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THE ASSOCIATION BETWEEN ARTERIAL STIFFNESS AND FLUID STATUS IN PERITONEAL DIALYSIS PATIENTS

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♦ ***Objectives:*** **In this study our aim was to evaluate the relationship between degree of fluid status and arterial stiffness measured by pulse wave velocity (PWV) in peritoneal dialysis (PD) patients. Fluid status was determined by different methods including fluid overload measured by bioimpedance (Body Composition Monitor, BCM), calf normalized resistivity (CNR), plasma N-terminal fragment of B-type natriuretic peptide (NT-proBNP) and extracellular to intracellular water ratio (ECW/ICW).**

♦ ***Methods:*** **Sixty PD patients were evaluated. They were stratified into normo- and hypervolemic groups according to their fluid overload (FO). CNR was calculated from resistance at 5 kHz using calf bioimpedance spectroscopy. Arterial stiffness was assessed by PWV. Additionally, all patients underwent transthoracic echocardiography and had levels of NT-proBNP measured.**

♦ ***Results:*** **PWV was higher in the hypervolemic compared to normovolemic patients (9.99 ± 2.4 m/sec vs 7.48 ± 2.3 m/sec, $p < 0.001$). Hypervolemic patients had higher NT-proBNP levels (3065 ± 981 pg/mL vs 1095 ± 502 pg/mL, $p < 0.001$), a higher ratio of ECW/ICW; (0.93 ± 0.11 vs 0.81 ± 0.08, $p < 0.001$) and lower CNR (13.7 ± 2.4 vs 16.0 ± 3.3 W $m^3/kg*10^{-2}$, $p = 0.005$). NT-pro BNP level, ECW/ICW ratio, relative FO, and left ventricular (LV) mass index were positively and CNR negatively correlated with PWV. Relative FO and CNR independently predicted PWV in multivariate analysis adjusted for age, duration of PD, body mass index and mean arterial pressure.**

♦ ***Conclusions:*** **Arterial stiffness is increased in fluid-overloaded PD patients. Our results indicated that fluid status is an independent predictor of PWV.**

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KEY WORDS: Arterial stiffness; fluid status; peritoneal dialysis.

The achievement of normal fluid status is one of the primary objectives of dialysis (1). Fluid overload has been related to cardiovascular morbidity (including arterial hypertension (HT), pulmonary and peripheral edema, left ventricular hypertrophy (LVH), and heart failure), and mortality (2). Available methods to assess fluid status include measurement of natriuretic peptides (atrial natriuretic peptide, brain natriuretic peptide, N-terminal fragment of B-type natriuretic peptide (NT-proBNP)), inferior vena cava diameter, continuous relative blood volume monitoring, and bioimpedance analysis. Bioimpedance analysis is a non-invasive and low cost means to objectively measure body fluid content in dialysis patients (3,4). A number of methods based on conventional bioimpedance spectroscopy (BIS) techniques can predict normal body fluid status, such as the extracellular water to total body water (ECW/TBW), and extracellular to intracellular water ratios (ECW/ICW) (5–7). A recently developed BIS device (Body Composition Monitor, BCM, Fresenius Medical Care, Bad Homburg, Germany) provides a figure for degree of excess fluid volume and estimates of ECW and TBW (8–10). Recently, Zhu *et al.* proposed a novel calf bioimpedance method for estimating fluid status in dialysis patients (5). Due to the effect of gravity, the relative volume of excess ECW is higher in the calf than in the arm or trunk (11,12). Zhu postulated that calf ECW can be used as a window to monitor changes in whole body ECW. Calf extracellular resistance, which is measured by segmental BIS, is directly related to changes in calf ECW. There is an inverse association between resistivity and calf ECW. Lower resistivity indicates increased ECW in the calf due to hypervolemia. When patients approach their optimal (normal) fluid status, calf resistivity approaches normal values (5).

Arterial stiffness is increased in end-stage renal disease (ESRD) patients. Studies have shown that arterial stiffness predicts the risk of future fatal and nonfatal cardiovascular events (13–15). PWV is used to measure arterial elasticity and stiffness and is related to the elastic properties of the vascular wall. Carotid-femoral PWV is considered as the gold standard in the measurement of central arterial stiffness (16,17). Vascular calcification, diabetes mellitus, hyperlipidemia, hypertension, endothelial dysfunction, chronic inflammation, advanced glycation end products (AGEs), and increased activity of the renin–angiotensin–aldosterone system are the main causes of increased arterial stiffness associated with chronic renal failure (18). Our aim was to evaluate the relationship between degree of fluid overload determined by different methods and PWV in peritoneal dialysis patients.

