Aortic stiffness and valvular calcifications in patients with end-stage renal disease

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Abstract: Objectives. To evaluate the presence and extent of cardiac calcifications and aortic stiffness in patients with end-stage renal disease (ESRD). **Patients and methods.** The study group consisted of 60 patients with ESRD with a mean age of 51.7 years, treated with peritoneal dialysis. In all patients transthoracic echocardiogram was performed to assess the following parameters: left ventricular end-systolic diameter, left ventricular end--diastolic diameter (LVEDd), interventricular septum end-diastolic diameter (IVSDd), posterior wall end-diastolic diameter (PWDd), ejection fraction (EF), fractional shortening (FS), aortic maximal and minimal diameter, aortic valve area, mitral valve area (MVA), left ventricular ejection time (LVET), maximal aortic velocity. Aortic stiffness index (AS) was calculated. Aortic and mitral valve calcifications were assessed. **Results.** Patients with ESRD had a larger left ventricle (LVEDd 5.4 cm vs. 4.76 cm) and its wall was thicker (IVSDd 1.36 cm vs. 1.02 cm; PWDd 1.31 cm vs. 0.94 cm). Patients had poorer left ventricle contractility (EF 56.1 vs. 61.6%; FS 28.5 vs. 33.2%). Atherosclerotic plaques, calcified plaques and valvular calcifications were more frequently detected in patients with ESRD. Patients with ESRD had significantly higher values of the AS index: (5.34 vs. 3.24). Among ESRD subjects with the stiffer aorta, atherosclerotic plaques including calcificones and the aortic valve damage were more frequently detected. **Conclusions.** Patients with ESRD are characterized by increased aortic stiffness. Atherosclerotic plaques in the aorta as well as cardiac and large vessels calcifications are more common among patients with ESRD. In patients with ESRD there is a correlation between an increase in aortic stiffness and damage of aortic valvular leaflets as well as calcifications of atherosclerotic plaques in the aorta. The degree of aortic stiffness is not related to impairment of mitral valvular leaflets and extravalvular calcifications. A relationship between aortic stiffness and aortic or aortic valve calcifications suggest a different pathogenesis of aorta calcification as compared to that underlying calcifications of other localizations.

Key words: aortic calcifications, aortic stiffness, atherosclerosis, echocardiography, end-stage renal disease

INTRODUCTION

End-stage renal disease (ESRD) results in the development of cardiovascular alterations. Cardiac and vascular remodeling has hemodynamic consequences and humoral disorders which worsen with the disease duration.

Epidemiological and clinical studies demonstrated that the presence of atherosclerotic lesions in large arteries is an important risk factor for the morbidity and mortality in patients with end-stage renal disease [1]. Adverse effects of the large artery disease are associated with two mechanisms such as the presence of atherosclerosis and arterial stiffness [2]. Formation of these alterations is initiated by an impairment of the endothelial function, which easily occurs in end-stage renal disease patients [3]. The presence of atherosclerotic plaques results in arterial stenosis, and is responsible for ischemia or infarction occurring distal to the stenosis. In the ESRD patients, calcifications of the elastic aorta membrane and elevated calcium levels have been reported [4]. Calcifications increase the stiffness of the large elastic arteries, e.g. the aorta or the common carotid artery [5]. Decrease in the artery wall elasticity is associated with an increase in systolic arterial blood pressure, which results in left ventricular hypertrophy [6].

Calcifications in the heart tissues are a common phenomenon in ESRD patients [7]. Heart valve calcifications predispose to cardiovascular mortality in patients with long-term extraperitoneal dialysis [8]. Growing evidence indicate that valvular calcifications, particularly those of the aortic valve, may be a marker for atherosclerosis found also in the coronary arteries [9].
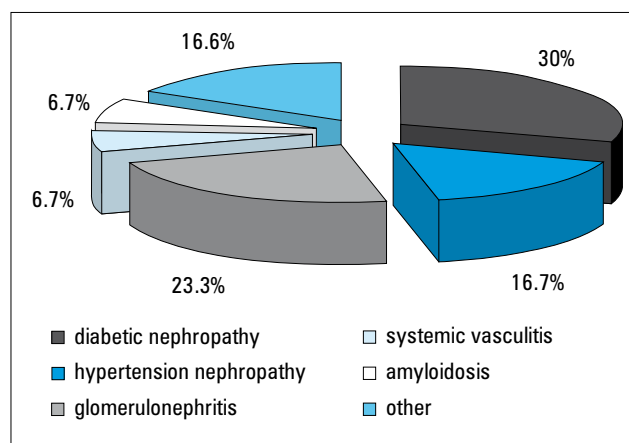
Fig. 1. Etiology of end-stage renal disease in the studied group

