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Original Article

Left ventricular function in patients with chronic kidney disease evaluated by colour tissue Doppler velocity imaging

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Abstract

Background. Cardiovascular disease is the leading cause of death in chronic kidney disease (CKD) patients. Tissue Doppler velocity imaging (TVI) is a new objective method that accurately quantifies myocardial tissue velocities, deformation, time intervals and left ventricular (LV) filling pressure. In this study, TVI was compared with conventional echocardiography for the assessment of left ventricular (LV) function in pre-dialysis patients with different stages of CKD. The results obtained by TVI were used to analyse possible relationships between LV function and clinical factors such as hyperparathyroidism and hypertension that could influence LV function.

Methods. Conventional echocardiography and TVI images were recorded in 40 patients (36 men and 4 women, mean age 60 ± 14 years, range 28–80 years) and in 27 healthy controls (21 men and 6 women, mean age 58 ± 17 years, range 28–82 years). Twenty-two patients had mild/moderate CKD (CCr >29 ml/min; Group 1) and 18 patients had severe CKD (CCr $\leq$29 ml/min; Group 2). Using TVI, the myocardial tissue velocities (v; cm/s) for isovolumetric contraction (IVCv), peak systole (PSv), early (E') and late (A') diastolic filling velocities as well as strain rate (SR), mitral annulus displacement, isovolumetric relaxation time (IVRT) and LV filling pressure were estimated using TVI. The average of six LV wall measurements was used to evaluate LV global function.

Results. Using TVI, we were able to identify significantly more patients with diastolic dysfunction than using conventional echocardiography (33 *vs* 26, $P < 0.05$). There was no difference in the prevalence of diastolic dysfunction between Group 1 and 2. However, using TVI, Group 2 CKD patients had lower E' velocities (6.2 ± 1.9 *vs* 8.0 ± 2.9 cm/s, $P < 0.05$) and higher IVRT (137.4 ± 13 *vs* 88.2 ± 26 ms, $P < 0.001$) in comparison with controls, indicating more accentuated diastolic dysfunction. Systolic blood pressure (SBP) was associated with E' velocities ($\rho = -0.68$, $P < 0.005$) and E'/A' was strongly associated with SBP ($\rho = -0.60$; $P < 0.01$) and PTH ($\rho = -0.64$, $P < 0.005$) in Group 2. Using conventional echocardiography, there was no difference in the prevalence of systolic and diastolic dysfunction between patients with and without LVH. However, using TVI, patients with LVH had significantly lower IVCv (2.8 ± 1.3 *vs* 3.8 ± 1.5 and 3.8 ± 1.5 cm/s, $P < 0.05$) and PSv (5.5 ± 1.0 *vs* 6.3 ± 1.2 and 6.4 ± 1.3 cm/s, $P < 0.05$) compared with patients without LVH and controls, and they also had lower E' velocities (7.1 ± 2.7 *vs* 8.0 ± 2.9 cm/s, $P < 0.05$) compared with controls, indicating disturbances in systolic and diastolic left ventricular function.

Conclusions. TVI provided additional information on left ventricular function in CKD patients. In patients with advanced renal failure, TVI revealed more accentuated diastolic dysfunction associated with increased systolic blood pressure (SBP) and increased levels of PTH. TVI also demonstrated disturbances in contractility and contraction in patients with LVH, which could not be detected by conventional echocardiography.

Keywords: chronic kidney disease; parathyroid hormone; predialysis; tissue Doppler echocardiography

Introduction

In dialysis patients, cardiovascular disease (CVD) is the predominant cause of mortality [1]. An increased risk of

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cardiovascular morbidity and mortality is also seen in earlier stages of chronic kidney disease (CKD). Multiple risk factors may contribute to the development of CVD, such as sodium and fluid retention, hypertension, anaemia, inflammation and hyperparathyroidism.

In CKD patients, left ventricular hypertrophy (LVH) is a common finding and it is associated with an increased CVD-related mortality [2]. The prevalence and severity of LVH increases in parallel with the severity of CKD [3]. Initially, LVH is a physiological response to pressure and volume overload. However, sustained overload in combination with CKD-associated factors such as anaemia and hyperparathyroidism may result in maladaptive LVH characterized by structural changes in the myocardium, such as collagen accumulation, fibrosis and calcification, resulting in systolic and diastolic dysfunction [4,5].

