collegium Medicum in Bydgoszcz, 85-094 Bydgoszcz, Poland*

[2] *Department of Laboratory Medicine, Nicolaus Copernicus University, Collegium Medicum in Bydgoszcz, 85-094 Bydgoszcz, Poland*

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Abstract: Elevated pulse wave velocity (PWV) reflects increased arterial stiffness. Several studies have investigated PWV in peritoneal dialysis (PD) patients, but direct comparisons with healthy controls were not done. The potential influence of peritoneal transport characteristics on arterial stiffness in PD patients was suggested in recent studies. The aims of this study were to compare PWV in PD patients and healthy volunteers, and to investigate factors associated with increased PWV. The carotid-femoral PWV was measured in 28 PD patients and 28 healthy controls, matched for age and gender. A peritoneal equilibration test (PET) was performed in all PD patients. Based on the PET, patients were classified as: high transporters (H) (n=8), high-average (HA) (n=12), low-average (LA) (n=6), and low transporters (L) (n=2). Six of the PD patients were diabetic. PWV was significantly higher in the PD patients than in the controls (9,9±2,4 vs. 8,0±0,9; p=0,0004). In the PD group, PWV was higher in H/HA than in L/LA patients (10,4 ± 2,5 vs. 8,6 ± 1,0; p=0,008), but all the diabetic patients were in the H/HA group. PWV was significantly higher in diabetic than in non-diabetic PD patients (12,8±2,0 vs. 9,1±1,7; p=0,004). In the PD patients, significant positive correlations were found between PWV and: age, pulse pressure, Kt/V, and duration of PD therapy. In conclusion, the carotid-femoral PWV is elevated in peritoneal dialysis patients. Increased PWV in PD patients is associated with age, diabetic status, and longer duration of PD therapy, but not with this type of peritoneal transport.

Keywords: *Arterial stiffness • Diabetes • Peritoneal dialysis • Peritoneal equilibration test • Peritoneal transport • Pulse wave velocity*

1. Introduction

Elevated pulse wave velocity (PWV) reflects increased arterial stiffness. The PWV is an independent cardiovascular risk factor in the general population, hypertensive patients, diabetic patients, and in hemodialysed (HD) patients [1-4]. Pulse wave velocity does not differ [5], or may even be higher [6], in peritoneal dialysis (PD) patients when compared with HD patients, but there is a lack of studies directly comparing PWV between PD patients and healthy controls. The type of peritoneal transport (especially high peritoneal permeability) is associated with increased cardiovascular risk due to hypervolemia, worse control of blood pressure, and malnutrition [7]. The higher transport status in PD patients is associated with increased risk of technique failure and patient death [7-9]. The results of recent studies evaluating the relationship between peritoneal permeability and arterial stiffness are equivocal. In one study, peritoneal fluid kinetics was an independent predictor of carotid-femoral PWV in continuous ambulatory peritoneal dialysis (CAPD) patients [10]. The authors of that study also suggested a link between high aortic stiffness and increased peritoneal small solute transport rate. On the other hand, Huang et al. did not find any relationship between peritoneal function tests and arterial stiffness

* *E-mail: st_pawel@cm.umk.pl*

determinated by brachial-ankle pulse wave velocity [11]. The aims of our study were to compare carotid-femoral PWV in PD patients with healthy controls, and to investigate factors associated with increased PWV in PD patients.

2. Material and Methods

The study was designed as a cross-sectional analysis in 28 PD patients (F=18, M=10) ages 46 ± 15 (18-74 years). The duration of peritoneal dialysis was 1-92 months (mean 26 months). The underlying renal diseases were: glomerulonephritis in 14 patients (50%), diabetic nephropathy in 6 (21%), and other in 8 (29%). Twenty-six patients (93%) were treated for hypertension: 19 (68%) patients with beta-blockers, 20 (71%) with calcium antagonists, 18 (64%) with angiotenisin-converting enzyme inhibitors or angiotensin II receptor blockers, and 20 (71%) received diuretics. Erythropoesis stimulating factors were given to 26 (93%) patients. Twenty-eight healthy subjects matched for age, sex, and BMI were analyzed as the control group. The protocol of the study was accepted by the Local Bioethical Committee and informed consent was obtained from each participant.

