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Original Paper

Alteration of Cardiovascular Structure and Function in Patients Undergoing Peritoneal Dialysis

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Key Words
End-stage renal disease · Peritoneal dialysis · Left ventricle · Atherosclerosis

Abstract
Aims: Cardiovascular alterations contribute to a high mortality rate in patients with end-stage renal disease (ESRD). The aims of the present study are to evaluate left ventricular (LV) function and common carotid artery (CCA) parameters and to determine risk factors associated with these changes in patients undergoing peritoneal dialysis (PD). ***Methods:*** This longitudinal prospective study was conducted in 50 ESRD patients in whom PD had been initiated and who were observed for 18 months after the commencement of dialysis treatment, with echocardiography and CCA ultrasound parameter evaluation. ***Results:*** LV hypertrophy was observed in 78% of patients at baseline and in 60% after 18 months of PD treatment. LV systolic and diastolic function was found to be significantly better after 18 months of PD treatment. Examining predictors of LV systolic function, it was found that total cholesterol was an independent positive predictor and endothelin-1 (ET-1) an independent negative predictor of LV systolic function after 18 months of treatment with PD ($p < 0.001$). Independent negative predictors of diastolic LV function were hemoglobin and type 2 diabetes mellitus, and daily collection of urine was an independent positive predictor ($p < 0.001$). Female gender was an independent negative predictor of CCA intima-media thickness, whereas body mass index, ET-1 and C-reactive protein were independent positive predictors ($p < 0.001$). ***Conclusions:*** The results suggest several novel modifiable mechanisms related to the short-term effects of dialysis that are potentially implicated in the development of uremic cardiomyopathy.

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Introduction

The mortality rate in patients with end-stage renal disease (ESRD) is much higher than in the general population despite advances in dialysis treatment. Cardiovascular structure and functional abnormalities, such as left ventricular hypertrophy (LVH), left ventricular (LV) systolic and diastolic dysfunction, accelerated atherosclerosis, arrhythmias and coronary artery calcification, contribute to a high cardiovascular mortality in patients with ESRD [1].

Patients with ESRD are a unique population harboring cardiovascular disease (CVD), while the analysis of risk factors in these patients may be obscured by comorbid conditions such as diabetes and preexisting atherosclerosis [2]. Until recently, the prevalence, severity and predictors of these cardiovascular abnormalities have not been investigated extensively in patients with ESRD from the start of dialysis treatment.

The aims of the present study were (1) to evaluate LV function and common carotid artery (CCA) parameters and (2) to determine risk factors associated with these cardiovascular changes in patients undergoing peritoneal dialysis (PD).

Methods

Study Population and Design

This longitudinal prospective study was conducted with 50 ESRD patients (type 2 diabetic and nondiabetic) in whom continuous ambulatory PD had been initiated and who were observed for 18 months after the commencement of dialysis treatment. All examined patients underwent 4–5 dialysis changes with 2 liters of dialysis solution.

Patients with a verified diagnosis of CCA stenosis (>70% internal CCA stenosis), cerebral vascular diseases (patients who had had a transient ischemic attack or stroke in the past 6 months) and patients with chronic rheumatic heart disease, congenital heart disease, underlying active malignancy or systemic lupus erythematosus, as well as patients with signs of peritonitis during the study period, were excluded from the study. In all patients, antihypertensive therapy as well as any therapy that can influence the values of monitored laboratory parameters (nitrites, sildenafil, captopril, NSAIDs, heparin and β_2-agonists) were excluded 24 h before taking blood samples for determination of endothelin-1 (ET-1) and nitric oxide concentration. The patients did not receive diuretic therapy prior to diuresis level measurement and sampling. The substitution therapy with recombinant human erythropoietin (epoetin β 6,000 IU weekly) was administered to all patients.

The institutional ethics committee approved the study protocol, and all participants gave written informed consent prior to the study. Our examinations of the patients conformed to good medical and laboratory practices and the recommendations of the Declaration of Helsinki on Biomedical Research Involving Human Subjects. Ultrasound measurements were performed after drainage of peritoneal fluid in PD patients.

