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Predictors of Increased Left Ventricular Filling Pressure in Dialysis Patients with Preserved Left Ventricular Ejection Fraction

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Aim To study the left and right ventricular function and to assess the predictors of increased left ventricular (LV) filling pressure in dialysis patients with preserved LV ejection fraction.

Methods This study included 63 consecutive patients (age 57 ± 14 years, 57% women) with end-stage renal failure. Echocardiography, including tissue Doppler measurements, was performed in all patients. Based on the median value of the ratio of transmitral early diastolic velocity to early myocardial velocity (E/E' ratio), patients were divided into 2 groups: the group with high filling pressure (E/E'>10.16) and the group with low filling pressure (E/E'≤10.16).

Results Compared with patients with low filling pressure, the group of patients with high filling pressure included a higher proportion of diabetic patients (41% vs 13%, $P = 0.022$) and had greater LV mass index (211 ± 77 vs 172 ± 71 g/m^3, $P = 0.04$), lower LV lateral long axis amplitude (1.4 ± 0.3 vs 1.6 ± 0.3 cm, $P = 0.01$), lower E wave (84 ± 19 vs 64 ± 18cm/s, $P < 0.001$), lower systolic myocardial velocity (S': 8.6 ± 1. 5 vs 7.0 ± 1.3 cm/s, $P < 0.001$), and lower diastolic myocardial velocities (E': 6.3 ± 1.9 vs 9.5 ± 2.9 cm/s, $P < 0.001$; A': 8.4 ± 1.9 vs 9.7 ± 2.5 cm/s, $P = 0.018$). Multivariate analysis identified LV systolic myocardial velocity – S' wave (adjusted odds ratio, 1.909; 95% confidence interval, 1.060-3.439; $P = 0.031$) and age (1.053; 1.001-1.108; $P = 0.048$) as the only independent predictors of high LV filling pressure in dialysis patients.

Conclusions In dialysis patients with preserved left ventricular ejection fraction, reduced systolic myocardial velocity and elderly age are independent predictors of increased left ventricular filling pressure.

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Cardiovascular disorders are the main cause of mortality and morbidity in patients with end-stage renal failure who are in regular hemodialysis programs (1,2). The left ventricular (LV) hypertrophy is a common finding in these patients. It reflects a physiological response to pressure and volume overload (3) and positively correlates with cardiovascular mortality (4). LV hypertrophy is frequently associated with LV dilatation and reduced systolic function (5). An increased incidence of atherosclerotic cardiovascular events in these patients has also been reported (6). Systolic dysfunction and LV hypertrophy have been identified as the best predictors of outcome in dialysis patients (4,7,8). However, the conventional systolic dysfunction appears in the late stages of the chronic renal failure (9).

In contrast to conventional echocardiography, tissue Doppler imaging of the myocardial velocities overcomes the load dependence of diastolic parameters (10). The ratio of transmitral early diastolic velocity (E) to early myocardial velocity (E′) (E/E′ ratio) has been shown to be an accurate method of the LV filling pressure estimation (8) and the best predictor of LV diastolic filling in various cardiac pathologies (11,12), thereby serving as one of the best predictors of outcome in heart failure patients (13-15) and patients with end-stage renal disease (16).

The aims of this study were to investigate the left and right ventricular function in patients with end-stage renal disease and preserved LV ejection fraction and to assess the predictors of increased LV filling pressure in these patients.

METHODS

Study population

Sixty-three consecutive patients (57 ± 14 years of age, 36 women) with end-stage renal disease who underwent hemodialysis in Hemodialysis Department of the Internal Medicine Clinic of the University Clinical Centre of Kosovo in Prishtina, Kosovo, were included in this study between November 2008 and March 2009. Patients were in dialysis treatment 3 times per week over a time period of 4.4 ± 4.2 years. All patients had normal LV dimensions (LV end-diastolic dimension [EDD]<5.7cm) and normal LV systolic function (LV ejection fraction [EF]>50%). Patients with rhythm disorders (atrial fibrillation, serious ventricular arrhythmias), reduced LV ejection fraction, and decompensated heart failure with chronic obstructive pulmonary disease were excluded from the study. Patients who had unstable angina, acute or previous myocardial infarction, stroke, severe anemia, and any febrile condition or infectious disease were also excluded. The study was approved by the institutional Ethics Committee and all patients gave their written informed consent.

