Original Report: Patient-Oriented, Translational Research

American Journal of Nephrology

Am J Nephrol 2008;28:128–132
DOI: 10.1159/000109981

Received: April 4, 2007
Accepted: August 21, 2007
Published online: October 17, 2007

Association between Arterial Stiffness and Peritoneal Fluid Kinetics

Xing-wei Zhe Xin-kui Tian Wei Chen Li-juan Guo Yue Gu Hui-min Chen
Li-jun Tang Tao Wang

Division of Nephrology, Peking University Third Hospital, Beijing, China

Key Words
Absorption rate, peritoneal fluid · Arterial stiffness · Peritoneal dialysis

Abstract
Background: A high peritoneal transport status in continuous ambulatory peritoneal dialysis (CAPD) patients is associated with a markedly increased morbidity and mortality. While the causes are as yet unknown, overall the proportion of deaths due to cardiovascular disease is estimated at 40–50% among dialysis patients. Arterial stiffness has been established as a cardiovascular risk factor, while the links between peritoneal transport status and aortic stiffness have not yet been investigated. ***Methods:*** We included 65 prevalent CAPD patients (24 males/41 females) from our center in a cross-sectional study. Arterial stiffness was assessed by brachial pulse pressure (PP) and carotid-femoral pulse wave velocity (C-F PWV). The patients' peritoneal fluid transport was assessed by kinetic modeling. The patients' peritoneal small solute transport rate was assessed by D/P_{cr} at 4 h. Extracellular water to total body water (E/T) ratio was assessed by means of bioimpedance analysis. C-reactive protein was also measured. ***Results:*** C-F PWV was positively correlated with patients' age ($r = 0.489$, $p < 0.01$), diabetic status ($r = 0.327$, $p < 0.01$), peritoneal fluid absorption rate (Ke; $r = 0.251$, $p < 0.05$), PP ($r = 0.483$, $p < 0.01$), and E/T ($r = 0.517$, $p < 0.01$). Multivariate regression analysis showed that C-F PWV was independently related to E/T ($p < 0.01$), PP ($p < 0.01$), age ($p < 0.05$), and Ke ($p < 0.05$). ***Conclusion:*** Peritoneal fluid transport (Ke), as well as E/T, age and PP were found to be independent predictors of elevated C-F PWV in CAPD patients, suggesting that there might be a link between high aortic stiffness and increased Ke rate, hypothetically through generalized vasculopathy.

Introduction

An increased peritoneal transport rate is associated with increased cardiac morbidity and mortality [1]. Although some of the increased mortality may be due to volume overload more commonly seen in high peritoneal transport rate patients [2], one cannot exclude a possible intrinsic link between an increased peritoneal transport rate and cardiovascular diseases hypothetically mediated through generalized vasculopathy.

Increased arterial stiffness is associated with increased cardiac mortality in end-stage renal disease patients [3–6]. Many studies have shown that increased endothelial cell layer permeability is accompanied by the accumulation of low-density lipoprotein in the artery wall, and thus may contribute to the development and/or progression of cardiovascular disease [7, 8]. Endothelial permeability is also thought to be a major cause of increased

KARGER

Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

0250–8095/08/0281–0128$24.50/0

Accessible online at:
www.karger.com/ajn

Tao Wang, MD, PhD
Division of Nephrology, Third Hospital, Peking University
49 North Garden Rd., Haidian District
Beijing 100083 (China)
Tel. +86 10 6201 7691, ext. 8850, Fax +86 10 8290 7314, E-Mail wangt@bjmu.edu.cn

peritoneal fluid transport status [9]. Vascular stiffening is associated with increased arterial permeability [10], and we therefore hypothesized that vascular dysfunction could be one of the links between increased peritoneal membrane transport and cardiovascular disease. Indeed, we have previously reported a link between high aortic stiffness and increased peritoneal small solute transport rate [11]. In the present study, we investigated the relationship between arterial stiffness and peritoneal fluid kinetics, one of the most important determinants of dialysis outcome.