Myocardial function in CKD patients has been studied extensively using conventional echocardiography. This method evaluates hydrodynamic responses and therefore it is load dependent, which is a disadvantage in CKD patients in whom fluid status may vary considerably. In addition, conventional echocardiography only allows semi-quantitative and partially subjective measurements. Furthermore, it has been shown to be too insensitive to distinguish between physiological and pathological LVH and to demonstrate diastolic dysfunction in patients with LVH [6] and normal ejection fraction [7].

In contrast to conventional echocardiography, tissue velocity imaging (TVI) is an objective and quantitative echocardiography technique for evaluating myocardial tissue function. TVI monitors directly the mechanical wall function, which evokes hydrodynamic responses. TVI measurements of regional myocardial velocities allow simultaneous estimations of systolic (isovolumetric and ejection phase) and diastolic function, time intervals and LV filling pressure. Studies have shown that systolic velocities are good markers of LV function, which correlate well with LV global ejection fraction and invasive measurements of LV contraction (ejection phase) and contractility (isovolumetric contraction) [8]. Furthermore, diastolic velocities have been demonstrated to correlate with the time constant of LV relaxation [9] and inversely with LV volumes and pressures obtained by invasive catheter-tip micromanometry [7]. TVI has also been shown to be a superior evaluation method in patients with impaired LV relaxation, regardless of the mitral inflow velocity flow pattern (restrictive, pseudonormalization or impaired relaxation) in comparison with conventional Doppler echocardiography. In addition, TVI has improved the evaluation of patients with LVH, as it is more sensitive for detecting abnormal LV relaxation compared with conventional echocardiography [10,11]. Furthermore, TVI parameters of systolic and diastolic function have been described as less load dependent than those assessed with conventional echocardiography. We have recently reported that in haemodialysis patients, myocardial dysfunction could be detected by TVI, but not by conventional echocardiography [12]. It is not known whether TVI can also give additional information on LV function in CKD patients at earlier stages of their disease.

The aims of the present study were, therefore, (i) to investigate whether TVI is more sensitive than conventional echocardiography in the assessment of LV ventricular function in patients with mild/moderate and severe CKD and (ii) to evaluate possible associations between risk factors (such as hypertension and hyperparathyroidism) and LV geometry and LV myocardial function in these patients.

Subjects and methods

Study population

Forty patients (36 men and 4 women) with CKD at different stages of the disease were studied using conventional echocardiography and colour TVI. The patients were placed in two groups according to the calculated clearance of creatinine (Cockroft–Gault equation). Group 1 consisted of 22 patients with mild and moderate renal failure (CCr >29 ml/min; CKD stages 1, 2 and 3) and Group 2 consisted of 18 patients with severe renal failure (CCr ≤ 29 ml/min; CKD stages 4 and 5). Clinical and biochemical characteristics of both groups are shown in Tables 1 and 2. All except one patient in Group 1 and one patient in Group 2 were receiving antihypertensive treatment. No differences were found regarding the prevalence of hypertension, diabetes, smoking or ischaemic heart disease (IHD) between Group 1 and 2. IHD was considered to be present if the patient had had a myocardial infarction or angina pectoris, or if the patient had undergone coronary bypass surgery or angioplasty. All patients were in sinus rhythm. Twenty-seven healthy volunteers (21 men and 6 women, mean age 58 ± 17 years) with normal conventional echocardiography parameters and normal stress echocardiography were investigated. All patients and control subjects gave their informed consent and the study was approved by the local Ethics Committee of Karolinska Institutet at Karolinska University Hospital at Huddinge.

Blood pressure

Blood pressure was measured, after resting in the supine position for 5 min and immediately before the echocardiographic examination by the same observer using standard sphygmomanometer.