METHODS

STUDY POPULATION

This single-center cross-sectional study was performed on monitored patients undergoing continuous ambulatory peritoneal dialysis (CAPD) at the Nephrology Department of the Medical Faculty of Erciyes University, Turkey, for a period of 10 months between February 2011 and October 2011. We screened 90 consecutive adult PD patients; 15 patients preferred not to be enrolled, another 11 patients were excluded because of major cardiovascular diseases as assessed by history and transthoracic echocardiography (three with valvular heart disease, five with coronary heart disease, 3 with congestive heart failure); four patients withdrew their consent. Finally, a total of 60 PD patients were enrolled in this study. All patients were informed about the study, and written consents were obtained. The study was approved by the local ethics committee and performed in accordance with the Declaration of Helsinki. The trial flow chart is illustrated in Figure 1.

BIOCHEMICAL AND NATRIURETIC PEPTIDE MEASUREMENTS

Ten-milliliter blood samples were taken with subjects in a seated position following a 20-min. rest after 12 hours of fasting. Glucose, creatinine, and lipid profiles were determined by standard methods. The specimens were centrifuged at 4 ˚C at 1500 rpm for 5 min; supernatant plasma was used for NT-proBNP measurement. NT-proBNP levels were measured with a commercially available electrochemiluminescence immunoassay (Elecsys proBNP assay, Roche Diagnostics Corporation, Indianapolis, IN, USA).

ECHOCARDIOGRAPHY

Upon enrollment, all patients underwent an echocardiographic assessment with a 2.5-MHz transducer and harmonic imaging (Vivid 7 instrument, GE Medical Systems, Milwaukee, WI, USA). Echocardiography was performed at baseline by a cardiologist according

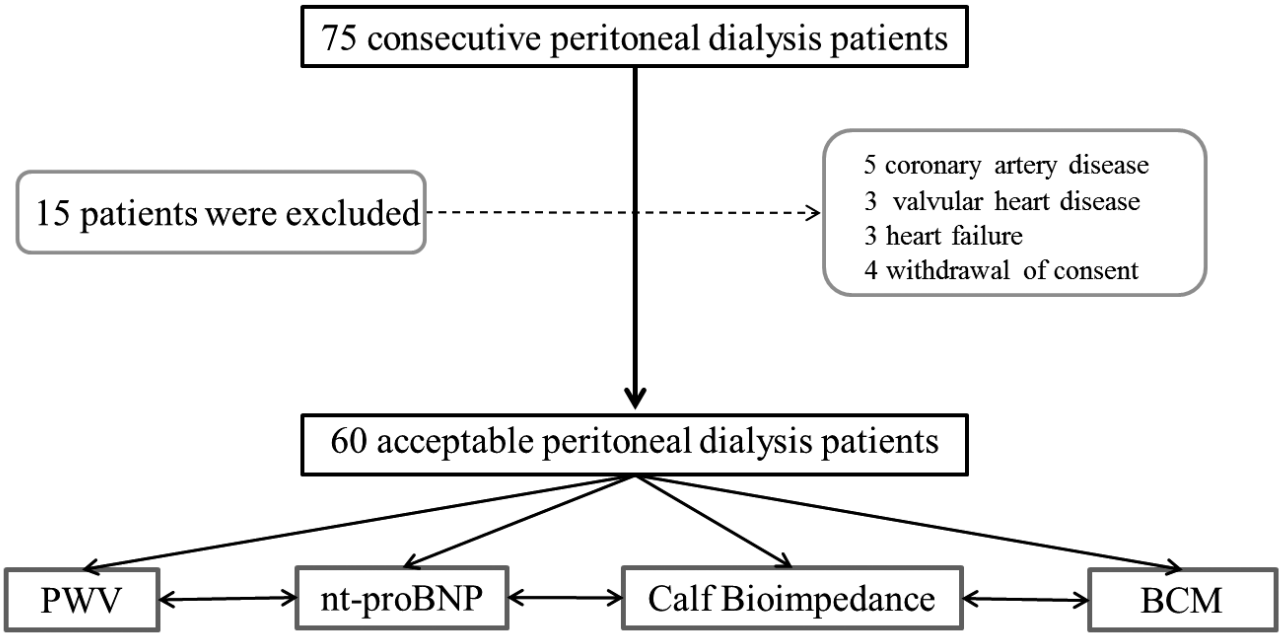

Figure 1 — Trial flow chart. PWV = pulse wave velocity; NT-proBNP = N-terminal fragment of B-type natriuretic peptide; BCM = body composition monitor.

to the recommendations of the American Society of Echocardiography (19).