Methods

Study Population

Continuous ambulatory peritoneal dialysis (CAPD) patients from our Peritoneal Dialysis Center were enrolled. All patients undergoing continuous therapy were considered for inclusion. The exclusion criteria were: (1) patients on peritoneal dialysis (PD) for less than 1 month; (2) peritonitis less than 1 month before the study, and (3) unwillingness to participate in the study. Written informed consent was obtained from every patient. The ethical committee of Peking University approved the study protocol.

Peritoneal Fluid Transport Modeling

Patients were asked to complete a written 10-day ultrafiltration (UF) record before undergoing a peritoneal equilibration test. All the patients were taught to appropriately record their dialysis exchanges, including exchange time, dwell time, dialysate glucose concentration, dwell volume, and drainage volume. The drainage volumes were double checked by weight measurement. The pooled UF records of the special protocol were used for computer simulation to estimate the peritoneal fluid kinetics, and three arbitrary coefficients, which reflect the patients' peritoneal fluid kinetics, were calculated [12]. Briefly, during a PD dwell, the rate of change in intraperitoneal volume at a given moment (dV/dt) equals the instantaneous net volume flow (J_V) occurring through the peritoneal membrane, which can be described according to the following phenomenological equation [13]:

$$\frac{dV}{dt} = J_v = LpS \cdot \left(\Delta P - \sigma_{pro} \cdot \Delta \pi_{pro} + \sigma_g \cdot \Delta \pi_g + \sum_{i=1}^{n} \sigma_i \cdot \Delta \pi_i \right) - L \quad (1)$$

Here LpS stands for the peritoneal UF coefficient. ΔP represents the mean hydrostatic pressure difference between the blood capillaries and peritoneal cavity, $\Delta\pi_{pro}$ and $\Delta\pi_g$ are the colloid and crystalloid osmotic pressure difference caused by the plasma proteins and glucose, respectively. $\Delta\pi_i$ represents the crystalloid osmotic pressure difference caused by other solutes across the peritoneum including NaCl. Osmotic pressure is particularly induced by a glucose-changed exponential during a dwell. σ_{prot}, σ_g and σ_i represent the average osmotic reflection coefficients for total protein glucose and other solutes across the peritoneum, respectively. L stands for the lymph flow from the peritoneal cavity to the blood, whereas V represents volume and t is time.

Equation 1 contains several exponential crystalloid osmotic pressure terms. Having the 'lumped' rate constant 'k' (min^{-1}) and other constant terms, ΔP, $\sigma_{pro} \cdot \Delta\pi_{pro}$, and L, equation 1 can be integrated over time (t) and yields the following [13]:

$$V_D(t) = V_0 + Q_T \cdot (1 - \exp(-k \cdot t)) - K_e \cdot t \quad (2)$$

Here $V_D(t)$ represents the drained dialysate volume as a function of time. V_0 is the volume instilled at time zero, whereas Q_T, K_e, and k are parameters that determine the change occurring in $V_D(t)$ as a function of time. The coefficient Q_T represents the maximal fluid volume that can be transported into the peritoneal cavity by glucose-induced osmosis during a dwell (the theoretical maximum drainable volume), when both lymphatic and capillary fluid absorptions to the blood are set to zero. Thus Q_T describes the 'height' of the $V_D(t)$ (or intraperitoneal volume) versus time curve [14]. The coefficient k can be approximated by the ratio of the glucose permeability-surface area product (glucose mass transfer area coefficient) to the mean intraperitoneal fluid volume during the measurement period. K_e represents the sum of capillary and lymphatic fluid absorption rate from the peritoneal cavity.

In the present study, we applied a nonlinear least squares regression analysis to determine Q_T, K_e, and k from the recorded UF volume versus time data. All computer simulations were performed with Matlab 6.5 (The Math Work, Inc., Natick, Mass., USA).

Fast Peritoneal Equilibration Test

The fast peritoneal equilibration test was performed as described by Twardowski et al. [15]. The dialysate to plasma creatinine (D/P_{cr}) and glucose ($D/P_{glucose}$) concentration ratio at 4 h of dwell was used to describe the peritoneal small solute transport rate.