Biochemical analyses

Venous blood samples were collected in the morning immediately before the echocardiographic investigation after an overnight fast. Plasma levels of parathyroid hormone, cholesterol, triglycerides, high density lipoprotein (HDL), high sensitive C-reactive protein (CRP), troponin T (TnT) and troponin I (TnI) were measured. Triglycerides and cholesterol were determined using standard enzymatic techniques (Boehringer Mannheim GmbH, Mannheim, Germany). HDL cholesterol levels were analysed after

Table 1. Clinical characteristics of Group 1 (mild/moderate CKD) and Group 2 (severe CKD) patients

Parameter	Moderate Group 1	Severe Group 2	*P*
Age (years)	59 ± 14	62 ± 14	NS
Gender (M/%m)	17 M (77%)	17 M (94%)	NS
SBP (mmHg)	149 ± 29	144 ± 16	NS
DBP (mmHg)	85 ± 9.5	85 ± 10	NS
DM	8 (36%)	7 (38%)	NS
Hypertension	21 (94%)	17 (94%)	NS
Smoking	7 (31%)	3 (16%)	NS
IHD	3 (13%)	2 (11%)	NS
CR	3 (13%)	1 (5.5%)	NS
Medication			
ACEI/ARB	19 (86%)	14 (77%)	NS
Betablockers	10 (45%)	9 (50%)	NS
CCB	9 (40%)	7 (38%)	NS
Furosemide	9 (40%)	9 (50%)	NS

Abbreviations: M, males; DM, diabetes mellitus; IHD, ischaemic heart disease; CR, coronary revascularization; ACEI/ARB, angiotensin converting enzyme inhibitors, or receptor blockers; CCB, calcium channel blockers.

Table 2. Biochemical characteristics of Group 1 (mild/moderate CKD) and Group 2 (severe CKD) patients

	Moderate Group 1	Severe Group 2	*P*
CCr (ml/min)	44.5 ± 14	19.4 ± 5.0	<0.001
Troponin I (μg/l)	0.01 ± 0.01	0.02 ± 0.03	NS
Haemoglobin (g/l)	130 ± 12	127 ± 15	NS
Creatinine (μmol/l)	185 ± 41	427 ± 106	<0.001
Urea (mmol/l)	14.7 ± 3.8	23.8 ± 5.9	<0.001
Albumin (g/l)	35.7 ± 4.7	36.7 ± 3.8	NS
Calcium (mmol/l)	2.4 ± 0.1	2.4 ± 0.1	NS
Phosphate (mmol/l)	1.1 ± 0.2	1.5 ± 0.4	<0.001
Ca × P ($mmol^2/l^2$)	3.9 ± 1.0	2.7 ± 0.5	<0.05
PTH (ng/l)	108.7 ± 84	120.6 ± 50	NS
Cholesterol (mmol/l)	5.1 ± 1.1	5.3 ± 1.3	NS
Triglycerides (mmol/l)	2.3 ± 1.1	2.3 ± 1.1	NS
HDL (mmol/l)	1.1 ± 0.2	1 ± 0.1	NS
CRP (mg/l)	7.3 ± 11.4	3.0 ± 1.9	NS

precipitation of apo B-containing proteins with phosphotungstic acid. Cardiac TnT was determined using the second generation TnT ELISA (Enzymun-Test Troponin-T) on an ES 300 system (Boehringer Mannheim GmbH). This assay uses the two cardio-specific monoclonal antibodies M11.7 and M7. cTnI was measured with the Opus Troponin I assay performed on the Opus analyser (Behring Diagnostics, Westwood, MA, USA). Serum CRP was measured by nephelometry with a high sensitive assay. Intact parathyroid hormone (PTH) was determined using a commercial electrochemical immunoassay (Elecsys PTH kit; Roche Diagnostics, Mannheim, Germany). Plasma levels of sodium, potassium, creatinine, urea, albumin, ionized calcium and phosphate were measured using routine methods.

Echocardiography

Ultrasound examinations were performed with GE System Five equipment with a 3.5 Hz sector transducer. American Society of Echocardiography guidelines were applied for registering all 2-D and conventional Doppler variables. Analyses were performed off-line using Echopac 6.3.4. The average of three consecutive heartbeats was used. Standard echocardiographic 2-D and M-mode measurements included left ventricular end-diastolic and end-systolic dimensions, end-diastolic and systolic wall thickness of interventricular septum and left ventricular posterior wall. Ejection fraction was calculated by Simpson and complemented by subjective visual estimation and the atrioventricular plane displacement method. LV mass was calculated according to the modified Penn formula. LV hypertrophy was defined as the left ventricular mass index (LVMI) $>50\,g/m^2$ in men and $>47\,g/m^2$ in women. The relative wall thickness (RWT) [(IVS + PWT)/LV end-diastolic diameter)] was calculated as an index of the LV geometric pattern (concentric LVH, RWT $\geq$0.45; eccentric LVH, RWT <0.45). Diastolic function was assessed by determining the velocities of early (E) and late (A) diastolic transmitral flow, the ratio E-to-A (E/A) and pulmonary vein flow velocities. In addition, isovolumetric relaxation time (IVRT), deceleration time of E wave (Edec) and velocity propagation (VP) were measured.