2.1. Peritoneal transport assessment

Peritoneal membrane transport for small solutes was evaluated by a peritoneal equilibration test (PET). The dialysate/plasma (D/P) creatinine ratio at 4 hours of standarized peritoneal dwell was calculated [12]. Based on the PET, patients were classified as: high transporters (H) (n=8), high-average (HA) (n=12), low-average (LA) (n=6), and low transporters (L) (n=2). Due to the small number of patients, we divided the patients into two groups: H and HA patients, and L and LA patients. The two groups were compared with each other. Systolic and diastolic blood pressure (SBP, DBP) were first measured using a mercury sphygmomanometer, and then pulse pressure (PP=SBP-DBP) and mean arterial perssure (MAP=DBP + 1/3PP) were calculated. Weekly Kt/V was assessed in all participants. Fasting blood was taken for hemoglobin (Hb), lipid profile, calcium, phosphorus, parathormon (PTH), and albumin concentrations. The calcium-phosphorus product was also calculated.

2.2. Pulse wave velocity measurement

Carotid-femoral PWV was measured using a Complior® device (Artech Medical, Pantin, France). Two transducers – one positioned over the carotid artery and the second over the femoral artery – were used to measure the time delay between pulse waves. Time delay was measured for 10 successive beats and then averaged. The distance between the carotid artery (suprasternal notch) and the femoral artery was measured externally. The PWV was calculated according to the formula: PWV = distance (m) / time delay (s). In all patients, PWV was measured with a full abdomen, but according to Covic et al, this does not affect the PWV results [6].

Table 1. Comparison of clinical and laboratory parameters and PWV between PD patients and control group.

	PD patients (n=28)	Control group (n=28)	P
Age (years)	46 ± 15	46 ± 10	0,91
Body weight (kg)	66 ± 14	69 ± 12	0,32
BMI (kg/m^2)	24,3 ± 4,8	24,7 ± 3,5	0,72
SBP (mmHg)	132 ± 26	120 ± 12	**0,03**
DBP (mmHg)	82 ± 14	75 ± 6	**0,04**
PP (mmHg)	50 ± 15	44 ± 8	0,09
MAP (mmHg)	98 ± 17	90 ± 8	**0,03**
Serum creatinine (mg/dl)	9,3 ± 3,3	0,9 ± 0,2	**< 0,001**
Hb (g/dl)	11,6 ± 1,0	13,6 ± 1,5	**< 0,001**
Ca (mmol/l)	2,33 ± 0,18	2,27 ± 0,12	0,22
P (mmol/l)	1,85 ± 0,57	1,03 ± 0,18	**< 0,001**
Ca x P (mmol^2/l^2)	4,34 ± 1,45	2,34 ± 0,43	**< 0,001**
Cholesterol (mg/dl)	183 ± 50	191 ± 35	0,56
LDL-cholesterol (mg/dl)	102 ± 42	110 ± 33	0,48
HDL-cholesterol (mg/dl)	45 ± 12	54 ± 16	**0,04**
Triglycerides (mg/dl)	185 ± 105	105 ± 84	**0,006**
PWV (m/s)	9,9 ± 2,4	8,0 ± 0,9	**0,0004**

2.3. Statistical analysis

Distribution of variables was analyzed using the Shapiro-Wilk test. Statistical analysis was performed using the Student's t-test. If the variable was not normally distributed, the Mann-Whitney U test was used. Qualitative data were compared with the χ^2- test. The linear correlation between variables was analyzed. P value < 0.05 was considered statistically significant. Data were expressed as mean ± SD.

3. Results

Clinical and laboratory characteristics of the PD patients and the control group are presented in Table 1. Comparison of PWV between the PD patients and the controls is presented in Figure 1.

