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REDUCED RESIDUAL RENAL FUNCTION IS ASSOCIATED WITH ENDOTHELIAL DYSFUNCTION IN PATIENTS RECEIVING PERITONEAL DIALYSIS

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♦ ***Background:*** **Endothelial dysfunction, which contributes to atherosclerosis and arteriosclerosis, commonly accompanies end-stage renal disease (ESRD). However, little is known about the role of residual renal function (RRF) in endothelial protection in ESRD patients. This study aimed to investigate the relationship between endothelial function and RRF in patients undergoing peritoneal dialysis (PD).**

♦ ***Methods:*** **This was a cross-sectional study involving 72 prevalent PD patients. Demographic and clinical data were recorded and residual glomerular filtration rate (GFR), Kt/V urea, and serum concentrations of inflammatory markers were measured. Endothelial function was assessed by brachial artery endothelium-dependent vasodilation [flow-mediated dilation (FMD)] to reactive hyperemia following 5 minutes of forearm ischemia.**

♦ ***Results:*** **In patients with FMD% above the median value (FMD > 2.41%), residual GFR was significantly higher compared to that in patients with FMD% below the median [1.50 (0 – 9.64) vs 0.48 (0 – 3.89) mL/min/1.73 m^2, $P = 0.026$]. Correlation analyses revealed that residual GFR ($\rho = 0.381$, $P = 0.001$) and total Kt/V urea ($\gamma = 0.408$, $P < 0.001$) were positively correlated with FMD%, whereas PD duration ($\gamma = -0.351$, $P = 0.003$), high-sensitivity C-reactive protein ($\rho = -0.345$, $P = 0.003$), pulse pressure ($\gamma = -0.341$, $P = 0.003$), and age ($\gamma = -0.403$, $P < 0.001$) were inversely correlated with FMD%. In contrast, there was no correlation between peritoneal Kt/V urea and FMD%. In multivariate linear regression analysis adjusted for these factors, residual GFR was found to be an independent determinant of FMD% ($\beta = 0.317$, $P = 0.017$).**

♦ ***Conclusion:*** **This study shows that RRF is independently associated with endothelial dysfunction in ESRD patients on PD, suggesting that RRF may contribute to endothelial protection in these patients.**

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KEY WORDS: Endothelial dysfunction; residual renal function.

Cardiovascular disease is the leading cause of morbidity and mortality in patients with end-stage renal disease (ESRD) (1). The increased risk of cardiovascular disease is attributed mainly to the high prevalence of traditional risk factors, such as hypertension, diabetes, smoking, and dyslipidemia, in this population. Recently, accumulating evidence has suggested that nontraditional risk factors, including inflammation, oxidative stress, and abnormal calcium–phosphorus metabolism, also contribute to accelerated atherosclerosis (2,3).

The endothelium modulates vascular tone and structure by producing and releasing nitric oxide, which also exerts a protective role against vascular atherosclerotic damage (4). Endothelial dysfunction is an important initiating event in the processes of atherosclerosis and arteriosclerosis (5) and is affected by both traditional and nontraditional risk factors. To date, numerous studies have demonstrated that endothelial function is impaired in ESRD patients (6,7) and predicts cardiovascular mortality in these patients, as in the general population (8).

Recently, the importance of residual renal function (RRF) has been highlighted in patients with ESRD. Decline in RRF is closely linked with fluid overload, anemia, inflammation, malnutrition, and mortality (9,10).

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In addition, a decrease in creatinine clearance was significantly associated with endothelial dysfunction (11) and arterial stiffness (12) in patients with chronic kidney disease, suggesting that kidney function plays an important role in vascular protection. However, it is not clear whether endothelial function is still affected by RRF in patients with ESRD. Therefore, in this study, we investigated the relationship between endothelial function and RRF in ESRD patients on continuous ambulatory peritoneal dialysis (CAPD).

PATIENTS AND METHODS

STUDY SUBJECTS AND DATA COLLECTION

This was a cross-sectional study of ESRD patients undergoing CAPD, who were between 18 and 75 years of age and who had been maintained on peritoneal dialysis (PD) for more than 3 months. Patients were considered eligible for this study if they had no history of malignancy or other chronic inflammatory diseases, such as systemic lupus erythematosus and rheumatoid arthritis, and had no overt infections or acute coronary syndrome during the 3 months prior to study entry. Patients were also excluded if they had a history of kidney transplantation or hemodialysis prior to CAPD. In addition, patients with any signs of volume overload, such as jugular vein distension, weight gain > 2 kg per day with peripheral pitting edema requiring frequent use of hypertonic PD solutions, or pulmonary congestion on chest x ray, were excluded. Of 156 patients screened, 72 were included in the final analysis (Figure 1). All patients were prescribed Baxter PD solution (Baxter Healthcare Corp., Singapore).

