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Myocardial fibrosis and diastolic dysfunction in patients on chronic haemodialysis

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Abstract

Background. Left ventricular (LV) diastolic dysfunction is linked to myocardial collagen content in many cardiac diseases. There are no data regarding such relationship in patients with end-stage renal disease (ESRD) undergoing haemodialysis.

Methods. Twenty-five patients with ESRD undergoing haemodialysis were studied by echocardiography. LV diastolic function was investigated by Doppler echocardiography, by analysing LV filling velocities at rest and during loading manoeuvres, which represent an estimate of LV filling pressure. According to the Doppler pattern, LV filling pressure in a given patient was judged to be normal or slightly increased or to be moderately or severely increased. The presence of myocardial fibrosis was estimated by ultrasound tissue characterization with integrated backscatter, which in diastole correlates with the collagen content of the myocardium.

Results. Integrated backscatter was higher in patients with moderate or severely increased than in patients with normal or slightly increased LV filling pressure (integrated backscatter: 51.0 ± 9.8 *vs* 41.6 ± 5.6%; $P = 0.008$). Integrated backscatter was a strong and independent determinant of diastolic dysfunction (odds ratio = 1.212; $P = 0.040$).

Conclusion. Our data support the hypothesis that, in a selected population of patients with ESRD undergoing haemodialysis, myocardial fibrosis is associated with LV diastolic myocardial properties.

Keywords: diastolic function; ESRD; myocardial fibrosis; tissue characterization

Introduction

Diastolic dysfunction, assessed by echocardiography, is associated with marked increase in all-cause mortality in population-based studies and in patients with specific disease [1,2]. The central disturbance in diastolic dysfunction involves abnormalities in myocardial relaxation and ventricular compliance [3,4], which are related to structural and functional cardiac abnormalities. Experimental and clinical data demonstrated that such abnormalities are mainly due to the increase of myocardial fibrosis [3]. As a consequence of fibrosis, relaxation becomes slower and left ventricular (LV) compliance decreases [3]. Thus, in order to complete LV filling and achieve a sufficient end-diastolic volume, which will provide adequate stroke volume, the left ventricle needs filling pressure higher than normal. Diastolic dysfunction, in fact, means that the left ventricle fills at higher pressure. This condition is frequent in patients with end-stage renal disease (ESRD) due to increased LV thicknesses and fibrosis. Myocardial fibrosis is particularly high in ESRD patients undergoing haemodialysis, because of hypertension, increased volume and hyperparathyroidism [5–8]. The relationship between myocardial fibrosis and diastolic dysfunction has been evaluated in many cardiac diseases [9–13], but no data exist in patients with ESRD.

Echocardiography is a worldwide accepted non-invasive method to assess diastolic function [1,14,15] and LV hypertrophy [16]. Moreover, there are consistent data in experimental [17–19] and clinical settings [20,21], suggesting that it can identify the presence of LV myocardial fibrosis by using the integrated backscatter signal in diastole (IBS).

Thus, this study was aimed to understand the relationship between LV diastolic function and LV fibrosis in ESRD patients undergoing haemodialysis.

Materials and methods

Population

Thirty-eight patients with ESRD undergoing standard haemodialysis (three times a week through an arteriovenous fistula) at the Department of Nephrology of our University Hospital were considered for the study. Patients with (i) a not high-quality 2D and Doppler echocardiogram from

a parasternal long axis and four chamber views (n = 2); (ii) LV ejection fraction <45% (n = 2); (iii) LV end-diastolic volume ≥102 ml/M^2 (n = 3); (iv) history of myocardial ischaemia, i.e. typical chest pain and/or positive stress test, and/or infarction, i.e. hospitalization, elevation of cardiac enzymes, and/or regional myocardial thinning (i.e. <7 mm) or with regional wall motion abnormalities (n = 2); (v) valvular heart disease (n = 1); (vi) atrioventricular heart blocks or atrial fibrillation (n = 2); (vii) previous pericardiectomy and/or suspected constrictive pericarditis (n = 1) were excluded from the study. Thus, 25 patients constituted the final population. They were 16 men and 9 women, with mean age of 47 ± 12, range 22–71 years. All patients were studied in the long interdialytic period, within 24 hours preceding the haemodialysis; thus, patients were studied on Monday and Tuesday. In each patient, their history of hypertension, i.e. systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg; history of dyslipidaemia (evidence of cholesterol >200 mg/dl and/or triglyceride >150 mg/dl); and history of diabetes (fasting glucose >126 mg/dl) were assessed. In each patient, haemoglobin and parathyroid hormone levels were evaluated. A haemoglobin level <13 g/dl and <12g/dl identified anaemia in men and women, respectively; parathyroid hormone level was considered optimal when between 150 and 300 pg/dl. By bioelectric impedance analysis resistance, reactance and extracellular water were measured in 10 patients. All enrolled patients gave their informed consent prior to the study.