Measurement of Pulse Wave Velocity

The aortic pulse wave velocity (PWV) was determined using an automatic device, the Complior (Colson, Garges les Gonesses, France) [16], which allowed on-line pulse wave recording and automatic calculation of PWV. Common carotid artery and femoral artery pressure wave forms were recorded noninvasively using a TY-306 Fukuda pressure sensitive transducer (Fukuda, Tokyo, Japan). 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. Details, as well as validation of this automatic method and its reproducibility, have been reported previously [16]. All the PWV measurements were performed by one doctor and the intra-observer coefficient of variation was about 1.74–7.95%. All our patients were asked to stop their antihypertensive medications for at least 24 h prior to evaluation. Patients were divided into high or low carotid-femoral (C-F) PWV groups according to mean C-F PWV value: those above the mean C-F PWV value were in the high C-F PWV group, while those below the mean C-F PWV value were in the low C-F PWV group.

Bioimpedance Analysis

Multiple-frequency bioelectrical impedance analysis was performed using the Hydra analyzer (Xitron Technologies, San Diego, Calif., USA). The procedure is described in detail elsewhere [17]. Briefly, after a patient drained the dialysate and was in a supine position for at least 10 min, the standard tetrapolar electrodes were placed on the left side of the body. Three consecutive measurements were performed during a 2-min period while recording extracellular water, intracellular water, and total body water. Based on these data, the ratio of extracellular water to total body water (E/T) ratio was calculated [18].

Inflammation

Serum C-reactive protein (CRP) was measured using a commercial high-sensitivity assay.

Statistic Analysis

Continuous variables are expressed as the mean ± SD or median (range) for non-normally distributed variables. Pearson's correlation was performed when the relationship between C-F PWV and other clinic parameters was explored. Multiple regression analysis was performed to identify the determinants of increased C-F PWV. Briefly, we performed a linear regression incorporating all factors significantly associated with PWV in univariate analysis. All tests were two-sided. A p value of < 0.05 was taken as statistically significant. All analyses were completed with SPSS software, version 12.0 (SPSS, Chicago, Ill., USA).

Results

Sixty-five CAPD patients were included in the present study, 24 male and 41 female patients with an average age of 61 ± 12 years. The mean time on PD in these patients was 22 ± 22 months. Their average height was 158 ± 8 cm, while their average weight was 61 ± 11 kg. Seventeen of the patients had diagnosed diabetes mellitus. The patients' clinical and biochemical data are shown in table 1. Comparison of the patients' clinical and biochemical parameters according to their C-F PWV is shown in table 2. Briefly, patients' age, diabetic status, systolic blood pressure, pulse pressure (PP), and C-F PWV were significantly higher in the high PWV group, compared to the low PWV group. In the high PWV group K_e was higher than in the low PWV group ($p = 0.077$).

In univariate analysis, C-F PWV was positively associated with patients' age ($r = 0.489$, $p < 0.01$), diabetic status ($r = 0.327$, $p < 0.01$), K_e ($r = 0.251$, $p < 0.05$), PP ($r = 0.483$, $p < 0.01$), systolic blood pressure ($r = 0.329$, $p < 0.01$), and E/T ($r = 0.517$, $p < 0.01$). There was also a positive correlation between K_e and D/Pcr ($r = 0.377$, $p < 0.01$). However, no significant correlation was observed between C-F PWV and CRP ($r = 0.219$, $p = 0.09$). C-F PWV was not significantly correlated with Q_T ($r = 0.262$, $p = 0.09$) and the coefficient k ($r = 0.091$, $p > 0.05$). Nor was C-F PWV associated with the patients' time on PD, diastolic blood pressure, serum hemoglobin, albumin, calcium, phosphate, and iPTH.