Tissue Doppler

TVI analyses were performed off-line on apical images [two chamber (ch), three ch and four ch] acquired with >100 frames/s. A 2 mm sampling volume was used from the apical views in two different regions: the mitral annulus and the basal wall. Myocardial velocities were measured in systole and in early and late diastole (Figure 1). The global LV systolic and diastolic function was calculated as the average velocities of six LV walls (septal, lateral, inferior, anterior, posterior and antero-septal). Systolic myocardial function was evaluated by measuring the isovolumetric contraction velocity (IVCv = contractility), peak systolic velocity (PSv = contraction) and strain rate (SR). The diastolic components measured were early diastolic filling velocity (E'), late diastolic filling velocity (A') and IVRT. To estimate the LV filling pressure, the mitral annular velocity at the lateral wall in the longitudinal axis was recorded and was used to calculate the E/E' ratio [14]. LV filling pressure was considered to be elevated when E/E' >15 and normal when E/E' <8 [7]. Diastolic dysfunction was defined when E' < 8 cm/s [13].

Statistical analysis

Data are expressed as the mean ± SD. For normally distributed continuous variables, a two-sample unpaired *t*-test or analysis of variance (ANOVA) followed by a Dunnett's test was performed. For variables with skewed distribution, Wilcoxon rank sum test and the χ-square test of Fisher's exact test were used. Possible associations were assessed by the Pearson and Spearman coefficients of correlation and linear regression analysis. $P < 0.05$ was considered significant.

Results

Conventional echocardiographic findings

Conventional echocardiography parameters in Group 1 and Group 2 are shown in Table 3. There were no