Demographic and clinical data were recorded at study entry: age, gender, body mass index calculated as weight/height^2, primary renal disease, previous history of cardiovascular disease, and duration of dialysis. Cardiovascular disease was defined as a history of coronary, cerebrovascular, or peripheral vascular disease. Coronary disease was defined as a history of angioplasty, coronary artery bypass grafts, myocardial infarction, or angina. Cerebrovascular disease was defined as a previous transient ischemic attack, stroke, or carotid endarterectomy, while peripheral vascular disease was defined as a history of claudication, ischemic limb loss and/or ulceration, or peripheral revascularization procedure. The Charlson Comorbidity Index was used to quantify comorbid conditions in the study subjects (13). The following laboratory data were measured from blood samples: hemoglobin, blood urea nitrogen, creatinine, calcium, phosphorus, albumin, total cholesterol, triglyceride, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and intact parathyroid hormone. Residual glomerular filtration rate (GFR) was calculated as the average clearance of urea and creatinine from a 24-hour urine collection (14). Kt/V urea was determined from the total loss of urea nitrogen in spent dialysate using the Watson equation (15). Estimated average glucose exposure was calculated by multiplying the instilled dialysate volume by the respective glucose concentration. The modified peritoneal equilibration test (13) was performed with 4.25% glucose dialysis solution as described previously (16). The dialysate-to-plasma creatinine (D/P Cr) and glucose (D/D0 glucose) concentration ratios at 4 hours of dwell were used to describe the peritoneal small solute transport rate.

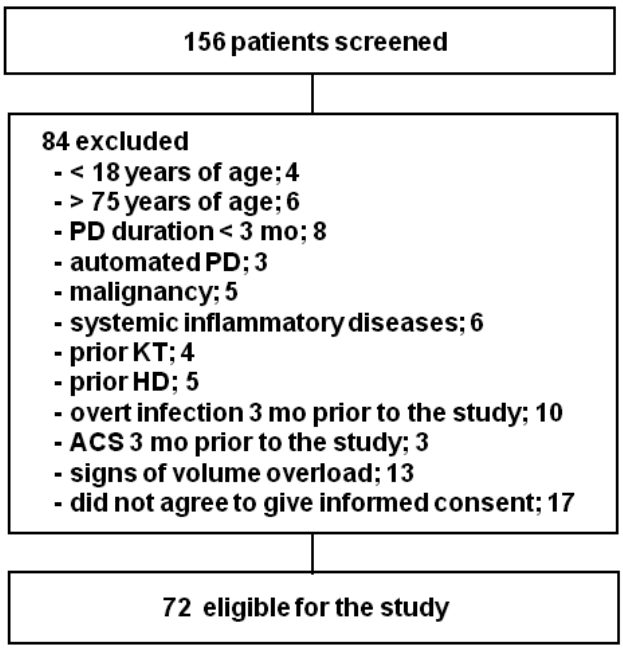

Figure 1 — Flow diagram indicating patient recruitment and exclusion. PD = peritoneal dialysis; KT = kidney transplant; HD = hemodialysis; ACS = acute coronary syndrome.

This study was approved by the institutional review board for human research at our center and informed consent was obtained from all patients.

MEASUREMENT OF INFLAMMATORY BIOMARKERS IN SERUM AND PLASMA

High-sensitivity C-reactive protein (hs-CRP) concentrations were determined by a latex-enhanced immunonephelometric method using a BN II analyzer (Dade Behring, Newark, DE, USA). Interleukin-6 (IL-6) levels were measured using an enzyme-linked immunosorbent assay kit (R&D Systems Europe, Abingdon, Oxon, UK) and fibrinogen concentrations in citrated plasma by a

modified clot rate assay using a Pacific Hemostasis Assay Set (Humlersville, NC, USA).