Echocardiographic Data

Comprehensive echocardiographic measurements were performed using an ultrasound machine (Toshiba 270SSA) with a 3.75-MHz sector probe by a single experienced cardiologist blinded to clinical information on patients at baseline and at the end of the study period. All images were obtained with standard techniques using M-mode, two-dimensional and Doppler measurements in accordance with the American Society of Echocardiography guidelines [3]. The LV mass was calculated using the modified formula proposed by Devereux et al. [4]. Echocardiographic evidence of LVH was defined as LV mass index divided by a body surface area >115 g/m^2 in men and >95 g/m^2 in women. LV systolic function was assessed by calculation of the ejection fraction (EF) using a modified Simpson's method [5], while fractional shortening (FS) was calculated according to the formula described by Lang et al. [6]. LV systolic weakness was defined as EF <50% and FS <30%. Pulsed Doppler echocardiography was used to evaluate transmitral LV filling velocities at the tips of the mitral valve. The peak early-diastolic flow velocity (E) and the peak late-diastolic velocity (A) shown as the E/A ratio were measured by analyzing the transmitral flow. LV diastolic dysfunction was defined as E/A ≤1. With these parameters, diastolic dysfunction was further categorized into four groups: normal, abnormal relaxation, pseudonormal and restrictive pattern [7].

CCA Ultrasound Data

Intima-media thickness (IMT) of the CCA and the presence of atherosclerotic plaques were measured by means of a high-resolution transducer probe of 7.5 MHz frequency in B mode (Wall Track System, Pie Medical, Maastricht, The Netherlands) by a single experienced angiologist blinded to all clinical details of patients during the follow-up period. The CCA, carotid bulbus and the first 2 cm of the internal and external CCA were scanned bilaterally. The measurements of IMT were done at a distance of 20 mm from bifurcation into the plaque-free area on the CCA. Three measurements were done on the left and right CCA, while the mean values of these measurements were utilized in the analysis. The plaque score in the CCA was calculated by summing the three IMT measurement values, bilaterally [8].

Parameters of PD

Adequacy of dialysis was calculated from weekly total removed urea mass by daily volume of dialysate and urine and divided by urea distribution volume. The distribution volume of urea was calculated using the Watson equation [9]. Residual renal function (RRF) was estimated as the mean value of renal creatinine clearance (ml/min). A simplified peritoneal equilibration test was performed using 4.25% glucose-based solution to obtain the dialysate to plasma creatinine concentration ratio at 4 h of dwell (D/P Cr) [10].

Statistical Analysis

Statistical analysis was performed using SPSS version 16.0 (SPSS, Inc.). Each value was expressed as the mean ± SD or as median and interquartile range where appropriate. The distribution of variables was tested by the Shapiro-Wilk test. Significant changes in the variables from baseline to 18 months after PD were tested by paired t test or by the Wilcoxon signed-rank test. The difference between two groups was analyzed by the Mann-Whitney test. Univariate correlation coefficients were determined by Pearson or Spearman analysis. A multiple regression analysis was applied to examine the relationship between ultrasound cardiovascular parameters and a set of clinical-biochemical parameters. The significant independent variables were ordered according to their standardized effect, defined as regression coefficient/standard error of the regression (β). A p value <0.05 was considered statistically significant.

Results

The main clinical and laboratory data are summarized in table 1. In our study, 52% of patients were diabetics. Significant reductions of blood pressure (BP) were observed after 18 months on PD. The median concentration of serum ET-1 decreased, while nitric oxide increased significantly after 18 months on PD. At the end of the follow-up period, dialysis adequacy was estimated by Kt/V_{urea} as satisfactory.

LVH was observed in 78% of patients at baseline and in 60% after 18 months of PD treatment. A significant reduction in LV mass index, CCA diameter, IMT and plaque score was observed. LV function was determined as significantly better after 18 months of PD (table 2).

In our study, the EF and E/A ratios were significantly associated with the presented traditional and nontraditional risk factors as well as with the CCA diameter. CCA IMT did not show a significant correlation with protein equivalent of total nitrogen appearance, parathyroid hormone, serum calcium and daily collection of urine (table 3).

Average EF values were significantly higher after 18 months of PD in the group of patients without atherosclerosis compared to baseline values, whereas in the group of patients with mild/moderate and severe atherosclerosis, the CCA average value of EF was greater at the end of the observed period, but there was no statistically significant difference (fig. 1).

LV diastolic function, assessed by the average value of the E/A ratio, was statistically significantly better after 18 months of PD compared to baseline values within all groups of patients (fig. 2).