End diastolic left ventricular septal and posterior wall thickness and internal dimensions were used to calculate left ventricular mass (LVM) as follows (20):

$$LVM\ (in\ g) = 0.8\ \{1.04\ [(LVDD+PWD+IVSD)^3 - IVSD^3]\}+0.6 \quad \text{Eq. 1}$$

Left ventricular hypertrophy was defined as a left ventricular mass index (LVMI, LVM in grams divided by body surface area in square meters) higher than 116.0 g/m^2 for men and 104.0 g/m^2 for women (20). Body surface area was calculated using Mosteller's formula (21).

LV diastolic function was evaluated according to the guideline (22).

EVALUATION OF HYDRATION STATUS: BIOIMPEDANCE METHODS

Body Composition Monitor (BCM): The Body Composition Monitor (BCM) measures ECW, TBW and provides a figure for degree of fluid overload (9,23). The BCM is the only commercially available device that can classify ESRD subjects in terms of volume status. Fluid status is determined using whole body bioimpedance spectroscopy (wBIS) at 50 different frequencies from 5 kHz to 1 MHz. After 10 to 15 minutes in the supine position, four electrodes were placed: two electrodes on the wrist and two on the ankle. Measurements were performed after peritoneal fluid had been drained.

Using the BCM, absolute fluid overload (FO), which is the difference between the expected patient's ECW under normal physiological conditions and the actual ECW and relative fluid overload (Rel. FO), defined as the FO to ECW ratio, were measured. Normal fluid status is defined when FO is between the 10th and 90th percentile for healthy, age- and gender-matched individuals from the reference population, i.e., between −1.1 L and +1.1 L (23,24). ECW volumes below and above this range define volume depletion and fluid overload, respectively.

The patients were stratified using the BCM method because, according to the literature, (23,24) this method is the only one that can classify subjects in terms of volume conditions comparing the other spectroscopy techniques.

Calf Bioimpedance Spectroscopy (cBIS): A Hydra 4200 device (Xitron Technologies, CA, USA) with 50 different frequencies from 5 kHz to 1 MHz was used to measure the calf extracellular (cRe) and intracellular (cRi) resistances, and calf normalized resistivity (CNR). The calf ECW (cECW) and ICW (cICW) were calculated using the Cole model (5,25).

Four electrodes were placed on the lateral side of the calf to inject alternate current (0.8 mA) and measure voltage. One sensing electrode (ES1) was placed at the point of maximal calf circumference (CMax), while the other sensing electrode (ES2) was placed 10 cm distal of ES1; the circumference at ES2 was defined as minimal circumference (CMin). Current injecting electrodes (EI1 and EI2) were placed 5 cm proximal and 5 cm distal of ES1 and ES2, respectively (Figure 2). CMax and CMin were measured using a soft measuring tape with 1 mm accuracy.

Calf resistivity was calculated from specific resistance at 5 kHz per unit of cross sectional area in (cm^2). Calf normalized resistivity (CNR) was defined as resistivity at 5 kHz divided by the body mass index (BMI). Calf resistivity was calculated from resistance at 5 kHz (obtained from Hydra 4200; Eq. 2).

$$\text{Calf resistivity} = R5 \times A/L \quad \text{Eq. 2}$$

where, A: is the calf cross-sectional area in cm^2; L is the distance (set to 10 cm) between the sensing electrodes, respectively.

The cross-sectional area (A) was calculated as.

$$A = Cave^2/(4\pi) \quad \text{Eq. 3}$$

where, Cave is the average of CMax and CMin (Cave = CMax + CMin)/2

To standardize for differences in body composition, resistivity at 5 kHz was normalized by the body mass index (BMI; calculated as body mass (kg) divided by (height in meters)^2 (m^2), and reported as calf normalized resistivity CNR with a unit of (Ωm^3/kg) x 10^{-2}

$$CNR = \text{calf resistivity}/BMI \quad \text{Eq. 4}$$

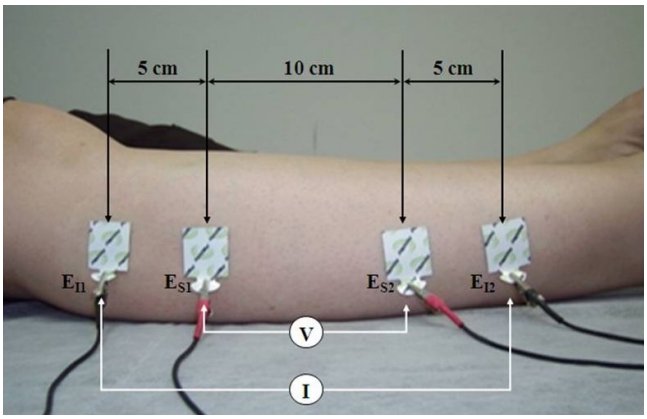

Figure 2 — Placement of calf electrodes. Electrodes EI1 and EI2 are used for injecting current and ES1 and ES2 are used for measuring voltage. The distance between ES1 and ES2 is fixed to 10 cm. ES = sensing electrode; EI = injecting electrode.