FLOW-MEDIATED DILATION (FMD)

Endothelium-dependent vasodilation was noninvasively assessed by determining FMD using high resolution ultrasonography (Logiq 7; GE Medical Systems, Milwaukee, WI, USA) as described previously (17). Subjects were informed to fast overnight, not to exercise, not to ingest substances that might affect FMD, such as caffeine, high-fat foods, or vitamin C, or use tobacco for at least 12 hours before the study. On the day of FMD measurement, blood pressure was measured three times with a mercury sphygmomanometer. Using ultrasonography, baseline diameter (mean of 3 measurements) and peak flow velocity (mean of 2 measurements) were determined. Thereafter, a pressure cuff placed on the forearm was inflated to at least 50 mmHg above systolic blood pressure. After 5 minutes, the cuff was released to induce reactive hyperemia. After that, the maximum peak flow velocity was measured within 15 seconds and brachial artery diameter was measured between 45 and 60 seconds. Endothelium-independent vasodilation was also assessed by measuring changes in brachial artery diameter 5 minutes after the administration of 0.4 mg sublingual nitroglycerine (nitroglycerine-mediated dilation; NMD). This NMD test was performed 15 minutes after the FMD test and after obtaining a new baseline brachial artery diameter value. FMD and NMD were calculated as percentage changes in brachial artery diameter relative to the mean baseline diameter during reactive hyperemia and after administration of nitroglycerine respectively.

All ultrasonographic measurements at each visit were performed by a single observer who was blinded to patients' clinical information. Intraobserver within-subjects coefficients of variation for FMD and NMD were 8.5% ± 2.7% and 9.1% ± 1.8% respectively. All assessments (*i.e.*, residual GFR, dialysis adequacy, peritoneal equilibration test, and FMD) were performed simultaneously on the same day.

STATISTICAL ANALYSIS

Statistical analysis was performed using the statistical package SPSS version 13.0 (SPSS Inc., Chicago, IL, USA). All data are expressed as mean ± SD or median and range for skewed data. The Kolmogorov–Smirnov test was used to analyze the normality of distribution of the measured parameters. Patients were divided into two groups based on the median value of FMD and variables were compared between the two groups. Results were analyzed using Student's t-test and the chi-square test for normally distributed data. In addition, Pearson's correlation analysis was used to elucidate the relationship between FMD and clinical and laboratory parameters. For skewed data, the Mann–Whitney U-test was used to compare variables between the two groups and the Spearman correlation coefficient was calculated to identify the relationship between covariates. Factors independently associated with FMD were determined using multivariate linear regression analysis adjusted for other factors with a *P* value less than 0.10 in univariate analyses. Because skewed data such as residual GFR and hs-CRP violate the assumption of a normal distribution, they cannot be included in a multiple linear regression model in an untransformed state. Therefore, the former was categorized into two groups according to the definition of anuria (*i.e.*, residual GFR 1.0 mL/min/1.73 m^2) (18) and the latter was log transformed and then entered into the final analysis. The level of significance was set at 0.05.

RESULTS

PATIENT CHARACTERISTICS

The baseline characteristics of the 72 patients are shown in Table 1. Mean age was 48.4 ± 11.3 years, 33 patients (45.8%) were male, and mean PD duration was 80.2 ± 50.7 months. A history of cardiovascular disease was noticed in only 5 patients (6.9%): 3 had coronary artery disease and 2 had cerebrovascular disease. Mean Charlson Comorbidity Index was 3.1 ± 1.3. Mean systolic and diastolic blood pressures were 133.3 ± 20.1 and 80.2 ± 9.7 mmHg respectively, and more than 90% of the subjects were taking antihypertensive medications. The median or mean concentrations of serum inflammatory markers were as follow: hs-CRP, 1.96 (0.46 – 6.86) mg/L; IL-6, 7.42 ± 2.87 pg/mL; and plasma fibrinogen, 486.0 ± 88.6 mg/dL. Total and peritoneal Kt/V urea were 1.94 ± 0.46 and 1.62 ± 0.36 respectively, and median residual GFR was 0.98 (0 – 9.64) mL/min/1.73 m^2.

COMPARISON OF CLINICAL AND LABORATORY PARAMETERS ACCORDING TO FMD%

Patients were divided into two groups based on the median value of FMD (2.41%). Compared to patients with FMD ≤ 2.41%, residual GFR was significantly higher [1.50 (0 – 9.64) vs 0.48 (0 – 3.89) mL/min/1.73 m^2, $P = 0.026$], whereas peritoneal Kt/V urea was significantly lower (1.43 ± 0.32 vs 1.82 ± 0.28, $P < 0.001$) in patients with FMD > 2.41%. However, total Kt/V urea and total ultrafiltration volume were not significantly different