Table 1. Clinical characteristics of the study group			
Variable	**Patients**		**p**
	without renal failure, n = 30	**with renal failure, n = 60**	
Age (years)	51.1 (±7.8)	51.7 (±7.1)	NS
Gender – men (%)	40.0	40.0	NS
Diabetes (%)	30.0	33.3	NS
Hypertension (%)	86.7	91.6	NS
Smoking (%)	33.3	35.0	NS
Hyperlipidemia (%)	56.7	60.0	NS
NS – not significant			

The pathophysiology of vascular and cardiac calcifications, though not entirely determined, is definitely multifactorial. Metabolic disorders characterized by abnormal calcium and phosphorus levels play a major role. Other factors which conduce to calcification formation are numerous and not fully determined uremic toxins, are also taken into account [4].

The aim of the study was to evaluate the presence and extent of cardiac calcifications, especially of the heart valves. Additionally, the elastic properties of the aorta were analyzed in relation to cardiac valve damage.

PATIENTS AND METHODS

The studygroup comprised 60 patients, aged 51.7 (±7.1) years, with chronic renal failure of various origins (Fig. 1), receiving peritoneal dialysis. The mean duration of chronic renal failure was about 6.6 (±1.6) years and the dialysis has been conducted for about 42 (±26) months. Patients with organic heart disease were excluded. The control group consisted of 30 patients without renal failure (Tab. 1). The history, including cardiovascular risk factors; hypertension, lipid disorders, diabetes, smoking, family history of cardiovascular diseases and atherosclerotic features in other vascular beds, was taken from all patients. Physical examination were performed. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) measurements were performed using the Korotkov method.

The transthoracic ultrasound examination with the use of the Hewlett-Packard, Sonos 5500 machine, was performed in a standard way [10,11]. During the examination, carried out in M-mode, the following parameters were assessed:
– left ventricular end-systolic diameter
– left ventricular end-diastolic diameter
– interventricular septum end-diastolic diameter
– left ventricular posterior wall end-diastolic thickness
– left atrial end-diastolic diameter

– maximum diameter of the descending aorta (Ao_{max}), measured 3 cm from the aortic annulus, at T-wave peak of simultaneous ECG trace
– minimal diameter of the descending aorta (Ao_{min}), measured 3 cm from the aortic annulus, at R-wave peak of simultaneous ECG trace.

The following parameters were obtained using the Teichholz method [10,11]:
– left ventricular ejection fraction
– left ventricular fractional shortening
– left ventricular end-diastolic volume
– left ventricular stroke volume.

Aortic stiffness index (AS) was calculated using the formula $AS = \log (SBP/DBP)/Ao_{max} - Ao_{min})/Ao_{min}$ [12].

The following parameters were assessed from the transverse parasternal projection:
– aortic valve area
– mitral valve area.

Left ventricular ejection time and maximal blood flow velocity across the aortic valve, were assessed from the aorta Doppler flow measurements.

Additionally, the presence of aortic semilunar and mitral valve calcifications was assessed. Calcifications of the valve annulus and the valve leaflets were considered. For a precise judgment of the valve leaflets calcification process intensity, the following scale was adopted:
– 0° – total absence of valvular calcifications
– 1° – leaflet thickening without calcifications
– 2° – small, fine valvular calcifications visible with valve careful assessment
– 3° – large, clearly visible valve calcifications
– 4° – massive calcifications, resulting in valvular leaflet motility disorders.