Normal range of CNR was defined as >18.5 W m^3/kg*10^{-2} for males and >20 W m^3/kg*10^{-2} for females. CNR correlates negatively with fluid overload, i.e., more excess fluid, lower CNR (5,25).

Measurements of Pulse Wave Velocity and Blood Pressure: Vascular studies were performed in a quiet, temperature-controlled room at 22°C with subjects resting in a supine position. Systolic and diastolic blood pressures (SBP; DBP) were measured in duplicate using a semi-automated, non-invasive oscillometric sphygmomanometer, following a 10-minute rest period. Pulse wave analysis was measured in the carotid and femoral arteries using a PWV machine (Micro Medical Pulse Trace, Rochester, UK) in accordance with the manufacturer's recommendations. Briefly, the transducers were positioned over the carotid and femoral arteries, always on the right side of the body. PWV was automatically calculated by measuring the time for the pulse wave to travel between the carotid and femoral arteries. All measurements were performed over 15 heart beats by a single operator blinded to the patient's group.

Hypertension was considered to be present if the SBP was 140 mmHg and/or DBP was 90 mmHg on two or more occasions (26). Mean arterial blood pressure (MAP) was calculated as follows (27):

$$MAP = [SBP + 2 \times DBP] / 3$$

STATISTICAL ANALYSIS

For continuous variables, results are presented as mean ± SD or median (minimum, maximum). Categorical variables were defined as a percentage. Parametric (independent samples *t*-test) and nonparametric (Mann-Whitney U) tests were used to compare continuous variables, according to the data distribution. Correlation analyses were performed using the Pearson or Spearman coefficients of correlation. Multivariate regression was used to evaluate independent relationship of indicators of fluid status with PWV. Each indicator (relative FO, CNR, NT-proBNP and ECW/ICW) was evaluated by a separate model. Variables with an unadjusted $p < 0.10$ in simple univariate linear regression analysis were included in the multivariate analysis. Models were adjusted for age, MAP, BMI and time on peritoneal dialysis. We used multivariate linear regression analysis with backward elimination and compared retained predictors using likelihood ratio tests. A two-sided p value < 0.05 was considered significant. 95% confidence intervals (CI) were calculated. All statistical analyses were performed using SPSS version 15 (SPSS, Inc., Chicago, IL, USA).

RESULTS

Patients were stratified into "normo" and "hypervolemic" groups according to absolute fluid overload measured by BCM (2.57 ± 0.91 L vs 0.74 ± 0.42 L, $p < 0.001$). Clinical and demographic characteristics of the patients are summarized in Table 1. The causes of end-stage renal failure (ESRF) were diabetes mellitus in 21 patients, hypertension in 14, polycystic kidney disease in 5, obstructive nephropathy in 5, glomerulonephritis in 2 and unknown in 13. ESRF causes were not different between the groups (Table 1).

Serum NT-proBNP levels were significantly higher in the hypervolemic group than in the normovolemic group (3,468 ± 981 pg/mL vs 1,095 ± 502 pg/mL $p < 0.001$). Other biochemical markers did not differ between the two groups. PWV, ECW and ECW/ICW were significantly higher and CNR was significantly lower in the hypervolemic group. No significant difference was noted for TBW. Although SBNP and MAP were higher in the hypervolemic group, DBP values did not differ (Table 1).

Echocardiographic characteristics are summarized in Table 2. While left ventricular end-systolic diameter (LVSD), left ventricular end-diastolic diameter (LVDD), interventricular septum diameter (IVSD), posterior wall diameter (PWD), left ventricular ejection fraction (LVEF) values and systolic pulmonary artery pressure were similar in the two groups, left ventricular mass indices were significantly higher in fluid overloaded patients. Indicators of left ventricular diastolic function such as mitral inflow late diastolic velocity, mitral valve deceleration time and mitral inflow early diastolic velocity/mitral lateral annular tissue Doppler early diastolic velocity (E/é1) values were significantly higher in the hypervolemic group. When other left ventricular diastolic functions were examined, the early to late ventricular filling velocities (E/A) values, left ventricular isovolumetric relaxation time (IVRT) and mitral lateral annular tissue Doppler early peak diastolic velocity were significantly higher in the normovolemic group than in the hypervolemic group.