TABLE 1
Baseline Patient Characteristics

Patients (*n*)	72	Calcium	8.8±0.6 mg/dL
Age	48.4±11.3 years	Phosphorus	5.1±1.4 mg/dL
Gender	33 males:39 females	PTH[a]	237.7 (1–996.6) pg/mL
Body mass index	22.6±2.8 kg/m^2	Serum albumin	3.78±0.37 g/dL
PD duration	80.2±50.7 months	Total cholesterol	188.0±35.6 mg/dL
Biocompatible PD solution	66 (91.7%)	Triglyceride	136.7±118.1 mg/dL
Previous cardiovascular disease	5 (6.9%)	HDL	53.8±15.9 mg/dL
Charlson Comorbidity Index	3.1±1.3	LDL	115.7±31.8 mg/dL
Primary disease		Plasma fibrinogen	486.0±88.6 mg/dL
Chronic glomerulonephritis	35 (48.6%)	hs-CRP[a]	1.96 (0.46–6.86) mg/L
Hypertension	19 (26.4%)	Interleukin-6	7.42±2.87 pg/mL
Diabetes mellitus	12 (16.7%)	8-Isoprostane[a]	308.6 (50.5–1586.9) pg/mL
Polycystic kidney disease	2 (2.8%)	FMD	3.14%±2.70%
Others	4 (5.6%)	NMD	12.6%±8.0%
Systolic blood pressure	133.3±20.1 mmHg	Residual GFR[a]	0.98 (0–9.64) mL/min/1.73 m^2
Diastolic blood pressure	80.2±9.7 mmHg	Total Kt/V urea	1.94±0.46
Pulse pressure	53.1±19.0 mmHg	Peritoneal Kt/V urea	1.62±0.36
Medications		Renal Kt/V urea[a]	0.32 (0–1.66)
RAS blockades	51 (70.8%)	Total UF volume	1347.9±504.5 mL/day
Beta blockers	40 (55.5%)	Peritoneal UF volume	1053.8±577.6 mL/day
Calcium channel blockers	42 (58.3%)	Renal UF volume[a]	294.2 (0–1350) mL/day
Statins	8 (11.1%)	D/P Cr at 4 hours	0.71±0.10
Active vitamin D	20 (27.8%)	D/D0 glucose at 4 hours	0.35±0.08
Hemoglobin	10.7±1.7 g/dL	Glucose exposure	115.4±26.1 g/day

PD = peritoneal dialysis; RAS = renin–angiotensin system; PTH = parathyroid hormone; HDL = high-density lipoprotein; LDL = low-density lipoprotein; hs-CRP = high-sensitivity C-reactive protein; FMD = flow-mediated dilation; NMD = nitroglycerine-mediated dilation; GFR = glomerular filtration rate; UF = ultrafiltration; D/P Cr = dialysate-to-plasma ratio of creatinine.
[a] Skewed data expressed as median (range).
Other data expressed as mean±SD.

between the two groups. In addition, pulse pressure (47.5 ± 18.9 vs 58.4 ± 17.8 mmHg, $P = 0.014$), serum hs-CRP levels [1.69 (0.46 – 5.79) vs 2.30 (0.46 – 6.86) mg/L, $P = 0.003$], and D/P Cr at 4 hours (0.68 ± 0.08 vs 0.75 ± 0.11, $P = 0.002$) were significantly lower in patients with higher FMD%. The proportions of patients on renin–angiotensin system blockades or statins were comparable between the two groups (Table 2).

COMPARISON OF CLINICAL AND LABORATORY PARAMETERS ACCORDING TO RESIDUAL GFR

Anuria was defined as residual GFR less than 1 mL/min/1.73 m^2 (18). Based on residual GFR value of 1 mL/min/1.73 m^2, patients were classified into lower (n = 52) and higher RRF (n = 20) groups. As shown in Table 3, patients with higher RRF had higher FMD% (5.03% ± 3.99% vs 2.51% ± 1.75%, $P < 0.001$), shorter duration of PD (27.3 ± 17.3 vs 97.9 ± 45.7 months, $P < 0.001$), and lower pulse pressure (40.2 ± 15.1 vs 57.3 ± 18.4 mmHg, $P < 0.001$) than the lower RRF group. In addition, serum concentrations of hs-CRP [1.27 (0.46 – 2.81) vs 2.19 (0.46 – 6.86) mg/L, $P = 0.027$] and plasma levels of fibrinogen (442.3 ± 63.5 vs 500.6 ± 91.4 mg/dL, $P = 0.015$) were significantly lower in the higher RRF group than in the lower RRF group (Table 3).