Assessment of the aorta dimensions was performed according to 5 consecutive heart evolution periods.

Statistical analysis

Results were analyzed with the use of the STATISTICA 5.0. PL, computer software. The values were presented as mean and

standard deviation or as numbers and percentages. The Student t-test and the χ^2 test with the Yates correction were used. The correlation analysis was performed and the correlation coefficients were calculated. The value of p <0.05 was considered as statistically significant.

RESULTS

In chronic renal failure patients the left ventricular dimensions and wall thickness were greater. A significantly worse left ventricular contractility was also observed. The aortic valve area was significantly smaller while the mitral valve area was significantly larger in ESRD patients (Tab. 2).

The atherosclerotic plaques were found significantly more frequently in ESRD patients. Plaques occurred rarely in the control group. Advanced calcific plaque forms were reported mainly in patients on dialysis, and were demonstrated only in one control group patient. Aortic valve calcifications were significantly more frequent in chronic renal failure patients. They were found mainly in the valve leaflets, rarely in the valve annulus. Mitral valve calcifications were also more frequent in ESRD patients. However, the majority were located rather within the valve annulus than the leaflets themselves. The calcification index calculated for the aortic valve which was significantly higher than for the mitral valve illustrates this fact (Fig. 2). Extravalvular calcifications of the myocardium or pericardium were rare and were reported solely in ESRD patients (Tab. 3).

In ESRD patients the aortic stiffness index was significantly higher than in the control group (Fig. 3). There was a correlation between the stiffness index and the disease duration (Fig. 4).

A comparison observed among ESRD patients, namely between patients with a higher than the mean and a lower than the mean aortic stiffness index, demonstrated that the number of atherosclerotic plaques including calcific ones is significantly higher in patients with less elastic aorta. The aortic and mitral valve damage were more common in patients with higher values of the aortic stiffness index (Tab. 4). As long as the degree of aortic valve leaflet damage was greater in the stiffer aorta subgroup, however, the extent of the mitral valve leaflet damage did not differ substantially between the subgroups (Fig. 5).

In ESRD patients with greater aortic stiffness indexes, we found a significant left ventricle cavity dilatation and its wall thickening. Reduced left ventricular systolic function parameters have also been demonstrated (Tab. 5).

DISCUSSION

The most important finding of the present study is to demonstrate that ESRD patients are characterized by increased aortic stiffness. Aortic stiffness is regarded as a risk factor for increased total and cardiovascular mortality in patients with arterial hypertension [13]. London et al. [14] demonstrated

Table 2. Selected echocardiographic parameters in patients without and with renal failure

Parameter	Patients		p
	without renal failure, n = 30	with renal failure, n = 60	
LVEDd (cm)	4.7 (±0.6)	5.4 (±0.7)	<0.05
IVSDd (cm)	1.02 (±0.15)	1.36 (±0.23)	<0.05
PWDd (cm)	0.94 (±0.16)	1.31 (±0.19)	<0.05
EF (%)	61.6 (±10.2)	56.1 (±7.8)	<0.05
FS (%)	33.2 (±6.2)	28.5 (±5.1)	<0.05
SV (ml)	90.3 (±19.2)	96.8 (±19.1)	NS
EDV (ml)	146.9 (±29.3)	168.3 (±29.6)	<0.05
LA (cm)	3.8 (±0.7)	4.3 (±0.7)	<0.05
AoVA (cm²)	3.12 (±0.51)	2.43 (±0.43)	<0.05
MVA (cm²)	4.89 (±0.91)	5.47 (±1.14)	<0.05
Ao_{min} (cm)	2.59 (±0.20)	3.01 (±0.24)	<0.05
Ao_{max} (cm)	3.21 (±0.31)	3.34 (±0.34)	NS
LVET (ms)	294.5 (±30.1)	301.8 (±31.5)	NS
AoV_{max} (cm/s)	102.5 (±14.2)	104.3 (±11.8)	NS