PWV correlated significantly with all indicators of fluid status. ECW/ICW ratio (r: 0.25, *p*: 0.046), NT-pro BNP level (r: 0.49, $p < 0,001$) and relative FO (r: 0.40, *p*: 0.001) correlated positively and CNR (r: -0.37, *p*: 0.004) negatively with PWV (Figure 3). Additionally, we found significant correlations among LV mass index with CNR (r: -0.28, *p*: 0.039), NT-proBNP (r: 0.32, *p*: 0.017), PWV (r: 0.28, *p*: 0.038) and ECW/ICW (r: 0.38, *p*: 0.004).

In multivariate regression analysis, relative FO (Model A), CNR (Model B) and MAP (Model A, B, C, D) independently predicted PWV (Table 3).

TABLE 1
Demographic, Biochemical, Physical Examination Characteristics of the Study Population, Stratified by BCM Measurements of Fluid Status

Parameters	Hypervolemic group (*n*=25)	Normovolemic group (*n*=35)	*p*
Age (years)	49±16	45±11	0.33
Gender, Female (%)	36	40	0.74
Duration of CAPD (months)	38.5± 34.0	41.6± 32.8	0.47
Hemoglobin (g/l)	10.8±1.9	11.3±1.8	0.38
Platelet count ($\times$1,000/mm^3)	243±62	249±65	0.84
White blood cell count (10^3/µL)	8.6±3.1	8.3±2.8	0.92
Kt/V_{urea}	2.05±0.18	1.98±0.25	0.13
D/P Creatinine	0.76±0.08	0.69±0.10	0.014
Use of antihypertensive drugs	20	23	0.17
BMI (kg/m^2)	24.9±4.8	25.6±5.5	0.77
PWV (m/sec)	9.99±2.4	7.48±2.3	<0.001
Urine volume (mL/day)	928±343	834±216	0.20
TBW (L)	37.1±5.3	33.9±7.7	0.07
ECW (L)	17.8±2.4	15.2±3.3	0.001
ECW/ICW	0.93±0.11	0.81±0.08	<0.001
Abs. FO (L)	2.57 ±0.91	0.74±0.42	<0.001
Rel. FO (%)	14.1 ±3.9	5.14±1.8	<0.001
CNR [(Ωm^3/kg)$\times10^{-2}$]	13.7±2.4	16.0±3.3	0.005
Systolic blood pressure (mmHg)	147.2±19.3	127.4±22.7	0.001
Diastolic blood pressure (mmHg)	86.0±11.9	78.5±18.0	0.07
Mean arterial pressure (mmHg)	104.8±12.8	94.8±14.5	0.009
Cause of end stage renal disease			0.90
Diabetes Mellitus	10	13	
Hypertension	5	9	
Polycystic Kidney Disease	2	3	
Obstructive Nephropathy	2	3	
Glomerulonephritis	1	1	
Unknown	5	6	
Physical examination			
Edema	11	2	
Rales	4	0	
Jugular venous distension	7	1	
Biochemical parameters			
Plasma fasting glucose (mg/dL)	115.0±34.1	117±42.1	0.64
Blood urea nitrogen (mg/dL)	54±14.8	61±12.8	0.15
Creatinine (mg/dL)	8.3±3.6	8.9±3.0	0.55
Calcium (mg/dL)	8.6±0.7	8.9±0.8	0.28
Phosphorus (mg/dL)	4.5±1.1	4.2±1.3	0.22
Fasting total cholesterol (mg/dL)	185±31	182±29	0.51
Fasting LDL cholesterol (mg/dL)	109± 25	105±32	0.63
Fasting triglyceride (mg/dL)	171±91	173±78	0.91
Albumin (g/dL)	3.4±0.4	3.7±0.4	0.009
NT-proBNP (pg/mL)	3468±981	1095±502	<0.001

BCM = body composition monitor; CAPD = continuous ambulatory peritoneal dialysis; D/P = dialysate/plasma; BMI = body mass index; PWV = pulse wave velocity; TBW = total body water; ECW = extracellular water; ICW = intracellular water; Abs. FO = Absolute fluid overload; Rel. FO = relative fluid overload; CNR = calf normalized resistivity; NT-proBNP = the N-terminal fragment of B-type natriuretic peptide. All data values are expressed as mean ± standard deviation or percentage.