Echocardiography

Echocardiography was performed using a Hewlett–Packard imaging system (Sonos 5500, Andover, Massachusetts) with an S3 transducer. Each patient underwent standard M-mode, 2D and Doppler echocardiographic study. In particular by M-Mode echocardiography, we measured LV internal dimensions, interventricular septum and posterior wall thicknesses according to the recommendations of the American Society of Echocardiography [16]. LV mass was indexed to body surface area [16], increased LV mass was defined in presence of a mass >95 g/M^2 in women and >115 g/M^2 in men [15]. LV systolic function was estimated by four-chamber view using the monoplane method of disks [16]. A non-dilated left ventricle was defined in presence of LV end-diastolic volume <102 ml/M^2 [22]; an LV ejection fraction ≥45% was considered normal [23]. The assessment of volume overload was done by measuring the inferior vena cava diameter by subcostal view and then normalized to body surface area (millimetre per square metre) [24].

Patients underwent pulsed wave Doppler examination of mitral inflow before and during loading manipulations, Valsava and legs-up manoeuvres [1,25,26], which induce a decrease and an increase in cardiac preload, respectively. Mitral flow velocities will decrease considerably during preload reduction in presence of high filling pressure (so-called pseudonormal pattern), whereas, in presence of normal filling pressure, they will show only little changes. Furthermore, in patients with particularly elevated diastolic dysfunction, LV filling pressure increases markedly and rapidly during early filling so that filling is reduced during late diastole; in these cases, mitral flow velocities will show an high early diastolic velocity with fast deceleration time and a low diastolic velocity at end-diastole (so-called restrictive pattern). This pattern can be observed at baseline studies, or can develop during an increase in end-diastolic volume, such as during legs-lifting manoeuvre, which will be attained at the expense of a far greater rise in filling pressure.

Moreover, by Doppler echocardiography, pulmonary venous inflow velocities were recorded as well as by Doppler tissue imaging mitral annulus velocities. Diastolic function was categorized according to the level of diastolic dysfunction: normal; mild, defined as impaired relaxation without evidence of increased filling pressure; moderate, defined as impaired relaxation associated with moderate elevation of filling pressure or pseudonormal filling; and severe, defined in presence of reversible, or inducible or fixed restrictive filling [1,25,26]. Participants were required to have two Doppler criteria consistent with moderate or severe diastolic dysfunction to be so classified. Subjects with one criterion for moderate or severe diastolic dysfunction, or those whose parameters were borderline and suggestive of but not definitive for diastolic dysfunction were classified as indeterminate rather than as normal and thus, excluded from the study [1].

According to these Doppler indexes, LV filling pressure in a given patient was judged to be normal or slightly increased in presence of normal or prolonged relaxation pattern, and to be moderate or severely increased, suggestive of filling pressure ≥18 mmHg [27], in presence of pseudonormal or restrictive patterns [1,25–28].

Integrated backscatter is the relative measure of the total ultrasonic energy backscattered by a small volume of the tissue under evaluation [29]. It is produced when ultrasound interacts with components of the tissue smaller than the transmitted wavelength; in this case, the reflected signal is scattered in all directions, hence, part of it, the so-called backscatter, is directed towards the probe [29]. Integrated backscatter can be evaluated during the overall cardiac cycle, the cyclic variation, or only during the last part of diastole (end-diastole), IBS; this latter parameter has been related to the entity of myocardial fibrosis [17–19]. Thus, to measure IBS at septal and posterior wall segments, an elliptical region of interest was placed in the mid-myocardial region and tracked manually on frame by frame carefully avoiding the brighter endocardial borders, and their position was adjusted in each frame so that the same area of myocardium was analysed throughout end-diastole [12,30]. In each frame, the Mean IBS was measured within the region of interest, expressed in decibels and averaged across the end-diastole. Pericardial reflectivity was measured in a single end-diastolic frame. IBS was then expressed as percentage of pericardial reflectivity [12,29,30]. Finally, the mean of septal and posterior wall IBS was also calculated [30] and thereafter, called Mean IBS. As control group for IBS measurements, 10 normal subject sex and age matched were studied. They were four women and six men with mean age of 41 ± 9, range 30–54 years.