Ao_{max} – aortic maximal diameter, Ao_{min} – aortic minimal diameter, AoV_{max} – maximal aortic velocity, AoVA – aortic valve area, EDV – left ventricular enddiastolic volume, EF – left ventricular ejection fraction, FS – left ventricular fractional shortening, IVSDd – interventricular septum enddiastolic diameter, LA – left atrium enddiastolic diameter, LVEDd – left ventricular enddiastolic diameter, LVET – left ventricular ejection time, MVA – mitral valve area, PWDd – left ventricular posterior wall enddiastolic diameter, SV – left ventricular stoke volume, others – see Table 1

that in 92 patients receiving hemodialysis, compliance of the aorta and other large vessels was reduced as compared to 90 healthy subjects. Blacher et al. [15] showed that in patients on hemodialysis aortic stiffness increases the risk of total and cardiovascular mortality. It results in the rise of arterial blood pressure, which is the direct cause for increased left ventricular afterload, leading to left ventricular hypertrophy, another cardiovascular risk factor. A previous study from our group demonstrated that ESRD patients are characterized by increased aortic stiffness and left ventricular cavity dilatation, its wall thickening and systolic function impairment at the same time. Additionally, ESRD patients with greater aortic stiffness were characterized by heart wall thickening and its contractility decrease. There is an interesting observation concerning the size of the valve area. The aortic valve area was significantly smaller in ESRD patients; this may be attributed to the valve leaflet damage resulting in a limitation of its opening. The valve flow velocity increase is supposed to be an important consequence of this phenomenon, which however did not occur in the our studies. On the contrary, the mitral area was larger in ESRD patients, which should be attributed to the left ventricular end diastolic diameter increase in this group of patients.

Fig. 2. The mean degree of aortic and mitral leaflets calcifications with end-stage renal disease (ESRD) and without ESRD. NS – not significant
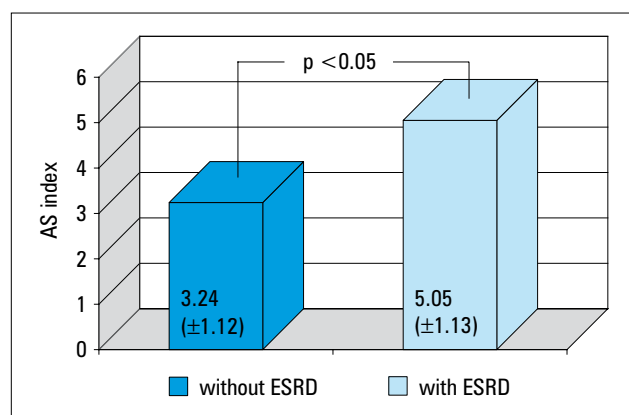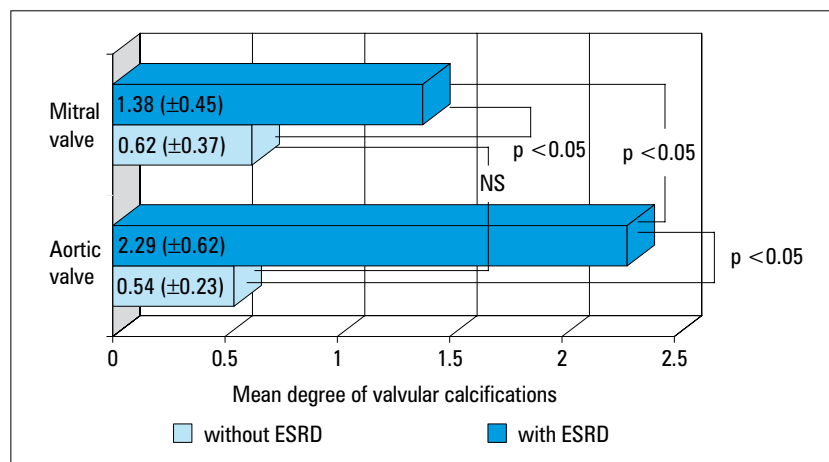