FACTORS ASSOCIATED WITH ENDOTHELIAL DYSFUNCTION

To identify factors associated with endothelial dysfunction, correlation analyses were first performed. FMD% was positively correlated with residual GFR and total Kt/V urea ($\gamma = 0.408$, $P < 0.001$), whereas it was inversely correlated with age ($\gamma = -0.403$, $P < 0.001$), PD duration ($\gamma = -0.351$, $P = 0.003$), pulse pressure ($\gamma = -0.341$, $P = 0.003$), serum hs-CRP levels ($\rho = -0.345$, $P = 0.003$), and D/P Cr at 4 hours ($\gamma = -0.238$, $P = 0.044$). Plasma fibrinogen levels were also associated with FMD% but this did not reach statistical significance ($\gamma = -0.215$, $P = 0.069$). In contrast, there was no significant correlation between peritoneal Kt/V urea and FMD% (Table 4). In a multivariate linear regression analysis adjusted for these factors, residual GFR was

TABLE 2
Comparison of Clinical and Laboratory Parameters According to Flow-Mediated Dilation (FMD%)

	FMD below median (FMD≤2.41%)	FMD above median (FMD>2.41%)	*P* Value
Patients (*n*)	37	35	—
Age (years)	50.6±11.8	46.0±10.3	NS
Gender (male:female)	18:19	15:20	NS
Body mass index (kg/m^2)	22.9±2.3	22.4±3.2	NS
PD duration (months)	93.2±48.1	66.5±50.5	0.024
Biocompatible PD solution	34 (91.9%)	32 (91.4%)	NS
Previous cardiovascular disease	3 (8.1%)	2 (5.7%)	NS
Diabetes mellitus	6 (16.2%)	6 (17.1%)	NS
Charlson Comorbidity Index	3.2±1.4	2.9±1.1	NS
Systolic blood pressure (mmHg)	136.3±21.3	130.1±18.6	NS
Diastolic blood pressure (mmHg)	78.0±9.2	82.6±9.8	NS
Pulse pressure (mmHg)	58.4±17.8	47.5±18.9	0.014
Medications			
RAS blockades	27 (73.0%)	24 (68.6%)	NS
Statins	4 (10.8%)	4 (11.4%)	NS
Active vitamin D	12 (32.4%)	8 (22.9%)	NS
Hemoglobin (g/dL)	10.5±1.6	11.0±1.8	NS
Calcium (mg/dL)	8.8±0.6	8.8±0.7	NS
Phosphorus (mg/dL)	5.1±1.4	5.1±1.3	NS
PTH (pg/mL)[a]	223.9 (1–996.0)	232.9 (6.2–711.3)	NS
Serum albumin (g/dL)	3.79±0.34	3.79±0.41	NS
Total cholesterol (mg/dL)	185.0±36.9	191.1±35.2	NS
Triglyceride (mg/dL)	126.2±118.8	147.9±118.0	NS
HDL (mg/dL)	54.0±15.2	53.6±16.7	NS
LDL (mg/dL)	115.4±30.1	116.1±33.9	NS
Plasma fibrinogen (mg/dL)	499.8±90.1	471.4±85.9	NS
hs-CRP (mg/L)[a]	2.30 (0.46–6.86)	1.69 (0.46–5.79)	0.003
Interleukin-6 (pg/mL)	7.54±3.17	7.20±2.59	NS
8-Isoprostane (pg/mL)[a]	316.8 (50.5–611.9)	239.7 (55.7–1586.9)	NS
Residual GFR (mL/min/1.73 m^2)[a]	0.48 (0–3.89)	1.50 (0–9.64)	0.026
Total Kt/V urea	1.93±0.40	1.96±0.52	NS
Peritoneal Kt/V urea	1.82±0.28	1.43±0.32	<0.001
Renal Kt/V urea[a]	0.10 (0–0.84)	0.30 (0–1.66)	<0.001
Total UF volume (mL/day)	1350.0±545.0	1345±465.9	NS
Peritoneal UF volume (mL/day)	1150.5±571.8	951.4±574.0	NS
Renal UF volume (mL/day)[a]	199.5 (0–1060)	394.3 (0–1350)	NS
D/P Cr at 4 hours	0.75±0.11	0.68±0.08	0.002
D/D0 glucose at 4 hours	0.33±0.08	0.38±0.07	0.004
Glucose exposure (g/day)	112.2±23.5	114.5±23.8	NS

PD = peritoneal dialysis; RAS = renin–angiotensin system; PTH = parathyroid hormone; HDL = high-density lipoprotein; LDL = low-density lipoprotein; hs-CRP = high-sensitivity C-reactive protein; GFR = glomerular filtration rate; UF = ultrafiltration; D/P Cr = dialysate-to-plasma ratio of creatinine; NS = not significant.
[a] Mann–Whitney U test was performed; data are expressed as median (range).

found to be an independent determinant of FMD% (β = 0.317, *P* = 0.017) (Table 5).