Examining predictors of LV EF using the model of logistic regression analysis, it was found that total cholesterol was an independent positive predictor and ET-1 an independent

Table 1. Baseline clinical characteristics

Clinical characteristics	At baseline	After 18 months of PD	p value
Age, years	60.5 (26–76)		
Men	25 (50)		
Smoker	18 (45)		
Body mass index	25.9±3.7	25.7±2.2	n.s.
Diabetes mellitus	26 (52)		
Mean arterial pressure, mm Hg	109.2±15.1	95.4±8.2	<0.001
Cause of ESRD			
Diabetic nephropathy	24 (48)		
Hypertensive nephrosclerosis	9 (18)		
Glomerulonephritis	7 (14)		
Pyelonephritis	7 (14)		
Other	3 (6)		
Antihypertensives, n			
On ARB or ACE inhibitor	32	24	
On diuretic	36	18	
On calcium channel blocker	21	29	
Other	9	3	
Laboratory measurements			
Hemoglobin, g/l	101.9±10.3	118.6±11.1	<0.001
Albumin, g/l	30.9±2.6	31.5±2.0	<0.01
Urea nitrogen, mmol/l	25.7±6.7	17.5±2.5	<0.001
Creatinine, μmol/l	912.3±223.3	733.9±131.0	<0.001
Cholesterol, mmol/l	6.5±1.6	5.5±1.3	<0.001
Triglyceride, mmol/l	2.4±1.3	2.0±2.5	<0.01
Low-density lipoprotein, mmol/l	4.7±1.4	3.6±0.8	<0.05
C-reactive protein, mg/l	11.1 (6.1–16.4)	4.5 (2.8–7.7)	<0.001
Fibrinogen, g/l	6.2±1.9	4.4±1.3	<0.001
Calcium, mmol/l	2.2±0.2	2.3±0.1	n.s.
Phosphorous, mmol/l	1.8±0.3	1.6±0.2	<0.05
CaxP	3.9±0.6	3.6±0.5	<0.001
β_2-Microglobulin	7.0 (2.9–11.2)	4.2 (2.3–9.7)	<0.05
Parathyroid hormone, pmol/l	225.5 (97.8–387)	200.0 (100.0–410)	n.s.
Plasma homocysteine, μmol/l	25.2 (20.2–30.1)	18.0 (14.0–20.9)	<0.001
B-type natriuretic peptide, pg/ml	183.9 (89.8–432.5)	69.6 (50.2–98.8)	<0.001
Troponine, ng/ml	0.022 (0.001–0.12)	0.001 (0.00–0.01)	<0.01
Nitric oxide, μmol/l	40.72 (19.4–56.7)	48.0 (32.8–60.4)	<0.01
ET-1, pg/ml	6.32 (3.2–8.8)	4.0 (2.27–6.3)	<0.001
RRF, ml/min/1.73 m^2	5.5±3.8	7.0±5.0	<0.05
Urine volume, ml/day	545.6±378.5	584.8±489.7	n.s.
nPNA, g/kg/day	0.98±0.13	1.11±0.1	<0.05
Weekly Kt/V_{urea}	1.9±0.8[a]	2.1±0.6	<0.05

Data are expressed as the mean ± SD, number (percentage) or median (range). n.s. = Not significant; ARB = angiotensin receptor blocker; ACE = angiotensin-converting enzyme; nPNA = protein equivalent of total nitrogen appearance. [a] After 6 months of PD.

negative predictor of LV systolic function after 18 months on PD. Independent negative predictors of the E/A ratio were hemoglobin and diabetes mellitus, and daily collection of urine was an independent positive predictor. Examining predictors of CCA IMT after 18 months on PD, it was found that female gender was an independent negative predictor, whereas body mass index, ET-1 and C-reactive protein were independent positive predictors.

Table 2. Clinical, echocardiographic and ultrasound measurements of CCA parameters