Data collection

The history-taking and physical examination was performed in all participants. Routine biochemical measurements were performed: blood count, hemoglobin, hematocrit, erythrocyte sedimentation rate, urea, creatinine, blood glucose, total cholesterol, triglycerides, fibrinogen, C-reactive protein, and electrolytes (potassium, sodium, and calcium). Weight and height were measured and used to calculate the body-surface area.

Echocardiographic examination

A single operator (GB) performed all echocardiographic examinations using a Philips Intelligent E-33 system (Phillips, Hamburg, Germany) with a multi-frequency transducer, and harmonic imaging as appropriate. The echocardiographic examination was performed less than one hour before the dialysis session. The images were obtained with the patient in the left lateral decubitus position and during quiet expiration. LV dimensions at end-systole and end-diastole were measured from the left parasternal cross-sectional recording of the minor axis with the M-mode cursor positioned by the tips of the mitral valve leaflets. LV volumes and ejection fraction were calculated from the apical 2 and 4 chamber views using the modified Simpson's method (17). Left atrial diameter was measured from aortic root recordings with the M-mode cursor positioned at the level of the aortic valve leaflets. Ventricular long axis motion was assessed by placing the M-mode cursor at the lateral and septal angles of the mitral ring and the lateral angle of the tricuspid ring. The total amplitude of long axis motion was measured as previously described (18).

LV and right ventricular (RV) diastolic function was assessed from their filling velocities using spectral pulsed wave Doppler with the sample volume positioned at the tips of the mitral and tricuspid valve leaflets, respectively. Peak LV and RV early (E wave), and late (A wave) diastolic velocities were measured and E/A ratios were calculated. LV and RV long axis myocardial velocities were studied using Doppler tissue imaging technique. From the apical 4-chamber view, longitudinal velocities were recorded with the sample volume placed at the basal segment of LV lateral and septal segments and at RV free wall. Systolic (S′)

and early and late (E' and A') diastolic myocardial velocities were measured with the gain optimally adjusted. Mean value of the lateral and septal LV velocities was calculated. Indirect assessment of LV asynchronous function was obtained by measuring total isovolumic time (t-IVT) and Tei Index. Total LV filling time was measured from the onset of the E wave to the end of the A wave, and ejection time from the onset to the end of the aortic Doppler flow velocity. Total isovolumic time (t-IVT) was calculated as 60 – (total ejection time + total filling time) and was expressed in s/min (19). Tei index was calculated as the ratio between t-IVT and ejection time (20). Mitral regurgitation severity was assessed by color and continuous wave Doppler and was graded as mild, moderate, or severe according to the relative jet area compared with that of the left atrium and the flow velocity profile, in line with the recommendations of the American Society of Echocardiography (21). Likewise, tricuspid regurgitation was assessed by color Doppler and continuous-wave Doppler. Retrograde transtricuspid pressure drop >35 mm Hg was evidence of pulmonary hypertension (21). All M-mode and Doppler recordings were made at the speed of 100 mm/s, with a superimposed ECG (lead II).

The LV mass was calculated using the modified American Society of Echocardiography cube formula proposed by Devereux et al (22) and indexed by body surface area. LV hypertrophy was defined as LV mass indexed by body surface area >131 g/m^2 in men and >100 g/m^2 in women (23,24).

Statistical analysis

Data are presented as mean ± standard deviation. Continuous data were compared using a two-tailed unpaired *t* test. Discrete variables were compared using χ^2 test or Fisher exact test, as appropriate. Multiple logistic regression analysis was used to identify the independent correlates of raised LV filling pressure. All variables showing significant differences between groups in univariate analysis and variables known to affect filling pressure (age, duration of dialysis treatment, and hemoglobin) were entered into the model. Statistical analysis was performed using SPSS, version 13 (SPSS Inc., Chicago, IL, USA). *P* value <0.05 was considered significant.

RESULTS

Based on the median E/E' ratio – the best echocardiographic parameter to assess the left ventricular filling pressure – patients were divided into 2 groups: patients with high filling pressure (E/E'>10.16; n = 32) and patients with low filling pressure (E/E'≤10.16; n = 31).