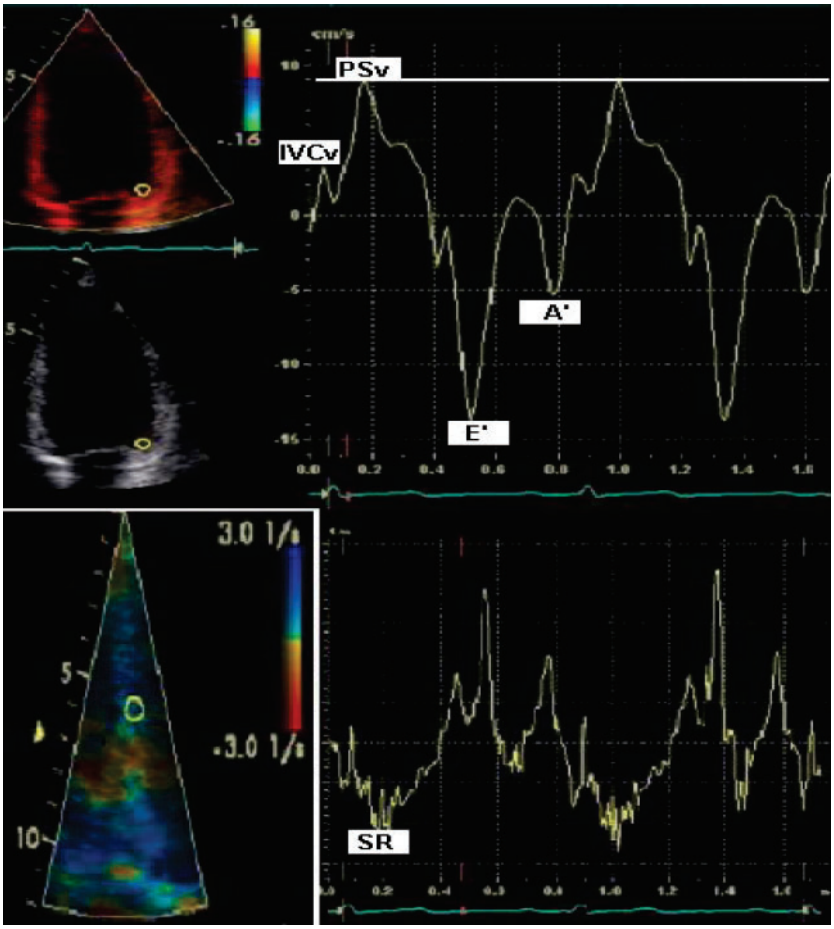

Fig. 1. Colour tissue Doppler profile illustrating: IVCv, peak positive isovolumetric contraction velocity; PSv, peak systolic velocity; E', early diastolic filling phase velocity; A', late diastolic filling phase velocity; and SR, strain rate.

Table 3. Conventional echocardiographic parameters in Group 1 (mild/moderate CKD) and Group 2 (severe CKD)

	Mild/moderate Group 1	Severe Group 2	*P*
LVMI (g/m^2)	53.1 ± 16	52.6 ± 12	NS
LA (mm)	39.0 ± 10	44.3 ± 5.8	NS
LA enlargement	5 (23%)	8 (44%)	<0.05
Aorta (mm)	26.4 ± 7.3	29.9 ± 3.4	NS
EF (%)	60.9 ± 9.8	60.8 ± 11	NS
E (cm/s)	72.7 ± 17	64.8 ± 13	NS
A (cm/s)	69.9 ± 17	66.6 ± 19	NS
E/A	1.0 ± 0.4	0.9 ± 0.4	NS
IVRT	121.9 ± 18	137.4 ± 13	<0.05
Edec (ms)	267.2 ± 89	292.3 ± 72	NS
LVH	14 (63%)	12 (66%)	NS
Diastolic dysfunction	14 (63%)	12 (66%)	NS
Systolic dysfunction	2 (9%)	0	NS

LA, left atrium.

significant differences between Group 1 and Group 2 in the prevalence of LVH (63% in Group 1 and 66% in Group 2), and parameters reflecting systolic and diastolic dysfunction.

Table 4. TVI variables: Group 1 (mild/moderate CKD) and Group 2 (severe CKD) patients and controls

	Controls $n = 27$	Mild/moderate Group 1	Severe Group 2	*P*
Systolic velocities				
IVCv (cm/s)	3.8 ± 1.5	2.9 ± 1.4	3.4 ± 1.5	NS
PSv (cm/s)	6.4 ± 1.3	5.5 ± 1.2	6.0 ± 1.0	NS
Diastolic velocities				
E' (cm/s)	8.0 ± 2.9[a]	6.8 ± 2.2	6.2 ± 1.9[a]	<0.05
A' (cm/s)	7.6 ± 2.2	6.6 ± 1.8	7.3 ± 1.7	NS
E'/A'	1.5 ± 0.1	1.1 ± 0.6	0.9 ± 0.4	NS
IVRT (ms)	88 ± 26[a]	121 ± 18	137 ± 13[a]	<0.001

NS, not significant.
[a]Significant differences between controls and patients are noted.

TVI parameters of systolic and diastolic function

TVI parameters in Group 1, Group 2 and controls are listed in Table 4. Systolic velocities (IVCv, PSv, SR) did not differ between Group 1 and 2 and controls. When using the definition of diastolic dysfunction E' < 8 mm [7], TVI was more sensitive than conventional echocardiography in detecting diastolic dysfunction (33 *vs* 26 patients, $P < 0.05$). E' velocities

Table 5. TVI parameters in patients with normal EF (38 patients), without LVH, concentric LVH and eccentric LVH and controls

	Controls $n=27$	Without LVH $n=14$	Concentric LVH $n=8$	Eccentric LVH $n=16$	P
IVCv (cm/s)	3.8 ± 1.5	3.9 ± 1.5	3.5 ± 1.7	2.6 ± 1.1	<0.05[a]
PSv (cm/s)	6.4 ± 1.3	6.5 ± 1.1	6.0 ± 1.1	5.4 ± 0.8	<0.05[a]
E' (cm/s)	8.0 ± 2.9	7.3 ± 2.2	7.1 ± 1.8	5.8 ± 1.8	<0.05[a]
HR	68.1 ± 9.6	60.4 ± 14	56.1 ± 3.9	64.2 ± 11	NS
IVRT (ms)	88.5 ± 28	94.2 ± 10	93.0 ± 6.8	102.2 ± 9.5	<0.05[a,b]