Ultrasound parameters	At baseline	End of follow-up	p value
Echocardiographic parameter M-mode and 2D			
LV end-diastolic diameter, mm	52.9±3.6	49.6±6.5	<0.05
LV end-systolic diameter, mm	35.0±3.5	34.3±3.9	n.s.
LV mass, g	280.7±43.2	243.8±40.8	<0.05
LV mass index, g/m^2	162.2±38.1	140.2±37.8	<0.001
Left atrium diameter, mm	43.3±5.7	40.5±6.7	<0.05
LV structure			
Normal	11 (22.0)	19 (38)	<0.05
LVH	39 (78.0)	30 (60)	<0.05
Concentric hypertrophy	22 (44)	19 (38)	0.056
Eccentric hypertrophy	15 (30)	11 (22)	<0.05
Concentric remodeling	2 (4)	1 (2)	n.s.
LV function			
Normal	10 (20.0)	32 (64.0)	<0.01
Systolic dysfunction	0	5 (10.0)	<0.001
LV EF, %	50.1±9.4	56.9±10.0	<0.05
FS	28.8±5.1	30.8±4.1	<0.001
Diastolic dysfunction	20 (40.0)	3 (6.0)	<0.01
E/A ratio	0.9±0.1	1.1±0.1	<0.05
Mixed systolic-diastolic dysfunction	20 (40.0)	10 (20.0)	<0.01
Grading of diastolic dysfunction			
Grade 1: impaired relaxation pattern	26 (65)	7 (53.85)	<0.01
Grade 2: pseudonormal pattern	13 (32.5)	3 (23.08)	<0.01
Grade 3: restrictive filling pattern	1 (2.5)	1 (7.69)	n.s.
Ultrasound measurements of carotid arteries			
CCA IMT, mm	0.76 (0.6–0.9)	0.68 (0.5–0.8)	<0.05
CCA diameter, mm	5.8 (5.2–6.4)	5.0 (4.9–5.4)	<0.05
Plaque score	4.15 (4.2–5.4)	3.95 (2.9–5.1)	<0.001

Data are expressed as the mean ± SD, number (percentage) or median (range). n.s. = Not significant.

Serum albumin and hemoglobin were independent negative predictors, while low-density lipoprotein and age were positive predictors of CCA diameter during dialysis treatment (table 4).

Discussion

CVD accounts for half of the deaths in patients treated with renal replacement therapy, whilst mortality from cardiovascular causes is far higher than in the general population [11, 12]. The influence of uremia and dialysis on cardiovascular structure and function was investigated as detailed by studies on patients with chronic renal failure [1, 13, 14].

There are two parallel processes involved in the development of CVD in ESRD patients. The first process involves cardiac changes including LVH and LV dysfunction as a response to mechanical or hemodynamic overload. The second process involves vascular changes, including atherosclerosis, arteriosclerosis and vascular calcification. Over the last decade, cardiac abnormalities such as LVH and LV dysfunction and vascular abnormalities, e.g. arterial stiffness, increased IMT and coronary calcification, have been accepted as early markers of cardiomyopathy and atherosclerosis [15].

Table 3. The factors correlated with LV function and CCA parameters after 18 months on PD

Factors	EF	E/A ratio	CCA IMT	CCA diameter
Mean arterial pressure	–0.62**	–0.46**	0.29*	0.45*
Hemoglobin	0.64**	0.57**	–0.49**	–0.71**
Cholesterol	–0.65**	–0.62**	0.42**	0.74**
Low-density lipoprotein	–0.73**	–0.59**	0.35*	0.58**
C-reactive protein	–0.68**	–0.61**	0.36*	0.51**
Calcium	0.08	–0.02	0.01	0.02
Phosphorous	–0.54**	–0.49**	0.33*	0.57**
CaxP	–0.49**	–0.46**	0.31*	0.54**
Parathyroid hormone	–0.5*	–0.39**	0.2	0.48*
nPNA	0.58**	0.57**	–0.07	–0.34*
Albumin	0.68	0.62*	–0.34*	–0.58*
RRF	0.43**	0.55**	–0.18	–0.37**
Urine volume, ml/day	0.49**	0.61**	–0.23	–0.51**
Kt/V_{urea}	–0.65**	–0.61**	0.38*	0.59**
Nitric oxide	0.745**	0.766**	–0.824**	–0.648**
ET-1	–0.708**	–0.695**	0.807**	0.698**
Homocysteine	–0.575**	–0.495**	0.605*	0.663*
Troponine	–0.697*	–0.76**	0.788*	0.629*
BNP	–0.578**	–0.409**	0.485*	0.317*

nPNA = Protein equivalent of total nitrogen appearance; BNP = B-type natriuretic peptide. * $p < 0.05$; ** $p < 0.001$.