The comparisons of clinical and laboratory parameters between H/HA patients and L/LA patients are presented in Table 2. The aortic PWV was significantly higher in H/HA when compared with L/LA transporters (Figure 2), but

Figure 1. Comparison of carotid-femoral pulse wave velocity in peritoneal dialysis patients and control group (* p = 0,0004).

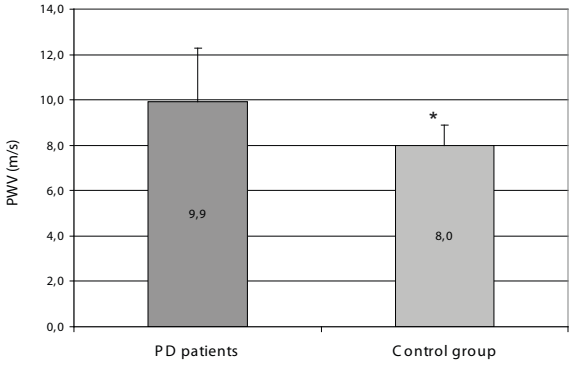


Table 2. Comparison of clinical and laboratory parameters between H/HA patients and L/LA patients.

	H + HA (n=20)	L + LA (n=8)	P
Age (years)	44 ± 16	50 ± 13	0,33
Gender (female)	12 (60%)	6 (75%)	NS
Body weight (kg)	66 ± 14	64 ± 16	0,80
SBP (mmHg)	134 ± 27	126 ± 24	0,46
DBP (mmHg)	82 ± 16	78 ± 13	0,37
PP (mmHg)	51 ± 16	48 ± 16	0,66
MAP (mmHg)	100 ± 18	94 ± 15	0,39
Kt/V	2,46 ± 0,62	2,24 ± 0,43	0,25
Hb (g/dl)	11,5 ± 1,0	11,9 ± 1,2	0,37
Ca (mmol/l)	2,3 ± 0,2	2,3 ± 0,1	0,87
P (mmol/l)	1,8 ± 0,5	1,9 ± 0,7	0,74
Ca x P ($mmol^2/l^2$)	4,28 ± 1,35	4,51 ± 1,77	0,74
PTH (pg/ml)	500 ± 371	393 ± 299	0,34
Albumin (g/dl)	3,95 ± 0,39	4,01 ± 0,26	0,69
Cholesterol (mg/dl)	175 ± 50	206 ± 48	0,74
LDL-cholesterol (mg/dl)	96 ± 43	119 ± 40	0,21
HDL-cholesterol (mg/dl)	41 ± 11	53 ± 12	0,26
Triglycerides (mg/dl)	192 ± 120	167 ± 52	0,07
Time on PD (months)	32 ± 28	11 ± 7	0,06
Diabetes (%)	30%	0%	**0,01**
PWV (m/s)	10,4 ± 2,5	8,6 ± 1,0	**0,008**

all diabetic PD patients had the H/HA type of peritoneal transport. No significant difference was found when non-diabetic H/HA patients were compared with L/LA patients (p=0,2). On the other hand, diabetic PD patients had a significantly higher PWV than non-diabetic PD patients (12,8±2,0 vs. 9,1±1,7 m/s; p=0,004) (Figure 3). The PWV in non-diabetic PD patients was still higher than in the controls (9,1±1,7 vs. 8,0±0,9; p=0,011)

In all the PD patients (n=28), significant positive linear correlations were found between PWV and: age (r=0,56; p<0,01), PP (r=0,63; p<0,001), Kt/V (r=0,45; p<0,02), and duration of PD therapy (r =0,36; p<0,05).

Figure 2. Comparison of carotid-femoral pulse wave velocity in peritoneal dialysis patients with H/HA and L/LA type of peritoneal transport (* p=0,008).