Statistics

All statistical calculations were performed by using SPSS for Windows, release 12 (SPSS, Chicago, Illinois). Data are given as mean ± 1 SD. Student's t-test, one-way analysis of variance and Pearson correlation were used when appropriate. Chi-squared was used for categorical variables. Odds ratios (OR) and 95% confidence limits (Cl) were calculated by using univariate and multivariate logistic regression models. To evaluate the variability of measurements, we calculated the percent precision and the repeatability coefficient, as previously outlined [12]. A probability value <0.05 was considered significant.

Results

Population

Two patients were excluded because of Doppler patterns which were classified as indeterminate. Patients were on haemodialysis for 48 ± 61 months, range 6 to 240 months. In 12 patients, there was history of isolated hypertension, combined to dyslipidaemia in four and to diabetes in two, and to diabetes and dyslipidaemia in one patient; in the one remaining patient, there was history of isolated dyslipidaemia. All but one patient had anaemia. Eleven patients had hyperparathyroidism. Five patients had no classical cardiovascular risk factors. All patients received medical therapy with ACE-inhibitors and/ or AT1 blockers; in the majority of patients, the drug dosage had changed continuously from the beginning of haemodialysis to the date of our control.

Diastolic function

In seven patients, there was evidence of normal diastolic pattern, in seven of altered relaxation pattern, in three patients, there was evidence of pseudonormal pattern, and in the remaining six, there was restrictive pattern. In these last four patients, the restrictive pattern was elicited during legs-up manoeuvre. Thus, in 14 patients, LV filling pressure was judged to be normal or slightly abnormal, whereas in nine patients, it was judged to be moderately to severely increased. Clinical and echocardiographic findings in these two groups of patients are reported in Table

Table 1. Clinical and echocardiographic characteristics of patients divided based on their estimated LV filling pressure

Clinical and echocardiographic variables	Filling patterns		*P*
	Normal and altered relaxation [14]	Pseudonormal and restrictive [9]	
Age (years)	49.4 ± 11.2	42.7 ± 12.4	0.19
Dialysis duration (months)	40.7 ± 55.6	58.7 ± 69.6	0.52
History of hypertension	10 (71%)	7 (78%)	0.68
History of dyslipidaemia	2 (14%)	4 (44%)	0.87
History of diabetes	2 (14%)	1 (11%)	0.42
Left atrial diameter (mm)	41.6 ± 4.1	40.2 ± 5.5	0.51
LV mass (g/M^2)	90.7 ± 25.2	85.5 ± 33.3	0.68
Increased LV mass (g/M^2)	3 (21%)	2 (22%)	0.87
LV volume index (ml/M^2)	53.9 ± 16.6	55.8 ± 18.5	0.80
LV ejection fraction (%)	59.6 ± 8.0	59.8 ± 9.6	0.96
Inferior vena cava index (mm/M^2)	8.7 ± 2.2	8.6 ± 1.6	0.85
Resistance (Ohm)	536.2 + 42.7	535.5 + 123.4	0.99
Reactance (Ohm)	59.7 + 6.8	56.3 + 20.6	0.77
Extracellular water (%)	43.9 + 3.0	46.7 + 4.5	0.27
Haemoglobin (g/dl)	11.2 ± 1.2	10.4 ± 1.0	0.11
Parathyroid hormone (pg/ml)	353.4 ± 191.2	278.9 ± 188.9	0.39

LV = left ventricular.

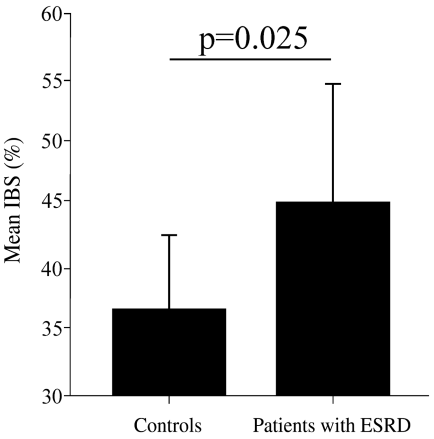

Fig. 1. Value of Mean IBS in the study population and in the control group. ESRD = end-stage renal disease.