Main baseline characteristics are shown in Table 1. Seventeen patients (27%) had diabetes and LV mass index was increased in 56 of 63 patients (89%). Baseline clinical and laboratory characteristics of patients are shown in Table 2. The percentage of diabetic patients was significantly higher among patients with high filling pressure than among patients with low filling pressure (41% vs 13%, *P* = 0.022). The other characteristics appeared to differ little between the 2 groups of patients (Table 2).

Echocardiography data are shown in Table 3. Patients with elevated LV filling pressure had higher LV mass index, small-

TABLE 1. Characteristics of dialysis patients with preserved left ventricular ejection fraction

Characteristic	Number/value
Age (years ± standard deviation, SD)	57 ± 14
Women	36 (57%)
Increased LV mass index	56 (89%)
Diabetes	17 (27%)
Duration of the dialysis maintenance (years ± SD)	4.4 ± 4.2

TABLE 2. Clinical and biochemical characteristics of dialysis patients with preserved left ventricular ejection fraction*

	Patients with		
Variable	E/E'≤10.16 (n = 31)	E/E'>10.16 (n = 32)	*P*
Sex (female, %)	52	63	0.450
Age (years)	54 ± 15	60 ± 12	0.091
Diabetes (%)	13	41	0.022
Arterial hypertension (%)	52	56	0.802
Dialysis time duration (years)	4.2 ± 3.0	4.6 ± 5.3	0.762
Fasting glycemia (mmol/L)	6.0 ± 1.3	6.5 ± 2.7	0.411
Urea (mmol/L)	26.1 ± 5.5	27.5 ± 5.6	0.323
Creatinine (μmol/L)	840 ± 181	855 ± 260	0.790
Erythrocytes (× 10^{12}/L)	3.1 ± 0.4	3.1 ± 0.6	0.985
Leukocytes (× 10^3/L)	8.6 ± 2.2	9.5 ± 2.3	0.084
Hematocrit (%)	30.0 ± 6.3	30.5 ± 6.1	0.741
Hemoglobin (g/L)	111 ± 19	110 ± 26	0.850
Platelet (× 10^3/μL)	187 ± 42	187 ± 43	0.974
Sodium (mEq/L)	135 ± 6.1	134 ± 6.4	0.771
Potassium (mEq/L)	4.3 ± 1.0	4.6 ± 1.0	0.204
Calcium (mmol/L)	1.3 ± 0.4	1.2 ± 0.3	0.318

*Abbreviations: E/E' ratio – the ratio of transmitral early diastolic velocity to early myocardial velocity. Data are presented as mean ± standard deviation or percentages for frequencies. Two-tailed unpaired t test was used for the comparison of continuous variables and χ^2 test for frequencies.

er LV lateral long axis amplitude, and higher E wave velocity on conventional transmitral Doppler than patients with low filling pressure. Systolic myocardial velocities in both

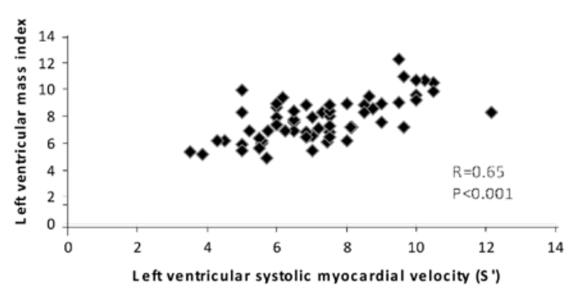
TABLE 3. Echocardiographic data in dialysis patients with preserved left ventricular ejection fraction*