Fig. 3. Aortic stiffness index (AS) in patients with end-stage renal disease (ESRD) and without ESRD
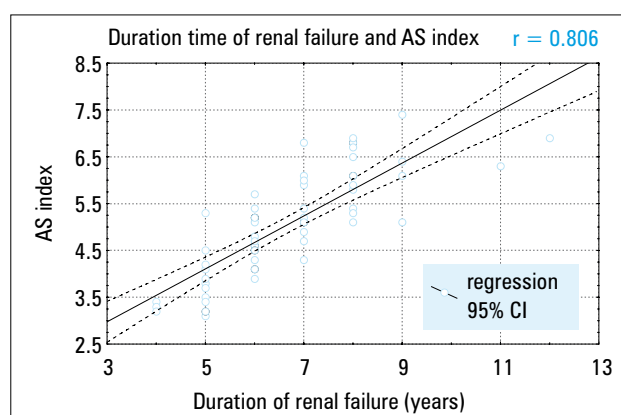

Fig. 4. Correlation between aortic stiffness index (AS) and duration of end-stage renal disease

Another important observation which confirms a well known phenomenon was the fact that there were more various localizations of calcifications in chronic renal failure patients, especially within the left-sided valves of the heart. According to Ribeiro et al. [16], among 92 patients whose the mean age was 60 years, 44% had mitral valve calcifications on echocardiography, and 52% had aortic valve calcifications. Nearly 60% of these patients demonstrated calcifications of both of the valves. In other studies with the use of the computed tomography of ESRD patients, mitral valve calcifications were reported in 45%, and aortic valve calcifications in 34% of patients, while both valves were affected in 21% of the patients studied [17]. Urena et al. [18] demonstrated a significant aortic valve stenosis in 16% of 110 patients receiving hemodialysis. Risk factors were age, male gender, high levels of the calcium-phosphorus product and elevated vitamin D levels. An important role of renal failure in heart valve damage, especially in the aortic valve lesions is highlighted by the fact that higher creatinine levels, even within normal values, accelerate its degeneration [19].

The results of the comparison of the aortic elasticity with calcifications of various localizations are surprising. They suggest that in ESRD patients, calcifications of various heart localizations and large vessel calcifications may only in part be of a common etiology. As demonstrated, the chronic renal failure and worse aortic elasticity patients subgroup is characterized by simultaneous greater aortic valve leaflet damage, reflected by their more extensive calcification. It does not apply to the aortic valve annulus or the mitral valve leaflets or its annulus, or to other localizations of calcifications in the myocardium and pericardium. It suggests that the pathogenesis of aortic stiffness and aortic valve leaflets damage may be similar or have some common grounds.

Atherosclerosis is now regarded as a combination of two phenomena, two separate diseases, namely atheromatic processes and sclerosis. Atherogenesis which means atheromatic plaques formation is a complex process in which inflammation is an important factor, and one of the main and most frequent consequences is the atheromatous plaque calcification. Histopathological studies demonstrate a similar base of coronary artery atherosclerosis and aortic valve sclerosis,
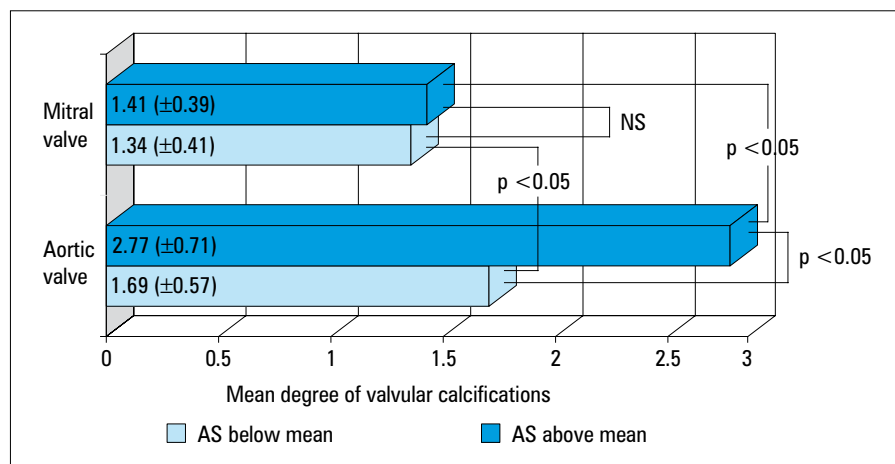
Fig. 5. Aortic stiffness index (AS) and the mean degree of aortic and mitral leaflet calcifications in patients with end-stage renal disease. NS – not significant