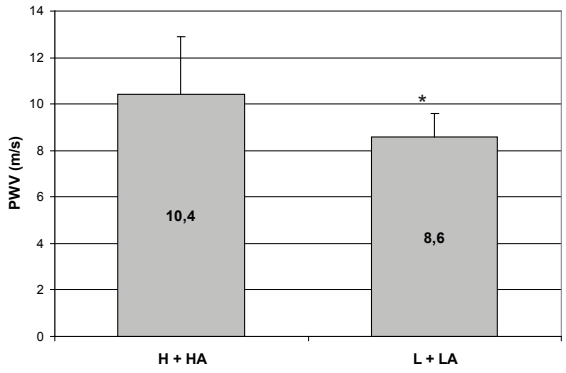
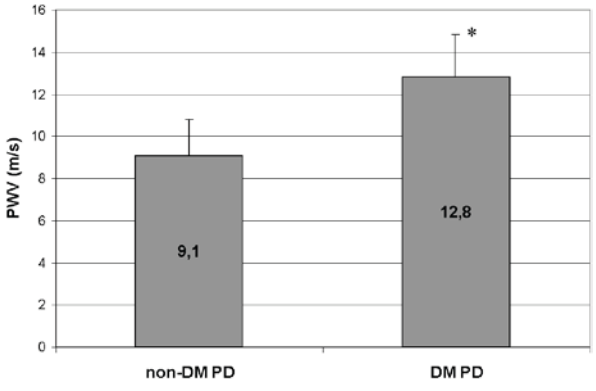


Figure 3. Comparison of carotid-femoral pulse wave velocity in peritoneal dialysis patients without diabetes (non-DM PD) and with diabetes (DM PD) (* p = 0,004).



4. Discussion

Pulse wave velocity (PWV) is a marker of arterial stiffness, and aortic PWV reflects central arterial stiffness [13]. PWV may represent an integrated index of vascular status and cardiovascular risk [3,14]. It was shown in the general population, in hypertensive patients, in diabetic patients, and in hemodialysed patients that increased aortic pulse wave velocity is associated with increased cardiovascular mortality [1-4]. PWV is also a marker of cardiovascular risk in renal transplant recipients [15]. Less is known about the PWV significance in peritoneal dialysis patients.

Several studies regarding arterial stiffness in PD patients were published recently [5,6,10,14,16-19]. Different methods were used to assess arterial function in these studies. The peritoneal dialysis was associated with similar [5], or even higher [6] arterial stiffness, measured with PWV, than observed in HD patients. On the other hand, the distensibility coefficient – parameter of arterial compliance – was reduced in HD but not PD patients when compared with controls in

the study by Konings et al. [17]. Sigrist et al. did not find significant differences in the carotid-radial and the radial-dorsalis pedis PWVs between HD, PD, and CKD stage 4 patients. However, other parts of the arterial tree (muscular type arteries) were assessed in this study [18]. Several factors associated with increased arterial stiffness – such as age, blood pressure, diabetic status, metabolic syndrome components, residual renal function, and therapy with angiotensin II receptor inhibitors – were identified in these studies. Age is one of the main determinants of PWV; physiological aging leads to an increase in PWV. A positive correlation was found between PWV and age in our analysis as well as in other studies [10,11,14,16,18].

Another recent study by Huang et al. found an independent negative correlation between the residual renal function and arterial stiffness assessed with brachial-ankle PWV. Age, MAP, diabetic status and BMI (negative correlation) were also independently associated with PWV in this analysis [11]. In the study by Zhe et al., a relationship was found between arterial stiffness and metabolic syndrome components in CAPD patients [14]. It is noteworthy that metabolic syndrome components, such as elevated blood pressure, elevated triglycerides and decreased HDL-cholesterol, were also observed in our PD population when compared with the control group, despite there being no differences in body weight and BMI.

Several studies suggest that PD patients have worse cardiovascular profiles in comparison with patients on hemodialysis. This is due to less successful blood volume control, worse lipid profile, and greater oxidative stress caused by PD solutions [6,20,21]. Also, epidemiological studies confirm increased mortality in PD patients when compared with HD patients, and longer duration of PD therapy escalates this unfavourable effect [22,23]. In our study, the duration of PD therapy was positively correlated with PWV.