Table 4. Significant independent predictors of LV function and carotid remodeling at the end of follow-up

Predictors	95% CI	p value
LV systolic function		
Cholesterol	2.647–45.433	0.001
ET-1	0.002–0.778	0.007
LV diastolic function		
Urine volume (ml/day)	0.401–1.004	0.001
Diabetes mellitus type 2	0.346–0.997	0.007
Hemoglobin	0.485–0.893	0.010
CCA IMT		
Female gender	0.002–0.898	0.042
Body mass index	1.035–2.304	0.033
C-reactive protein	1.124–2.200	0.008
ET-1	1.874–3.007	0.024
CCA diameter		
Serum albumin	0.134–0.809	0.015
Hemoglobin	0.741–0.991	0.037
Low-density lipoprotein	1.131–14.591	0.032
Age	1.018–1.383	0.029

LV diastolic dysfunction is frequently observed in dialysis patients and results from LVH, cardiac fibrosis and impaired cardiac relaxation [13]. Also, the presence of LVH and LV systolic dysfunction are well-recognized risk factors for cardiovascular mortality in this population [14, 16].

Considering the large risk, our data may emphasize the importance of early recognition of LV dysfunction and may have significant therapeutic implications at the start of dialysis.

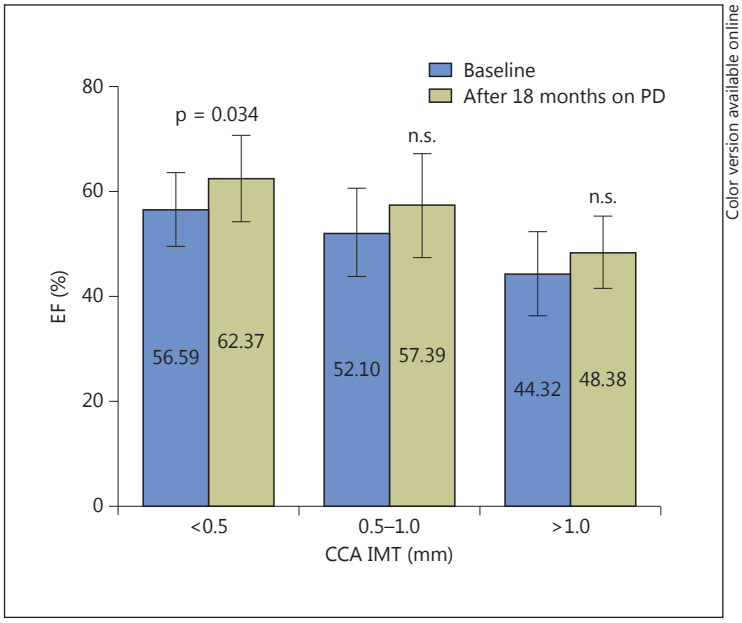

Fig. 1. LV EF in patients during follow-up in relation to the level of CCA atherosclerosis. n.s. = Not significant.

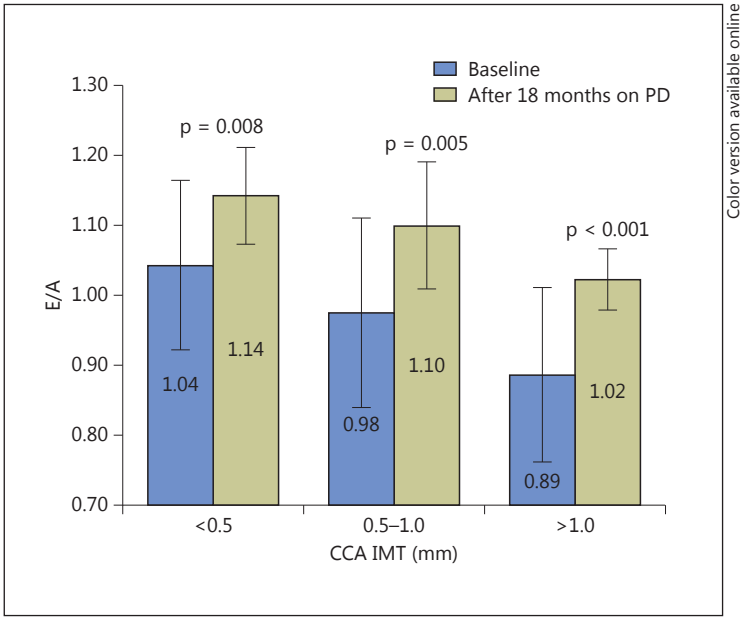

Fig. 2. E/A ratio in patients during follow-up in relation to the degree of CCA atherosclerosis.