HR, heart rate. Statistically significant differences between patients with eccentric LVH and controls are marked [a]$P<0.05$ and between patients without LVH and eccentric LVH are marked [b]$P<0.05$.

were significantly lower in Group 2 compared with controls (6.2 ± 1.9 *vs* 8.0 ± 2.9 cm/s, $P<0.05$), but there was no significant difference between controls and Group 1, indicating more pronounced diastolic dysfunction in the patients with severe renal failure. After omitting patients with evidence of IHD, the E' velocities were still lower in Group 2 compared with controls (6.1 ± 1.9 *vs* 8.0 ± 2.9 cm/s, $P<0.05$). In addition, IVRT was significantly longer in the Group 2 patients than in the controls, again indicating impaired diastolic function in patients with severe renal failure (Table 4). Elevated LV filling pressure (E/E' > 15) was present in three patients in Group 1 and three patients in Group 2, i.e. in 15% of the CKD patients.

In Group 2 patients, E' velocities correlated positively with serum albumin ($r^2=0.59$, $P<0.01$) and negatively with plasma PTH ($r^2=-0.50$, $P<0.05$), systolic blood pressure (SBP) ($\rho=-0.68$, $P<0.01$) and pulse pressure ($r^2=-0.50$, $P<0.05$). A' velocities correlated positively with PTH ($r^2=0.62$, $P<0.01$) (Figure 2). IVRT showed positive correlations with PTH ($\rho=-0.51$, $P<0.05$) and diastolic blood pressure (DBP) ($\rho=0.56$, $P<0.05$). The relationship between E'/A' and SBP and PTH in group 2 patients is shown in Figure 2.

Linear regression analysis demonstrated that E' velocities are dependent on SBP ($P<0.001$) and also that E'/A' are dependent on PTH ($P<0.005$).

Left ventricular hypertrophy

The TVI parameters in patients with normal ejection fraction (EF) with and without LVH are shown in Table 5. LVH was present in 26 patients (65% with eccentric hypertrophy and 35% with concentric hypertrophy) without any significant difference in prevalence of LVH and of the two different patterns of LVH between Group 1 and 2 (Group 1, 4 patients with concentric LVH and 10 patients with eccentric LVH; Group 2, 4 patients with concentric LVH and 8 patients with eccentric LVH; $P=$ not significant). Conventional echocardiography parameters of systolic and diastolic function did not differ between patients with and without LVH, and neither was there any difference in the prevalence of systolic and diastolic dysfunction when diagnosed by conventional echocardiography (systolic dysfunction, 3.8 *vs* 7.1% and diastolic dysfunction, 53 *vs* 50%, respectively).

However, TVI demonstrated that patients with LVH had significantly lower IVCv (LVH 2.8 ± 1.3, no LVH 3.9 ± 1.5 and controls 3.8 ± 1.5 cm/s, $P<0.05$) and PSv (LVH 5.5 ± 1.0, no LVH 6.4 ± 1.2 and controls 6.4 ± 1.3 cm/s, $P<0.05$) than patients without LVH and controls. Patients with LVH also showed lower E' velocities than controls (7.1 ± 2.7 *vs* 8.0 ± 2.9 cm/s, $P<0.05$). These findings were even more pronounced when sub-analyses of patients with different types of LVH were performed. Patients with eccentric LVH had significantly lower IVCv, PSv and E' and significantly higher IVRT compared with controls, indicating contractility, contraction and relaxation disturbances (Table 5).

Analysing only patients with eccentric LVH, we found that patients with severe renal failure had significantly lower E' in comparison with controls (5.16 ± 1.49 *vs* 8.0 ± 2.9, $P<0.05$) whereas patients with mild/moderate renal failure did not differ in E' compared with controls (6.33 ± 2.27 *vs* 8.0 ± 2.9; $P=$ not significant).

Discussion

This is the first study using TVI in CKD patients before the start of dialysis therapy. The main finding is that TVI seems to be a more sensitive tool than conventional echocardiography for the detection of impaired diastolic function, in particular in patients with severe CKD. Interestingly, systolic blood pressure was associated with E', and PTH and SBP were associated with E'/A' in patients with severe CKD.