Since there was a correlation between residual GFR and PD duration, two additional multivariate regression analyses were conducted: one excluding residual GFR and the other excluding PD duration in the model. The results of these analyses revealed that RRF remained as an independent associate of FMD, whereas PD duration did not. In addition, we checked whether there was multicollinearity between residual GFR and PD duration and found

TABLE 3
Comparison of Clinical and Laboratory Parameters According to Residual Glomerular Filtration Rate (GFR)

	Residual GFR ≤1 mL/min/1.73 m^2	Residual GFR >1 mL/min/1.73 m^2	*P* Value
Patients (*n*)	52	20	—
Age (years)	49.1±11.2	46.1±11.2	NS
Gender (male:female)	25:27	8:12	NS
Body mass index (kg/m^2)	22.8±2.5	22.1±3.5	NS
PD duration (months)	97.9±45.7	27.3±17.3	<0.001
Biocompatible PD solution	48 (92.3%)	18 (90%)	NS
Previous cardiovascular disease	4 (7.7%)	1 (5%)	NS
Diabetes mellitus	8 (15.4%)	4 (20.0%)	NS
Charlson Comorbidity Index	3.1±1.4	2.8±1.0	NS
Systolic blood pressure (mmHg)	136.8±18.8	122.8±20.9	0.01
Diastolic blood pressure (mmHg)	79.4±8.2	82.6±13.3	NS
Pulse pressure (mmHg)	57.3±18.4	40.2±15.1	<0.001
Medications			
RAS blockades	39 (75.0%)	12 (60.0%)	NS
Statins	5 (9.6%)	3 (15.0%)	NS
Active vitamin D	15 (28.8%)	5 (25.0%)	NS
Hemoglobin (g/dL)	10.5±1.6	11.3±1.9	NS
Calcium (mg/dL)	8.8±0.7	8.9±0.6	NS
Phosphorus (mg/dL)	5.2±1.4	4.8±1.2	NS
PTH (pg/mL)[a]	217.2 (16.5–754.0)	237.7 (1–996.6)	NS
Serum albumin (g/dL)	3.74±0.35	3.93±0.43	NS
Total cholesterol (mg/dL)	183.2±32.7	202.3±42.0	NS
Triglyceride (mg/dL)	121.89±100.5	181.7±154.5	NS
HDL (mg/dL)	54.8±16.2	50.9±14.9	NS
LDL (mg/dL)	112.4±29.6	125.9±36.7	NS
Plasma fibrinogen (mg/dL)	500.6±91.4	442.3±63.5	0.015
hs-CRP (mg/L)[a]	2.19 (0.46–6.86)	1.27 (0.46–2.81)	0.027
Interleukin-6 (pg/mL)	7.72±2.93	6.50±2.56	NS
8-Isoprostane (pg/mL)[a]	336.4 (122.5–1539.0)	270.3 (50.5–1586.9)	NS
FMD (%)	2.51±1.75	5.03±3.99	<0.001
NMD (%)	10.08±5.40	20.2±9.85	<0.001
D/P Cr at 4 hours	0.72±0.10	0.69±0.10	NS
D/D0 glucose at 4 hours	0.35±0.08	0.36±0.08	NS
Glucose exposure (g/day)	122.5±30.2	118.0±24.4	NS

PD = peritoneal dialysis; RAS = renin–angiotensin system; PTH = parathyroid hormone; HDL = high-density lipoprotein; LDL = low-density lipoprotein; hs-CRP = high-sensitivity C-reactive protein; FMD = flow-mediated dilation; NMD = nitroglycerine-mediated dilation; D/P Cr = dialysate-to-plasma ratio of creatinine; NS = not significant.
[a] Mann–Whitney U test was performed; data are expressed as median (range).

that values of variance inflation factor for these two factors were 1.78 and 1.74 respectively, suggesting that there is little evidence of multicollinearity (data not shown).

DISCUSSION

Our results show that residual GFR is independently associated with endothelial function in ESRD patients undergoing PD, suggesting that preservation of RRF, even in PD patients, may be beneficial in terms of vascular protection.