TABLE 2
Echocardiographic Characteristics

Conventional parameters	Hypervolemic group (*n*=25)	Normovolemic group (*n*=35)	*p*
LVSD (cm)	3.1±0.3	3.0±0.3	0.34
LVDD (cm)	4.8±0.3	4.6±0.4	0.12
IVSD (cm)	1.2±0.2	1.1±0.2	0.14
PWD (cm)	1.1±0.2	1.0±0.2	0.11
LVEF (%)	62±5	62±7	0.63
sPAB (mmHg)	32.8±8.3	28.6±6.4	0.27
LV mass index (g/m^2)	190.4±30.2	146.6±32.7	<0.001
Left ventricular diastolic functions			
Peak E velocity (cm/sec)	69.6±21.4	74.0±21.5	0.44
Peak A velocity (cm/sec)	106.2±21.4	75.0±27.0	<0.001
E/A	0.65±0.1	1.06±0.3	<0.001
DT (ms)	240.2±66.8	134.4±40.7	<0.001
IVRT (ms)	83.7±13.4	114.6±32.4	<0.001
Peak é (cm/s)	7.3±2.6	11.6±3.1	<0.001
E/é	10.5±4.6	6.7±2.4	<0.001
Pulmonary vein AR velocity (m/sec)	3.50±0.07	3.48±1.1	0.94
Left atrium volume (mL)	29.5±7.9	24.6±15.9	0.17

LVSD = left ventricular end-systolic diameter; LVDD = left ventricular end-diastolic diameter; IVSD = ınterventricular septum diameter; PWD = posterior wall diameter; LVEF = left ventricular ejection fraction; sPAB = systolic pulmonary artery pressure; LV = left ventricle, E = mitral inflow early diastolic velocity; A = mitral inflow late diastolic velocity; DT = deceleration time of early mitral inflow; IVRT = left ventricular isovolumetric relaxation time; é = mitral lateral annular tissue Doppler early diastolic velocity; AR = atrial reversal.
All data values are expressed as mean ± standard deviation (mean±SD).

DISCUSSION

To the best of our knowledge, this is the first study to examine the association between arterial stiffness, as determined by PWV, and extracellular fluid status in peritoneal dialysis patients. The use of several methods to assess fluid status strengthens the interpretation of our results. We have demonstrated by several methods that hypervolemia may affect arterial distensibility function both directly and through hypervolemia-induced hypertension in PD patients. The achievement of normal fluid status is essential in dialysis patients to prevent complications of fluid overload on the cardiovascular system such as hypertension, LVH and cardiac failure. There are several objective methods to estimate dry weight (DW) in peritoneal dialysis patients, such as measurements of inferior vena cava diameter, natriuretic peptides, determination of ECW/ICW or ECW/TBW ratio in addition to clinical evaluation (3,4). The use of these techniques in daily clinical practice is not very efficient, because their accuracy is limited and there are no certain cutoff levels which indicate normal fluid status (3–5).

We used several tools to estimate fluid status in order to increase accuracy of our study. However, the BCM method was chosen for patient stratification, since it provides cut-off values discriminating normal from abnormal fluid states. The BCM has been validated and introduced into use in everyday clinical practice (23,24,28). Wizemann *et al.* recently demonstrated that relative fluid overload, as measured by BCM, is related to increased cardiovascular mortality (29). However, BCM prediction of normal fluid status in hemodialysis patients has been shown to be influenced by the degree of fluid overload, in that the more fluid-overloaded the patient, the higher the body weight which is predicted to be normal fluid status (10). According to BCM measurement, more than 40% of our study population were hypervolemic. Patients with hypervolemia had higher NT-pro BNP levels and ECW/ICW ratio and lower CNR compared to those with normovolemia. These results strengthened the hypervolemia diagnosis by BCM. CNR was significantly lower in the hypervolemic group (13.7 ± 2.4) than in the normovolemic group (16.0 ± 3.3), which agrees with the difference in fluid status between the two groups as defined by BCM. We found a significant negative correlation between CNR and