	Patients with		
Systolic LV function	E/E'≤10.16	E/E'>10.16	*P*
LV EDD (cm)	4.9±0.7	5.1±0.6	0.271
LV ESD (cm)	3.1±0.5	3.3±0.6	0.247
LV EDD volume index (mL/m^2)	68±25	72±25	0.622
LV ESD volume index (mL/m^2)	26±10	30±13	0.072
LV mass index (g/m^3)	172±71	211±77	0.040
LV shortening fraction (%)	36±5	34±7	0.094
LV ejection fraction (%)	66±7	63±7	0.065
Lateral long axis amplitude (cm)	1.6±0.3	1.4±0.3	0.010
Septal long axis amplitude (cm)	1.3±0.2	1.3±0.2	0.437
Left atrium diameter (cm)	4.0±0.5	4.0±0.6	0.779
Left atrium area (cm^2)	22.3±5.8	23.5±5.5	0.395
Lateral S' wave (cm/s)	8.9±2.0	7.2±1.7	<0.001
Septal S' wave (cm/s)	8.3±1.5	6.7±1.4	<0.001
S' mean wave (cm/s)	8.6±1.5	7.0±1.3	<0.001
Diastolic LV function			
E wave velocity (cm/s)	64±18	84±19	<0.001
A wave velocity (cm/s)	78±14	86±22	0.071
E/A ratio	0.85±0.30	1.05±0.49	0.056
E wave deceleration time (ms)	148±40	157±49	0.441
Lateral E' (cm/s	9.5±2.9	6.3±1.9	<0.001
Septal E' (cm/s)	7.2±1.5	6.2±1.6	0.013
E' mean (cm/s)	8.4±1.7	6.2±1.3	<0.001
Lateral A' (cm/s)	10.1±3.2	8.4±2.4	0.026
Septal A' (cm/s)	9.4±2.4	8.4±2.0	0.083
A' mean (cm/s)	9.7±2.5	8.4±1.9	0.018
Global LV function			
T-IVT (s/min)	9.7±3.9	9.3±4.1	0.667
Tei index	0.49±0.40	0.47±0.30	0.752
RV function			
Long axis amplitude (cm)	2.8±1.2	2.6±0.6	0.389
E wave (cm/s)	50±11	54±13	0.201
A wave (cm/s)	60±15	57±16	0.425
E/A ratio	0.86±0.20	1.14±0.70	0.031
E wave deceleration time (ms)	164±53	150±49	0.277
Right E' (cm/s)	13.4±3.5	13.4±3.7	0.987
Right A' (cm/s)	17.1±4.0	16.5±5.2	0.599
Right S' (cm/s)	14.2±3.6	13.3±3.7	0.297

*Abbreviations: LV – left ventricle; RV – right ventricle; A – atrial diastolic velocity; E – early diastolic filling velocity; EDD – end-diastolic dimension; ESD – end-systolic dimension; T-IVT – total isovolumic time; S' – systolic myocardial velocity, E' – early diastolic myocardial velocity; A' – late diastolic myocardial velocity. Data are presented as mean±standard deviations and two-tailed unpaired *t* test was used for the comparisons.
†According to Tei et al (20).

lateral and septal sides of the mitral annulus, as well as their mean values, early diastolic velocities, and the mean value of lateral and septal A' velocity were significantly lower in patients with high LV filling pressure. The other echocardiographic variables of LV and the left atrial systolic function (LV EDD and LV ESD, LV EDD and LV ESD volume indexes, LV shortening and ejection fractions, septal long axis amplitude, and left atrium diameter and area), LV diastolic function (A wave velocity, E/A ratio, E wave deceleration time, and septal A' wave), and global LV function (T-IVT and Tei index) did not differ significantly between the groups. The E/A ratio of the right ventricular function was the only echocardiographic variable that significantly differed between the groups (1.14±0.7 vs 0.86±0.2, $P=0.031$), whereas the other variables did not show significant differences. There was a weak but significant correlation between E/E' ratio and LV mass index (R=0.24; $P=0.030$). The S' wave had a very good correlation with LV mass index (R=0.65; $P<0.001$, Figure 1).

Figure 1.



Correlation between left ventricular systolic myocardial velocity (S') and left ventricular mass index.

Multiple binary logistic regression was used to define the independent correlates of the elevated LV filling pressure while adjusting for potential confounding variables. The model showed that LV systolic myocardial velocity – S' wave (adjusted odds ratio, 1.909; 95% confidence interval; 1.060-3.439; $P=0.031$) and age (1.053; 1.001-1.108; $P=0.048$) were the only independent correlates of elevated LV filling pressures in these patients. Full results of the multivariable analysis are shown in Table 4.