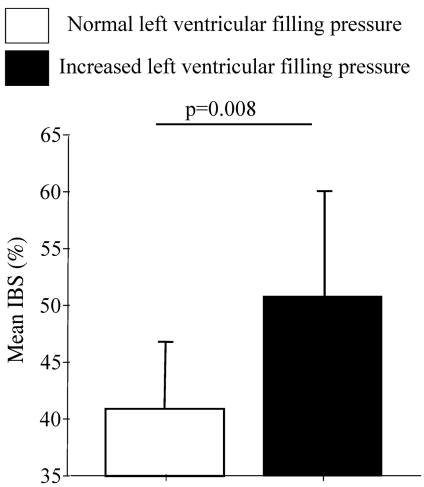

Fig. 2. Value of Mean IBS in the population divided in two groups according to the estimated left ventricular diastolic pressure.

1 which shows no clinical and echocardiographic differences between the two groups (Table 1).

IBS

Intraobserver variability was tested in 10 consecutive patients: percent precision was 2%, and the repeatability coefficient was 1.35. Mean IBS was greater in patients with ESRD than in controls (Mean IBS 45.2 ± 8.6 *vs* 36.8 ± 6.1%, $P = 0.025$) (Figure 1). Mean IBS resulted to be higher in patients with moderate and severely increased LV pressure than in patients with normal or slightly abnormal LV pressure (Mean IBS 51.0 ± 9.8 *vs* 41.6 ± 5.6%; $P = 0.008$) (Figure 2). There were no differences of Mean IBS value between patients without and with hypertension (Mean IBS: 44.10 ± 7.3 *vs* 45.2 ± 7.0%; *P* = not significant (NS)), diabetes (Mean IBS: 46.4 ± 7.9 *vs* 38.4

Table 2. Determinants of diastolic dysfunction by univariate logistic regression analysis

Variable	Odds ratio	Cl 95%	*P*-value
Age	0.949	0.876–1.027	0.19
Dialysis duration (months)	1.005	0.990–1.020	0.50
History of hypertension	1.400	0.199–9.869	0.74
History of dyslipidaemia	1.083	0.154–7.642	0.12
History of diabetes	0.750	0.058–9.719	0.83
Left atrial diameter (mm)	0.936	0.775–1.131	0.49
LV mass (g/M^2)	0.993	0.962–1.025	0.66
Increased LV mass (g/M^2)	1.048	0.138–7.934	0.69
LV volume index (ml/M^2)	0.977	0.862–1.108	0.79
LV ejection fraction (%)	1.033	0.906–1.010	0.95
Inferior vena cava index (mm/M^2)	0.945	0.543–1.645	0.84
Resistance (Ohm)	1.000	0.983–1.017	0.99
Reactance (Ohm)	0.978	0.882–1.084	0.67
Extracellular water (%)	1.273	0.842–1.925	0.25
Haemoglobin (g/dl)	0.481	0.189–1.227	0.13
Parathyroid hormone (pg/ml)	0.998	0.992–1.003	0.63
Mean IBS	1.212	1.009–1.457	0.04

LV = left ventricular.
IBS = integrated backscatter.

± 7.5%), dyslipidaemia (Mean IBS: 45.3 ± 9.9 *vs* 43.8 ± 6.3%; P = NS). Mean IBS was greater in patients with increased LV mass than in patients with normal LV mass (Mean IBS: 51.9 + 12.4 *vs* 43.0 + 7.1%; P = 0.046).

Determinants of increased LV pressure

By univariate logistic regression analysis, we analysed the determinants of diastolic dysfunction. Diastolic dysfunction was defined in presence of a pseudonormal and restrictive patterns. Thus, a binary logistic regression analysis was performed. Only Mean IBS resulted to be a determinant of diastolic dysfunction (Table 2).

Discussion

This study demonstrates that, in a selected population of patients with ESRD undergoing haemodialysis, LV diastolic function worsens together with increasing of IBS, and that IBS is a major determinant of diastolic dysfunction in these patients.

LV diastolic dysfunction, as occurs in patients with hypertension, diabetes mellitus and/or ageing, carries a substantial risk of heart failure development and reduced survival, even when it is asymptomatic or 'preclinical' [1,2]. Although diagnostic Doppler echocardiography has improved to identify patients with such condition, therapeutic strategies are still poor and will depend on research directed at the understanding of the mechanisms of the disease [3,4].