Table 1. Clinical and biochemical data of the study population

Variables	
SBP, mm Hg	146 ± 25
DBP, mm Hg	83 ± 13
PP, mm Hg	63 ± 22
C-F PWV, m/s	11.1 ± 2.3
Hemoglobin, g/l	115 ± 18
Albumin, g/l	35 ± 9
CRP, mg/l	10.00 (0.35–262.04)
Calcium, mmol/l	2.2 ± 0.4
Phosphate, mmol/l	1.6 ± 0.5
iPTH, pg/ml	184 ± 182
K_e, ml/min	0.58 ± 0.33
E/T	0.51 ± 0.04

SBP = Systolic blood pressure; DBP = diastolic blood pressure; PP = pulse pressure; C-F PWV = carotid-femoral pulse wave velocity; CRP = C-reactive protein; iPTH = intact parathyroid hormone; K_e = peritoneal fluid absorption rate; E/T = extracellular water to total body water ratio.

Multivariate regression analysis results are shown in table 3. Briefly, both E/T, PP, age, and K_e were found to be independently associated with PWV and together explained 50.6% of the total variance.

Discussion

In the present study, we evaluated correlations between PD transport markers and arterial stiffness in 65 stable CAPD patients. We show that C-F PWV is associated with an increased peritoneal fluid absorption rate (K_e) independent of previously reported associations to fluid status, age and pulse pressure.

High peritoneal transport patients have been shown to have a worse clinical outcome, including more hypoalbuminemia, reduced lean body mass, and more uremic symptoms, hypertension, and hospitalizations [19–21]. Survival studies have shown significantly increased mortality in patients with an increased peritoneal transport rate [1, 2, 22]. We have also previously found an association between arterial stiffness and increased peritoneal small solutes transport rate [11]. In the present study, we extend this finding by showing a significant association between peritoneal fluid absorption rate (K_e) and PWV.

Table 2. Comparison of patients' clinical and biochemical parameters according to their C-F PWV

	Low C-F PWV group	High C-F PWV group
Patients, n	33	32
Age, years	57 ± 13	65 ± 8*
Time on PD, months	20 ± 22	25 ± 22
Diabetes	4	13*
Weight, kg	61 ± 12	61 ± 10
Height, cm	159 ± 8	157 ± 7
SBP, mm Hg	138 ± 20	156 ± 27*
DBP, mm Hg	84 ± 13	82 ± 13
PP, mm Hg	54 ± 15	74 ± 24*
C-F PWV, m/s	9.4 ± 1.1	12.9 ± 1.7*
Hemoglobin, g/l	113 ± 18	118 ± 19
Albumin, g/l	35.7 ± 9.4	34.8 ± 7.9
CRP, mg/l	5.29 (0.52–34.28)	14.86 (0.35–262.04)
Calcium, mmol/l	2.1 ± 0.4	2.2 ± 0.3
Phosphate, mmol/l	1.5 ± 0.5	1.6 ± 0.5
iPTH, pg/ml	187 ± 207	180 ± 153
K_e, ml/min	0.51 ± 0.23	0.66 ± 0.40**
E/T	0.50 ± 0.04	0.53 ± 0.04

See table 1 for definitions of abbreviations.
* $p < 0.01$ between low and high C-F PWV group; ** $p = 0.077$ between low and high C-F PWV group.

While we cannot say if the observed vascular stiffening is a cause or consequence of disturbed vascular permeability [10], it is well known that vascular permeability is one of the major determinants of peritoneal small solute transport rate [23]. Our results support a previous hypothesis that high peritoneal transport may be just one symptom of a generalized vascular disorder related to accelerated atherosclerosis in CAPD patients [24].

Consistent with previous reports [25–27], we also found significant associations between PWV and CRP, PP, and age. Additionally, we found that E/T, a marker of fluid status [28], was also a strong and independent risk factor, further underscoring the putative link between volume status and arterial stiffness. We also found that patients' peritoneal small solute transport rate is positively correlated with the peritoneal fluid absorption rate, which is consistent with our previous study [29]. Mateijsen et al. [30] have previously suggested that there are two types of high peritoneal transport. However, there was no difference in time on PD between patients with low and high PWV, suggesting that other causes may be more important than the type of high transport. The relationship between peritoneal transport rate, fluid absorption, volume status and arterial stiffness in the present study warrants further studies.