DISCUSSION

In this study, we assessed the predictors of elevated LV filling pressure in patients with end-stage renal disease undergoing a prolonged dialysis treatment. To the best of

TABLE 4. **Results of multivariate analysis regarding the predictors of raised filling pressure in dialysis patients with preserved left ventricular ejection fraction***

Variable	χ^2	Odds ratio (95% confidence interval)	*P*
Left ventricular S' wave	4.639	1.909 (1.060-3.439)	0.031
Age	3.927	1.053 (1.001-1.108)	0.048
Hemoglobin	2.347	1.314 (0.927-1.862)	0.126
Diabetes	1.790	0.292 (0.048-1.774)	0.181
LV mass index	1.241	0.994 (0.984-1.004)	0.265
Lateral long axis amplitude	0.461	2.543 (0.172-37.635)	0.497
Left ventricular A' wave	0.139	1.074 (0.738-1.563)	0.710
Duration of hemodialysis	0.054	0.982 (0.847-1.140)	0.815

*Abbreviations: LV – left ventricle; S' – systolic myocardial velocity, A' – late diastolic myocardial velocity.

our knowledge, this is the most comprehensive analysis of clinical and echocardiographic factors associated with elevated LV filling pressures in patients with end-stage renal disease on long-term dialysis (over 4.4 years). The main finding of our study is that the independent predictors of high LV filling pressure in dialysis patients with preserved LV ejection fraction are the reduced systolic myocardial velocity (S' wave) and elderly age.

Several previous studies have shown that heart failure is a common finding in end-stage renal failure patients (25), due to existence of various cardiovascular disorders in these patients (1,2). The E/E' ratio has been shown to be the best correlate of LV filling pressure (10) in heart failure patients and one of the best predictors of outcome in patients with heart failure (13,26), myocardial infarction (27), and end-stage renal disease (28). It was also recommended by European Society of Cardiology as a variable to non-invasively estimate LV filling pressure (29). The increased LV filling pressure can be detected earlier by tissue-Doppler imaging, which directly measures myocardial velocities of the LV and is much less load-dependent than conventional Doppler variables, thus being a more sensitive method for detecting of LV diastolic dysfunction, especially in patients with LV hypertrophy and normal LV ejection fraction (30). Determination of myocardial velocities is a quantitative method that measures mechanical wall motion, whereas the conventional Doppler echocardiography measures the hydrodynamic responses of the LV. It seems that the reduction in the systolic myocardial velocities appears earlier than the reduction in conventional left ventricular systolic function, measured by LV ejection fraction. It appears that the systolic wall motion velocity is impaired in patients with LV hypertrophy, which is very common in hemodialysis patients. This is a very important echocardiographic finding to predict and prevent the progress of heart failure in these patients. In the present study, this parameter showed a very good correlation with LV mass index. This finding suggests that in most of patients who had LV hypertrophy, myocardial systolic function was impaired and its degree of impairment depended on the degree of the hypertrophy, even though the conventional LV ejection fraction was within the reference range. Thus, the impaired myocardial systolic function is the best correlate of impaired LV filling pressure, and it can be of help in detecting the risk of developing heart failure in dialysis patients. Furthermore, it may allow a better treatment of arterial hypertension, according to the current guidelines (31).

The other predictor of high LV filling pressure found in our study was the age of patients. In several previous studies, age has been shown to be an independent predictor of cardiac events, including mortality, in patients with heart failure (13,32) and end-stage renal disease (28). The effect of age on the LV diastolic dysfunction may be explained with fibrotic changes in myocardium that build up with advancing age. Also, older patients have usually been longer on dialysis treatment or have had arterial hypertension for a longer time than younger patients.

Our study has several limitations. First, it included a relatively small number of patients, therefore confirmation from larger prospective studies is required. Second, we could not perform the invasive measurement of LV filling pressure simultaneously with other measurements. However, in previous studies it has been shown that the E/Em ratio is the best correlate of LV filling pressure (10,33).

In conclusion, the present study demonstrated that in patients with end-stage renal disease and preserved conventional systolic function undergoing dialysis treatment, the reduced systolic myocardial velocity and elderly age were independent correlates of elevated LV filling pressure. These factors should be used to better monitor and adjust treatment in these patients in daily practice.

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