Higher transport status in PD patients is associated with an increased risk of technique failure and patient death [7-9]. High peritoneal permeability is associated with an inflammatory state and increased risk of atherosclerosis [24]. Patients with H/HA peritoneal transport characteristic have lower albumin concentration, higher C-reactive protein concentration, and higher rHuEPO demand than L/LA patients. The risk of atherosclerosis-related event is significantly higher in the H/HA group than in the L/LA group of PD patients [24].

Despite the significant difference in PWV between the H/HA and L/LA patients in our study [25], further analysis does not support the hypothesis that higher peritoneal permeability is associated with increased arterial stiffness. The difference in PWV between the groups may be explained by the fact that all the diabetic patients had the H/HA type of peritoneal transport. Diabetic patients had significantly increased PWV when compared with non-diabetic PD patients (Figure 3).

Diabetes mellitus leads to increased arterial stiffness. This relationship is especially expressed in patients with diabetes and renal failure [28]. Elevated PWV is associated with higher mortality in diabetic and glucose intolerant patients [3]. In PD patients, high peritoneal transport rapid reabsorption of glucose leads to systemic exposure to glucose [9] and subsequent hyperinsulinaemia. Elevated glucose, insulin and triglyceirides are associated with increased arterial stiffness [28,29].

In recent studies, peritoneal fluid kinetics was an independent predictor of carotid-femoral PWV in CAPD patients [10]. A relationship between increased peritoneal small solute transport and increased arterial stiffness had also been suggested. Zhe et al. believed that high peritoneal transport may be a symptom of generalized vasculopathy related to accelerated atherosclerosis in PD patients [10]. This hypothesis can also be supported by the results of a study by Covic et al., in which CAPD patients had the highest PWV and augmentation index among patients with different modalities of renal replacement therapy. This study also revealed affected vasorelaxation related to the endothelial-dependent vasomotor function [6]. In the study by Stompór et al., it was shown that chronic ureamia-dependent inflammation may be one of the factors increasing aortic stiffness in peritoneal dialysis patients [19]. Chronic inflammation was also associated with increased coronary artery calcification in peritoneal dialysis patients [30]. In addition, the vascular calcification score correlates with PWV in patients with chronic renal failure [18].

In our study, a significant positive correlation was found between the duration of PD therapy and PWV. Long-term peritoneal dialysis therapy is associated with changes in peritoneal membrane characteristics and an increase in D/P ratio for creatinine in a proportion of PD patients [28,29]. Long-term PD patients often develop an increase in small solute transport leading to decreased ultrafiltration capacity [29]. Decreased peritoneal ultrafiltration leads to chronic volume overload and worse control of blood pressure, and may increase arterial stiffness by distension of large arteries.

The proportion of patients with the H/HA type of peritoneal transport (72%) in our study was higher than in other analyses (47.4%), but in our study, the PET results after an average of 26 months of PD therapy (range 1-92) were analysed, while in Chung et al.'s study, the PET was performed at a mean of 7 days after the initiation of

dialysis therapy [8]. These observations are consistent with other findings, indicating that peritoneal permeability increases with the duration of PD therapy [28,29]. In our analysis, the duration of PD therapy was longer in the H/HA group with borderline significance (p=0,06) than in L/LA patients. It may suggest that both diabetes and longer duration of PD therapy, but not type of peritoneal transport, are responsible for higher PWV in the H/HA group.

This study has several limitations. The studied PD population is quite low and the proportion of L/LA patients is only 28%, while in other studies it was 52-53% [8,11]. Vascular calcifications (VC) were not assessed in our study, while the extent of VC partly explains the increase in arterial stiffness in dialysed patients. Residual renal function was assessed only as preserved diuresis, and not by calculation of creatinine clearance or renal weekly Kt/V for urea. However, despite the fact that several relevant studies regarding arterial stiffness were published recently, to our knowledge, our study was the first in which carotid-femoral pulse wave velocity was directly compared between PD patients and a control group of healthy volunteers.

5. Conclusions

Carotid-femoral PWV is elevated in peritoneal dialysis patients. In PD patients, increased arterial stiffness is associated with age, diabetic status, and long duration of PD therapy, but not with the type of peritoneal transport.

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