Table 3. Result of a multivariate regression analysis of predictors of PWV in 65 CAPD patients

	B	SE	Standardized coefficient	t value	p value
Intercept	–3.571	2.613		– 1.367	0.177
E/T	16.685	5.810	0.310	2.872	0.006
PP	0.035	0.010	0.345	3.569	0.001
Age	0.048	0.020	0.260	2.379	0.021
K_e	1.544	0.731	0.197	2.113	0.039

The initial model included all parameters associated with PWV in univariate analysis, i.e. age, diabetic status, pulse pressure (PP), extracellular water to total body water ratio (E/T) by bioimpedance analysis, peritoneal fluid absorption rate (K_e) and small solute transport assessed by D/P glucose.

In conclusion, the present study shows that C-F PWV is associated with increased K_e in CAPD patients. K_e, in addition to E/T, age and PP, is an independent risk factor for elevated C-F PWV in CAPD patients, suggesting that there might be a link between high aortic stiffness and an increased peritoneal fluid transport rate.

Acknowledgements

This work was funded by a grant from the Cheung Kong Scholar Programme, Ministry of Education, People's Republic of China (36-1) and by the National '211 project' Peking University EBM group (38-18). The manuscript benefited significantly from the intellectual support of Assoc. Prof. Jonas Axelsson and Prof. Bengt Lindholm, from the Department of Renal Medicine and Baxter Novum of the Karolinska Institutet, Stockholm, Sweden. Baxter Novum is an unconditional grant from Baxter Healthcare Inc. (Deerfield, Ill., USA) to the Karolinska Institutet.