It has been reported that endothelial dysfunction is significantly related to kidney function in predialysis patients (11,19,20) and frequently accompanies (6,7) chronic kidney disease (11,21), suggesting that RRF may contribute to vascular endothelial protection. However, prior to this study, it was not clear whether the

TABLE 4
Factors Associated with Flow-Mediated Dilation (FMD)

	Correlation coefficient	*P* Value
Residual GFR[a]	0.381	0.001
PD duration	−0.351	0.003
Total Kt/V urea	0.408	<0.001
Peritoneal Kt/V urea	−0.160	0.178
Renal Kt/V urea[a]	0.584	<0.001
Age	−0.403	<0.001
Pulse pressure	−0.341	0.003
Hemoglobin	0.008	0.946
Calcium × phosphorus	−0.028	0.815
Total cholesterol	0.080	0.504
LDL cholesterol	0.180	0.367
hs-CRP[a]	−0.345	0.003
Fibrinogen	−0.215	0.069
Interleukin-6	−0.167	0.168
8-Isoprostane[a]	−0.155	0.234
D/P Cr at 4 hours	−0.238	0.044

GFR = glomerular filtration rate; PD = peritoneal dialysis; LDL = low-density lipoprotein; hs-CRP = high-sensitivity C-reactive protein; D/P Cr = dialysate-to-plasma ratio of creatinine.
[a] Spearman correlation analysis was conducted for the skewed data.

TABLE 5
Multivariate Linear Regression for Flow-Mediated Dilation (FMD)[a]

	β	*P* Value
Residual GFR[b] >1 mL/min/1.73 m^2	0.317	0.017
Age	−0.357	0.002
Peritoneal Kt/V urea	−0.103	0.333
PD duration	0.001	0.993
Log hs-CRP	−0.397	0.004
Fibrinogen	0.158	0.300
Pulse pressure	−0.032	0.785
D/P Cr at 4 hours	−0.060	0.579

GFR = glomerular filtration rate; PD = peritoneal dialysis; hs-CRP = high-sensitivity C-reactive protein; D/P Cr = dialysate-to-plasma ratio of creatinine.
[a] Adjusted for residual GFR, peritoneal Kt/V urea, PD duration, pulse pressure, age, log hs-CRP, fibrinogen, and D/P Cr at 4 hours.
[b] Compared to patients with residual GFR ≤ 1 mL/min/1.73 m^2.

maintenance of endothelial integrity in ESRD patients is still affected by RRF. Wang *et al.* (22) attempted to clarify this issue by measuring serum levels of soluble vascular cell adhesion molecule-1, a marker of endothelial dysfunction, and found that there was a significant inverse correlation between levels of this marker and RRF in long-term PD patients; however, no functional imaging was performed in that study. In addition, arterial stiffness measured by brachial–ankle pulse wave velocity was inversely correlated with RRF in a retrospective study of 146 PD patients (23). In line with these findings, we evaluated endothelial function using FMD in the present study and, based on our findings, suggest that endothelial function is significantly affected by RRF, even in ESRD patients with low RRF and considerable PD duration. In contrast, Cheng *et al.* found that endothelial dysfunction was closely associated with volume overhydration but not with RRF in PD patients (24). This discrepancy may partly be due to some differences in the demographic characteristics of patients: patients were younger and less obese in our study. In addition, differences in the volume status of the patients may also contribute to these divergent results. In the present study, we excluded from the analysis patients with any clinical signs of volume overload. Nevertheless, since assessment of volume status based on clinical parameters may not be accurate, a more reliable method would be helpful to evaluate volume status in these patients.

Preservation of RRF is of paramount importance in patients with ESRD (9,10). It is widely acknowledged that fluid overload, anemia, and malnutrition are less common in patients with higher RRF compared to those with lower RRF (9). In addition, blood pressure is better controlled (25,26) and serum concentrations of inflammatory markers are lower in patients with preserved RRF (27,28). Based on the fact that hypertension and inflammation are key contributors to the development of atherosclerosis (29,30), it can be presumed that endothelial dysfunction may be more evident in patients with lower RRF due to higher blood pressure and inflammation. In fact, in the present study, blood pressure and concentrations of serum hs-CRP and plasma fibrinogen were significantly higher in patients with residual GFR ≤ 1 mL/min/1.73 m^2 compared to those with residual GFR > 1 mL/min/1.73 m^2, which might contribute to worse endothelial function in the former group.

Interestingly, Pearson's correlation analysis revealed that there was a significant correlation between FMD% and total Kt/V urea (the sum of peritoneal and renal Kt/V urea), suggesting a possible effect of dialysis adequacy on endothelial dysfunction. When each component of Kt/V urea was analyzed individually, however, FMD% was significantly associated with renal Kt/V but not with peritoneal Kt/V. In addition, renal Kt/V urea and RRF were significantly higher in patients with higher FMD% relative to those with lower FMD%. Moreover, RRF was found to be an independent predictor of FMD% in multivariate linear

regression analysis. In contrast, such associations were not observed between peritoneal Kt/V urea and FMD%. The results of the present study suggest that RRF rather than peritoneal clearance *per se* may better contribute to preservation of vascular endothelial function.