In our study, 70% of patients showed Doppler indexes of diastolic dysfunction, and within this group, in more than 50%, such abnormalities were severe, i.e. indicating a moderate to severe increase in LV diastolic pressure (Table 1). This result was expected, because LV structural alterations resulting in diastolic dysfunction, such as hypertrophy and increased wall thickness associated with increased myocardial fibrosis, are exaggerated in patients with ESRD [6,30]. Such a high prevalence of diastolic dysfunction may explain why patients with chronic kidney disease have a high prevalence of diastolic heart failure [2] indicating that increased filling pressure is probably the most important haemodynamic alteration in this group of patients. Moreover, diastolic dysfunction is a frequent cause of hypotension during haemodialysis, a condition which can contribute to LV remodelling [5]. The identification of the precise mechanism of increased filling pressure may play a role in the management of patients with ESRD.

IBS, myocardial fibrosis and cardiac structure in patients with ESRD

The intensity of IBS signal depends on fibre orientation and tissue structure, which is influenced by the ratio between cardiomyocyte components and extracellular matrix. IBS has been reported, in fact, to correlate with myocardial collagen content, and therefore, represents an estimate of myocardial fibrosis [17–21].

Experimental data suggest that LV hypertrophy in uraemic rats is associated with an expansion of the myocardial interstitium, with extracellular deposition of collagen fiber [6]. Many structural lesions described in the heart of uraemic animals have been confirmed in adult patients with ESRD. Autopsy studies revealed that interstitial myocardial fibrosis is more pronounced in dialysis patients than in patients with primary hypertension, and identified uraemia as an independent determinant of these lesions [31]. Factors which determine such a high increase in myocardial fibrosis have been demonstrated in animal studies and are multiple and complex: hyperphosphataemia and increased level of parathyroid hormone, which stimulate deposition of myocardial fibrosis; activation of renin–angiotensin–aldosterone system, which plays a role in increasing extracellular matrix in patients with hypertension, and oxidative stress, whose blockage decreases fibrosis in uraemic rats [32,33]. Thus, although a direct evidence of the entity of myocardial fibrosis lacks in this study, it is reasonable that IBS in our population of patients is related primarily to interstitial fibrosis, as recently suggested by other authors [30].

IBS and diastolic function in ESRD

Fibrosis raises the viscoelastic burden of the myocardium and compromises relaxation, diastolic suction and passive stiffness [3]. Pathophysiologic consequences included elevated atrial pressure and ventricular filling pressure. Such an elevated pressure may return to lower values when preload reduces or can further augment when preload increases. Thus, it is reasonable that patients with ESRD undergoing haemodialysis, in whom there are multiple levels of preload between haemodialysis sessions, have continuous variations in filling pressure. These variations in pressure and load will allow different patterns of diastolic filling by Doppler echocardiography [34]. By varying loading in the single patient during echocardiography, we can better estimate the presence and the degree of LV filling pressure increase [25,26]. In fact, in our patients, variations of load during echocardiography lead us to identify patients with Doppler indexes suggestive of moderate to severely increased LV diastolic pressure. The mechanism of such dysfunction was related to increase Mean IBS, suggesting an increased myocardial fibrosis (Figure 2). Moreover, in our population, although Mean IBS was higher in patients with LV hypertrophy, this latter was not a determinant of diastolic dysfunction, as shown by the univariate analysis (Table 2). Thus, in patients with ESRD undergoing haemodialysis with normal ejection fraction, without valve disease, myocardial fibrosis has to be considered as a cause of diastolic dysfunction.

Conclusion

Our data suggest that myocardial fibrosis, a typical feature of uraemic cardiomyopathy, is a determinant of LV diastolic properties in a selected population of patients with ESRD undergoing haemodialysis. Understanding the mechanisms linked to diastolic dysfunction may be important for future treatment strategies in such patients.

Limitation of the study

The population sample of our study is small and highly selected. In fact, patients with normal ejection fraction without valve or ischaemic heart disease and without pericardial disease are hard to find in the setting of patients with ESRD undergoing haemodialysis. However, to investigate the relationship between IBS and diastolic function, patients with confounding factors must to be excluded. Thus, although the number of patients is small, we suggest that our study adds information regarding the complex cardiac pathophysiology of patients with ESRD undergoing haemodialysis, and that it could be viewed as hypothesis generating for further work in larger groups of patients.

Conflict of interest statement. Results presented in this paper have not been published previously in whole or part, except in abstract format.

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