References

1 Churchill DN, Thorpe KE, Nolph KD, Keshaviah PR, Oreopoulos DG, Page D: Increased peritoneal membrane transport is associated with decreased patient and technique survival for continuous peritoneal dialysis patients. The Canada-USA (CANUSA) Peritoneal Dialysis Study Group. J Am Soc Nephrol 1998;9:1285–1292.
2 Wang T, Heimburger O, Waniewski J, Bergstrom J, Lindholm B: Increased peritoneal permeability is associated with decreased fluid and small-solute removal and higher mortality in CAPD patients. Nephrol Dial Transplant 1998;13:1242–1249.
3 Blacher J, Guerin AP, Pannier B, Marchais SJ, Safar ME, London GM: Impact of aortic stiffness on survival in end-stage renal disease. Circulation 1999;99:2434–2439.
4 Covic A, Goldsmith DJ, Florea L, Gusbeth-Tatomir P, Covic M: The influence of dialytic modality on arterial stiffness, pulse wave reflections, and vasomotor function. Perit Dial Int 2004;24:365–372.
5 Konings CJ, Dammers R, Rensma PL, Kooman JP, Hoeks AP, Kornet L, Gladziwa U, van der Sande FM, Leunissen KM: Arterial wall properties in patients with renal failure. Am J Kidney Dis 2002;39:1206–1212.
6 London GM, Guerin AP, Marchais SJ, Pannier B, Safar ME, Day M, Metivier F: Cardiac and arterial interactions in end-stage renal disease. Kidney Int 1996;50:600–608.
7 Navab M, Berliner JA, Watson AD, Hama SY, Territo MC, Lusis AJ, Shih DM, Van Lenten BJ, Frank JS, Demer LL, Edwards PA, Fogelman AM: The Yin and Yang of oxidation in the development of the fatty streak. A review based on the 1994 George Lyman Duff Memorial Lecture. Arterioscler Thromb Vasc Biol 1996;16:831–842.
8 Nielsen LB: Transfer of low density lipoprotein into the arterial wall and risk of atherosclerosis. Atherosclerosis 1996;123:1–15.
9 Verkman AS: Aquaporin water channels and endothelial cell function. J Anat 2002;200:617–627.
10 Symons JD, Mullick AE, Ensunsa JL, Ma AA, Rutledge JC: Hyperhomocysteinemia evoked by folate depletion: effects on coronary and carotid arterial function. Arterioscler Thromb Vasc Biol 2002;22:772–780.
11 Zhe XW, Tian XK, Chen W, Guo LJ, Gu Y, Chen HM, Tang LJ, Wang T: Association between arterial stiffness and peritoneal small solute transport rate. Artif Organs 2007; in press.
12 Zhe XW, Shan YS, Cheng L, Wang T: A simple method for the estimation of peritoneal fluid transport. Blood Purif 2007;25:161–168.
13 Stelin G, Rippe B: A phenomenological interpretation of the variation in dialysate volume with dwell time in CAPD. Kidney Int 1990;38:465–472.
14 Rippe B: A three-pore model of peritoneal transport. Perit Dial Int 1993;13(suppl 2):S35–S38.
15 Twardowski ZJ, Nolph KD, Khanna R, Prowant BF, Ryan LP, Moore HL, Nielsen MP: Peritoneal equilibration test. Perit Dial Int 1987;7:138–147.
16 Asmar R, Benetos A, Topouchian J, Laurent P, Pannier B, Brisac AM, Target R, Levy BI: Assessment of arterial distensibility by automatic pulse wave velocity measurement. Validation and clinical application studies. Hypertension 1995;26:485–490.
17 Davies SJ, Phillips L, Russell GI: Peritoneal solute transport predicts survival on CAPD independently of residual renal function. Nephrol Dial Transplant 1998;13:962–968.
18 Jones CH, Newstead CG: The ratio of extracellular fluid to total body water and technique survival in peritoneal dialysis patients. Perit Dial Int 2004;24:353–358.
19 Blake PG, Flowerdew G, Blake RM, Oreopoulos DG: Serum albumin in patients on continuous ambulatory peritoneal dialysis–predictors and correlations with outcomes. J Am Soc Nephrol 1993;3:1501–1507.
20 Heaf J: CAPD adequacy and dialysis morbidity: detrimental effect of a high peritoneal equilibration rate. Ren Fail 1995;17:575–587.
21 Nolph KD, Moore HL, Prowant B, Twardowski ZJ, Khanna R, Gamboa S, Keshaviah P: Continuous ambulatory peritoneal dialysis with a high flux membrane. ASAIO J 1993;39:904–909.
22 Davies SJ, Woodrow G, Donovan K, Plum J, Williams P, Johansson AC, Bosselmann HP, Heimburger O, Simonsen O, Davenport A, Tranaeus A, Divino Filho JC: Icodextrin improves the fluid status of peritoneal dialysis patients: Results of a double-blind randomized controlled trial. J Am Soc Nephrol 2003;14:2338–2344.
23 Flessner MF: The transport barrier in intraperitoneal therapy. Am J Physiol Renal Physiol 2005;288:F433–F442.
24 Heaf J: High transport and malnutrition-inflammation-atherosclerosis (MIA) syndrome. Perit Dial Int 2003;23:109–110.
25 Brunner FP, Selwood NH: Profile of patients on RRT in Europe and death rates due to major causes of death groups. The EDTA Registration Committee. Kidney Int Suppl 1992;38:S4–S15.
26 Johnson JG, Gore SM, Firth J: The effect of age, diabetes, and other comorbidity on the survival of patients on dialysis: a systematic quantitative overview of the literature. Nephrol Dial Transplant 1999;14:2156–2164.
27 Stenvinkel P, Heimburger O, Paultre F, Diczfalusy U, Wang T, Berglund L, Jogestrand T: Strong association between malnutrition, inflammation, and atherosclerosis in chronic renal failure. Kidney Int 1999;55:1899–1911.
28 Woodrow G: Extracellular water expansion: part of the malnutrition-inflammation-atherosclerosis syndrome? Perit Dial Int 2006;26:566–570.
29 Wang T, Waniewski J, Heimburger O, Werynski A, Lindholm B: A quantitative analysis of sodium transport and removal during peritoneal dialysis. Kidney Int 1997;52:1609–1616.
30 Mateijsen MA, van der Wal AC, Hendriks PM, Zweers MM, Mulder J, Struijk DG, Krediet RT: Vascular and interstitial changes in the peritoneum of CAPD patients with peritoneal sclerosis. Perit Dial Int 1999;19:517–525.