In this study, we determined traditional and nontraditional risk factors in patients on dialysis. Our results confirmed that ESRD patients have increased traditional and uremia-related risk factors. Important observations are that, before undergoing PD, ESRD patients have significant LVH, dominant atherosclerotic changes in the CCA and impaired LV function.

In patients with ESRD, assessment of cardiovascular structure and function is essential for planning appropriate management. Many reports have warned of the risks of LVH for future cardiac failure [17]. Many factors are associated with cardiac hypertrophy in patients on PD [18]. In our study, at the end of the follow-up, significantly fewer patients with LVH were recorded, suggesting a positive effect of PD on LV remodeling and a correction of observed cardiovascular risk factors.

It is known that LV systolic function usually remains normal despite LVH in patients with ESRD [19]. Many studies have shown that diastolic dysfunction may ultimately be a risk factor for LV systolic dysfunction and future congestive heart failure [20]. We also found that none of our patients had congestive heart failure and all had normal systolic function despite increased LV mass index, though with a significantly better LV systolic function after 18 months of PD treatment. Total cholesterol and ET-1 were identified as independent predictors of LV systolic function in PD patients.

Some studies suggested that abnormalities of diastolic function precede those of systolic function [21]. Doppler measurement of mitral inflow velocity is widely used to assess LV diastolic function. Using this method, our study suggested that LV relaxation (E/A ratio) was impaired in ESRD patients as compared with the values after 18 months of PD therapy. In the present study, the linear regression analysis revealed that hemoglobin levels, diuresis and diabetes mellitus type 2 were independent predictors of poor diastolic function (E/A ratio). Our results are similar to previous studies [22, 23].

Unlike hemodialysis, which is associated with typically marked body water content fluctuations, PD is characterized by its almost steady state, which probably has a major impact on LV function. Also, the data of our study indicate that RRF is lower in ESRD than in PD. Wang [24] has found that RRF may play a role in limiting the increase in cardiovascular remodeling by improving the overall Kt/V_{urea} and removal of uremic toxins.

In our PD patients, there was a positive correlation between LV function parameters (EF, FS and E/A ratio), daily urinary output and RRF. This is a very important result, because it suggests the existence of some nondialyzable uremic toxins that may be important in the progression of pathological cardiovascular alteration in this population.

The second process playing a role in the development of CVD in ESRD patients is vascular injury. The measurement of CCA IMT using high-resolution ultrasonography has been suggested as an excellent marker of subclinical atherosclerosis. However, there are few studies about CCA IMT and atherosclerosis indicating that the CCA diameter represents an indirect indicator of the stiffness of the arterial wall [25]. In our study, female gender, body mass index, C-reactive protein and ET-1 were determined as independent predictors of an increased CCA IMT, whereas serum albumin, hemoglobin, low-density lipoprotein and age were identified as predictors of rigidity of the arterial wall. Also, our results suggest a high prevalence of atherosclerosis in the predialysis period, but also a significant positive effect of PD in the first year on the process of stopping accelerated atherogenesis.

Our results showed two phases of the cardiovascular effects of PD. Significant reductions in BP, LV mass and B-type natriuretic peptide were probably related to strict volume control, while in the later stage, better control of BP seemed to be related to changes in blood volume and possibly to sympathetic activity.

Our study had several shortcomings. First, a relatively small number of patients with diabetes mellitus were included in the trial which were not specifically separated from patients without diabetes mellitus; second, a longer period is needed for patient monitoring in order to be able to estimate a clear effect of PD, and third, there is a need to include patients after kidney transplantation.

The findings indicate that monitoring the traditional and nontraditional risk factors provides significant prognostic information for the estimation of alterations of LV structure and function and subclinical atherosclerosis, and that repeated measurements of such parameters are useful in the clinical practice for the management of PD patients.

Conclusion

In conclusion, LVH, increased CCA IMT and diameter, impaired diastolic function and normal systolic function are highly present in uremic patients before initiation of renal replacement therapy.

PD in the first 18 months of treatment has a positive effect on stopping or even on achieving partial regression of cardiovascular remodeling. The better control of BP and good volume control lead to significant improvements in cardiac function and arterial stiffness. The results suggest several novel modifiable mechanisms related to the short-term effects of dialysis that are potentially implicated in the development of uremic cardiomyopathy.

Disclosure Statement

The authors declare that they have no conflicts of interest.

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