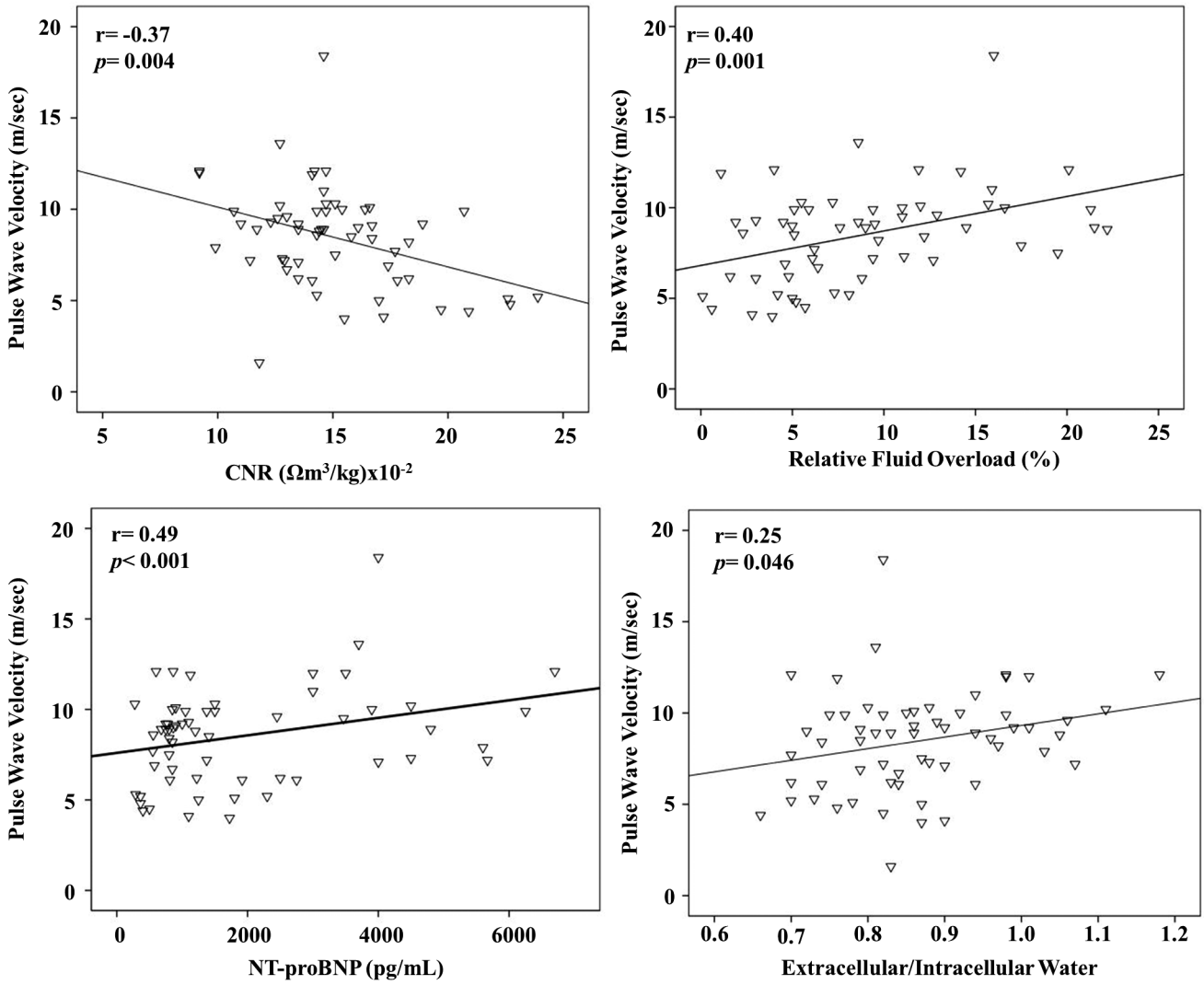

Figure 3 — The correlation analysis is between PWV (pulse wave velocity) and CNR (Calf Normalized Resistivity), relative FO (fluid overload), NT-proBNP (N-terminal fragment of B-type natriuretic peptide), ECW/ICW (extracellular/intracellular water).

absolute fluid overload (r = -0.375 p = 0.004). In addition, most of the patients in the normovolemic group did not reach the dry weight criterion according to CNR because the average CNR (16.0 ± 3.3) was less than the threshold of the normal range. This may be evidence to confirm that normal hydration as estimated by BCM still represents a degree of fluid overload as previously shown (10). Higher left ventricular mass index value in the hypervolemic group indicated that these patients might have been exposed to chronic hypervolemia. We also showed that left ventricular diastolic functions were more impaired in the hypervolemic group than in the normovolemic group. Myocardial hypertrophy and myocyte ischemia, which are generated by volume overload, lead to activation of cellular apoptotic signals and activation of pathways causing an increase in production of extracellular matrix and thus interstitial myocardial cell fibrosis and diastolic dysfunction (30,31).