In accordance with previous findings in haemodialysis patients [12], TVI was shown to be more sensitive to evaluate diastolic dysfunction in CKD patients detecting more patients with diastolic dysfunction than conventional echocardiography [13,14]. Our findings are in accordance with Naqvi *et al.* [15] demonstrating an increased sensitivity of TVI to detect diastolic dysfunction in patients with LVH and normal EF. The reason for that may be that TVI is a quantitative method that measures the mechanical wall motion whereas conventional echocardiography is a subjective and semi-quantitative method that evaluates the hydrodynamic responses.

When patients with mild/moderate CKD and controls were compared, patients with severe CKD showed

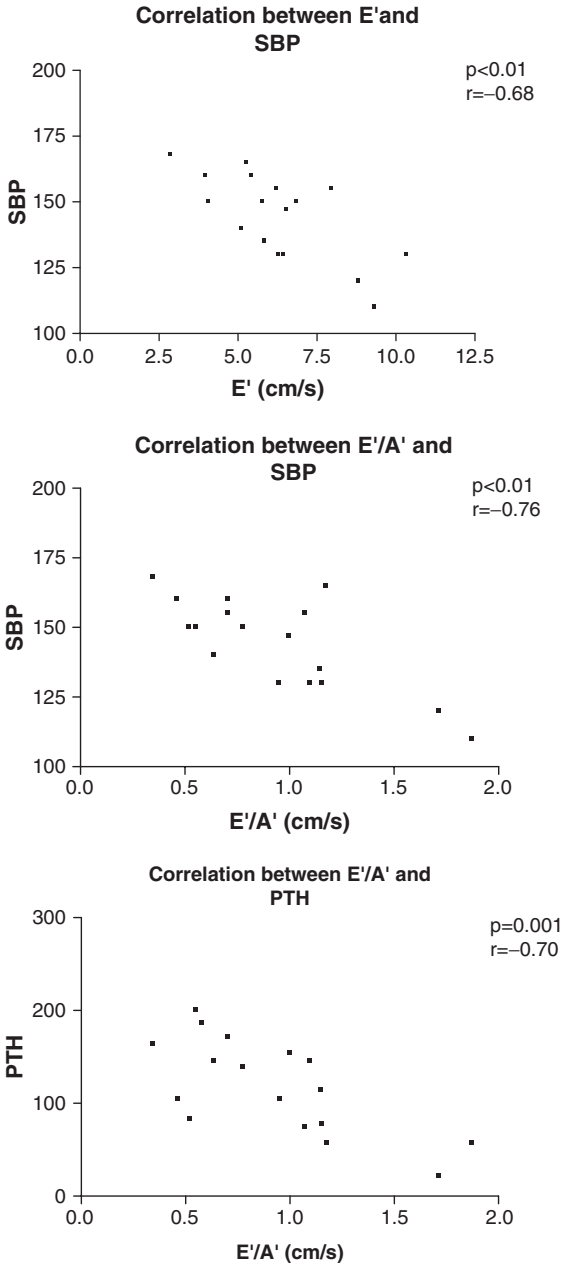

Fig. 2. The relationship between E' and SBP, and between E'/A' and SBP and PTH, respectively, in patients with severe CKD (Group 2).

more pronounced diastolic dysfunction as demonstrated by significantly lower E', without significant impairment of systolic function. This finding seems not to be due only to the presence of LVH, as the prevalence of LVH was not different between the groups. Further, when we analysed only patients with eccentric LVH, patients with severe renal failure but not patients with mild/moderate renal disease still demonstrated significantly lower E' compared with controls. Therefore, in patients with advanced renal failure, factors other than LVH may cause diastolic dysfunction.

In a previous study using TVI, we found that haemodialysis patients have both diastolic and systolic dysfunction. This finding may be due to a more prolonged duration of CKD, a more severe stage of CKD resulting in more severe anaemia and fluid overload, or to specific dialysis-associated factors that further impair left ventricular function in heart disease patients. As SBP and PTH were associated with E' and E'/A', respectively, this suggests a possible role of hypertension and hyperparathyroidism in the pathogenesis of diastolic dysfunction in CKD patients.