The aging process accelerates atherosclerosis in general (31) and numerous studies have demonstrated that age is significantly correlated with endothelial dysfunction (30,32). In agreement with those studies, old age was revealed as a strong determinant of endothelial dysfunction in this study. In addition, serum inflammatory markers such as hs-CRP, which is one of the key players in atherosclerosis, were independently associated with endothelial dysfunction. In contrast, even though pulse pressure was inversely correlated with FMD% in the Pearson's correlation analysis, multivariate regression analysis disclosed that it was not independently associated with endothelial dysfunction. This may be partly explained by the confounding effect of RRF. A loss of RRF was reported to be associated with higher arterial pulse pressure (33). Our study also showed that pulse pressure was significantly higher in patients with lower residual GFR. Interestingly, when RRF was not entered into the multivariate analysis, pulse pressure became modestly associated with FMD% ($\beta = -0.193$, $P = 0.081$; data not shown). Moreover, pulse pressure showed a significant inverse correlation with residual GFR ($\rho = -0.446$, $P < 0.01$; data not shown). Based on these findings, pulse pressure appears to be related to RRF, resulting in lack of an independent association between this parameter and endothelial dysfunction.

Several recent studies have suggested that peritoneal solute transport may also affect vascular function in PD patients. Zhe *et al.* (34) found that D/P Cr at 4 hours was a significant predictor of arterial stiffness, while such an association was not observed in two other studies (23,35). In the present study, D/P Cr at 4 hours was associated with FMD% only in the Pearson's correlation analysis, not in the multivariate analysis. Even though Zhe *et al.* (34) suggested that high peritoneal transport might be simply attributable to the generalized vascular disorder related to accelerated atherosclerosis, the association between peritoneal transport and endothelial dysfunction remains to be further investigated.

Several shortcomings of this study should be discussed. First, this was a cross-sectional study with a relatively small sample size. A cross-sectional design does not allow cause-and-effect relationships to be drawn between RRF and endothelial dysfunction. It is possible that RRF contributes to better endothelial function, directly or indirectly. Alternatively, better endothelial function might contribute to greater preservation of RRF. Hence, the causality of our findings should not be overinterpreted and requires further confirmation. All data were collected at a single time; therefore, they do not represent the precise and usual status of the patients. Particularly, the measurement accuracy of RRF with 24-hour urine collections can be variable. In addition, there is a possibility that selection bias due to a relatively small sample size might have distorted our data. The study subjects were also relatively young and had a low prevalence of cardiovascular diseases and diabetes. Therefore, it is possible that the proportion of patients with severe endothelial dysfunction included in the present study was low. Moreover, the duration of PD in our subjects was long, with low RRF, and thus our patient group may not be a representative cohort of dialysis patients in Korea.

Second, in this study, we excluded patients with volume overload based on clinical findings only, which may not be accurate in assessing volume status. Furthermore, because volume status is largely dependent on RRF in ESRD patients, and fluid overload *per se* can induce hypertension, a key factor that leads to vascular dysfunction, more accurate assessment using bioimpedance or measurement of inferior vena cava diameter would be informative and might allow detection of subtle differences in the fluid status of patients. Considering these facts, we surmise that the impact of volume status on the results of the present study cannot be completely disregarded.

Third, other measures, such as pulse wave velocity and carotid intima medial thickness, that would complement this study were not performed. In fact, FMD is a surrogate marker of vascular health and may not be a good measure of vascular function. Nevertheless, FMD is well known as a noninvasive and reproducible tool and is the most commonly used assessment tool of endothelial function (36) with prognostic significance in ESRD patients (8).

Finally, patients undergoing hemodialysis were not included in the present study. Considering the results of recent studies indicating the important contribution of RRF to overall survival in hemodialysis patients (37), we expect to see a similar effect of RRF on endothelial dysfunction in patients on hemodialysis as well.

In conclusion, our results suggest that higher RRF is associated with better endothelial function in patients with ESRD, even in patients with low RRF and considerable PD duration. Further studies in a larger, less selective population of incident PD patients with earlier stages of PD and higher RRF are needed to confirm our findings.

DISCLOSURES

The authors have nothing to disclose.

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