The effect of fluid status on arterial stiffness has not been well documented. Vuurmans *et al.* (32) examined the impact of acute volume changes on PWV in 19 hemodialysis (HD) patients who had reached their dry weight. Dry weight was assessed by clinical features. PWV was measured before and 24 hours after the HD session in which ultrafiltration volume was determined according to clinical dry weight assessment. Volume reduction with dialysis had no significant effect on PWV (pre-dialysis: 9.9 ± 3.1 m/s, post-dialysis: 9.3 ± 2.5 m/s, P 0.16). Lin *et al.* (33) investigated how body fluid distribution affects large-artery structure and function in a cross-sectional study. Fluid status was estimated in 157 HD patients by the ECW/ICW ratio derived from bioimpedance spectroscopy. ECW/ICW ratio showed a significant positive independent association with PWV. The authors speculated that the relation between hypervolemia and increased arterial stiffness may result from increased salt intake. Increased

TABLE 3
Multiple Regression Analysis of Predictors of Pulse Wave Velocity in All Study Subjects (n=60)

Variables	β	Std. errors	p
Model A PWV, m/sec			
Rel. FO, %	0.31	0.04	0.009
MAP, mmHg	0.26	0.02	0.04
Model B PWV, m/sec			
CNR, [(Ωm^3/kg)×10^{-2}]	-0.34	0.10	0.006
MAP, mmHg	0.28	0.02	0.02
Model C PWV, m/sec			
MAP, mmHg	0.37	0.02	0.004
Model D PWV, m/sec			
MAP, mmHg	0.37	0.02	0.004

PWV = Pulse wave velocity; Rel.FO = relative fluid overload; MAP = mean arterial pressure; CNR = calf normalized resistivity; ECW/ICW = Extracellular water/Intracellular water ratio; NT-proBNP = N-terminal fragment of B-type naPWVtriuretic peptide; BMI = body mass index.
Regression models include rel. FO (Model A, Adjusted r^2=0.26), CNR (Model B, Adjusted r^2=0.30), NT-proBNP (Model C, Adjusted r^2=0.15) and ECW/ICW ratio (Model D, Adjusted r^2=0.12), respectively.
All models were adjusted with age, MAP, BMI and duration of peritoneal dialysis.
Bold values indicate the significant values (p<0.05).

salt intake causes hypervolemia by stimulating thirst, and also changes the function and structure of large conduit arteries independently from blood pressure and atherosclerosis. In another cross sectional study (34) of the association between hydration state and arterial stiffness, the ECW/TBW ratio was used to estimate hydration state. Data from 73 HD patients showed that a higher ECW/TBW ratio was related to higher PWV. Onofriescu *et al.* (8) studied, in a randomized trial, the effect of BIS-guided versus clinical-guided ultrafiltration on several end-points in 135 HD patients. At the end of the one-year follow-up, PWV had decreased significantly only in the BIS-guided group, whereas PWV had increased in the clinically-guided group. To make any comment on association between fluid status and PWV in this study is difficult because fluid status determined by absolute or relative fluid overload did not differ at baseline and at the end of the study in both groups. In our study, PWV showed a positive correlation with relative FO, ECW/ICW ratio, and NT-proBNP and an inverse correlation with CNR in univariate analysis. MAP independently predicted PWV in each linear regression model. Hypertension generates arterial remodeling by tensile and shear stress. Endothelial cells serve as mechanosensors for the conversion of physical forces into biochemical signals leading to vessel wall remodeling (35). Several studies have revealed a strong relationship between PWV and endothelial function and these studies showed that high blood pressure or increased luminal pressure also stimulates collagen production that results in decreased distensibility (36,37). However, relative fluid overload and CNR showed an independent relationship with PWV in multivariate analysis. These results indicated that hypervolemia might affect PWV independently from raised blood pressure. Endothelial dysfunction triggered by hypervolemia may cause structural and functional change in the large arteries.

Once the balance between the elastic components of the arterial wall is disturbed with advancing age, increased arterial stiffness may occur. Advanced age may affect arterial stiffness independently in peritoneal dialysis patients (38). However, we did not find any correlation between age and arterial stiffness in our study. Possibly, the small sample size of this study prevented this relationship from being revealed. In addition, there might be other concurrent factors that might prevent this effect from being shown which also affect the arterial stiffness in this cohort.

While novel in scope and patient population, our study has some limitations. First, the relatively small sample size and the cross-sectional design. Second, the paucity of information concerning antihypertensive drug use. Third, we did not employ invasive procedures to assess aortic elasticity and pulse pressure, which are generally considered more accurate than PWV.

In conclusion, in prevalent peritoneal dialysis patients fluid status may affect arterial distensibility, both directly and through hypervolemia-induced hypertension. The correction of hypervolemia has the potential to not only prevent hypertension and LVH but also to improve arterial stiffness, a well-recognized cardiovascular risk factor. Additional prospective studies are necessary to confirm these findings and further identify pathophysiological mechanisms.

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DISCLOSURES

This study was conducted in full accordance with the Declaration of Helsinki. The manuscript has been

read and approved by all authors. The manuscript has not been published elsewhere. Drs. Peter Kotanko and Nathan Levin hold stock in Fresenius Medical care. All other authors do not have any potential financial conflicts of interest.

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