Our findings regarding PTH are in accordance with experimental and clinical studies showing that PTH may affect left ventricular function. PTH acts on cardiomyocytes by binding to the PTH/PTHrP receptor, which induces a rise in the intracellular levels of calcium. Increased calcium levels activate protein kinase C and mediate hypertrophic as well as metabolic effects. PTH has been shown to decrease myocardial energy production and utilization and to contribute to the process of death of cardiomyocytes, and it has also been demonstrated to stimulate the proliferation of cardiac fibroblasts, thereby playing an important role in the genesis of myocardial fibrosis, which is a prerequisite of diastolic dysfunction [16]. In patients with primary hyperparathyroidism, the increased prevalence of diastolic dysfunction has been reported whereas LV systolic function was not affected [17]. In some studies investigating patients with primary hyperparathyroidism, diastolic dysfunction improved after parathyroidectomy [17]. Further, in haemodialysis patients, PTH has been shown to be a risk factor for cardiovascular death. Hyperphosphataemia and a high calcium phosphate product (Ca×P), which are findings associated with secondary hyperparathyroidism in CKD, also predict mortality in ESRD patients [18]. In addition, hyperphosphataemia has been shown to affect the structure of the heart, including the microvasculature, and to increase the stiffness in elastic arteries thereby imposing greater workload upon the uraemic heart and an increased risk of left ventricular dysfunction.

In accordance with previous findings in non-uraemic patients, impaired ventricular diastolic function in the CKD patients in the present study was associated with increased blood pressure. Such a relationship has previously been reported for dialysis patients in whom a 10 mmHg mean BP increase was associated with a 44% increased risk of developing LV dysfunction resulting in congestive heart failure and a high risk of mortality [19].

The origin of LVH in uraemia is multifactorial. Pathophysiological factors include LV pressure, volume overload and uraemia-associated factors. Initially, LVH might be a beneficial compensatory process in patients with CKD, allowing the LV to produce additional force to increase the cardiac work and to maintain constant wall tension. However, as the disease progresses, structural changes may occur in the myocardium, such as collagen accumulation, myocyte hypertrophy and myocyte death, leading to the development

of myocardial fibrosis [4]. This constellation of maladaptive events may result in manifest diastolic dysfunction, and even more deleterious, in systolic failure. In order to prevent this devastating process, early identification and treatment of factors involved is of utter importance. Therefore, TVI seems to be a superior instrument for investigation of the relationship between risk factors and LV function parameters.

Many indexes of contractility have been developed and each of them has imperfections. The most used index of systolic function in clinical practice is the ejection fraction, since it is easy to apply and to understand; however, measurements of ejection fraction in LVH may be misinterpreted. A normal EF may be maintained by subnormal function of sarcomeres laid down in parallel. Animal [10] and human studies have shown that TVI could demonstrate abnormal contractility in pathological LVH when conventional echocardiography fails to detect functional abnormalities. We also demonstrated that TVI revealed contractility and contraction disturbances in CKD patients with LVH and normal EF. These findings were more pronounced in eccentric LVH, suggesting that LV geometry can affect systolic function. Eccentric LVH has been described to be more frequently associated with systolic dysfunction than concentric LVH. In pressure overload hypertrophy, Norton *et al.* [20] demonstrated that LV remodelling is a major contributor to the process of decompensation and that the progressive changes in LV volume and shape associated with eccentric remodelling present a considerable mechanical disadvantage to the heart and result in impaired LV pump function. In renal patients, Paoletti *et al.* [21] demonstrated that ELVH was associated with a greater incidence of adverse cardiovascular events.

In summary, the present study demonstrates that TVI, in comparison with conventional echocardiography, is a more sensitive method for the detection of left ventricular dysfunction in pre-dialysis CKD patients, in particular in patients with severe CKD, in whom left ventricular dysfunction appears to be associated with hyperparathyroidism, hypertension and LV geometry. However, the validity of our study is limited by the relatively small number of patients. Therefore, these findings have to be confirmed in larger prospective studies investigating the importance of early detection and treatment of hyperparathyroidism, hypertension and LVH, as they may be important risk factors for cardiovascular morbidity and mortality in CKD patients.

Conflict of interest statement. None declared.

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