Table 3. Localization of cardiac and aortic calcifications in patients with end-stage renal disease and without end-stage renal disease

Parameter	Patients		p
	without renal failure (%) n = 30	with renal failure (%) n = 60	
Atheromatous plaques in the aorta	3 (10)	16 (26.7)	<0.05
Calcifications in the aorta	1 (3.3)	10 (16.7)	<0.05
Calcifications in the aortic valve	3 (10)	18 (30.0)	<0.05
Calcifications in the aortic leaflets	3 (10)	13 (21.7)	<0.05
calcifications in the aortic annulus	0	1 (1.7)	NS
calcifications in the aortic leaflets and annulus	0	4 (6.7)	NS
Calcifications in the mitral valve	2 (6.7)	26 (43.3)	<0.05
calcifications in the mitral leaflets	2 (6.7)	5 (8.3)	<0.05
calcifications in the mitral annulus	0	7 (11.7)	<0.05
calcifications in the mitral leaflets and annulus	0	14 (23.3)	<0.05
Concurrent calcifications in the aortic valve and mitral valve	0	16 (26.7)	<0.05
Calcifications in the myocardium	0	1 (1.7)	NS
Calcifications in the pericardium	0	5 (8.3)	<0.05
NS – not significant			

where an ongoing inflammatory process plays the main role [20]. The atherosclerotic plaque formation is an inflammatory response to the presence of oxLDL cholesterol. Calcification is an active process in which the vessel wall smooth muscle cells participate [21]. The association of aortic valve damage with aortic atherosclerosis has also been confirmed by clinical studies demonstrating that a high rate of semilunar aortic valve calcifications suggests the presence of the thoracic aorta disorders, and the prevalence of atherosclerosis risk factors is more common in patients with aortic valve damage [22]. Agmon et al. [23] have reported a higher prevalence of atheromatous plaques of various thicknesses, and that of mobile fragments in the aorta of patients with increased aortic valve damage. There have also been reports indicating an association between sig-

nificant atherosclerotic lesions in the coronary vessels and the aortic organic valve disease, while there was no such association in patients with the mitral valve organic diseases [24]. In the study by Adler et al. [25] it has been demonstrated that in patients with aortic valve calcifications, lesions in the internal carotid, external carotid and vertebral artery, as well as with complex lesions; multivessel disease on one side and stenosis on both sides have been more frequently reported. End-stage renal disease has an adverse effect on the prevalence and progression of atherosclerosis [26] and on the aortic valve damage [18]. The important role of the inflammation status in the pathogenesis of coronary artery calcifications in ESRD patients is emphasized by repors on the presence of inflammatory markers such as CRP and fibrinogen [27].

Table 4. Aortic stiffness (AS) and localization of cardiac and aortic calcifications in patients with end-stage renal disease

Parameter	AS index		p
	below mean (%) n = 28	above mean (%) n = 32	
Atheromatic plaques in the aorta	4 (14.3)	12 (37.5)	<0.05
Calcifications in the aorta	2 (7.1)	8 (25.0)	<0.05
Calcifications in the aortic valve	5 (17.9)	13 (40.6)	<0.05
Calcifications in the aortic leaflets	3 (10.7)	10 (31.3)	<0.05
calcifications in the aortic annulus	0	1 (3.1)	NS
calcifications in the aortic leaflets and annulus	2 (7.1)	2 (6.3)	NS
Calcifications in the mitral valve	12 (42.8)	14 (43.8)	NS
calcifications in the mitral leaflets	2 (7.1)	3 (9.4)	NS
calcifications in the mitral annulus	4 (14.3)	3 (9.4)	NS
calcifications in the mitral leaflets and annulus	7 (25.0)	7 (21.9)	NS
Concurrent calcifications in the aortic valve and mitral valve	5 (17.9)	11 (34.4)	<0.05
Calcifications in the myocardium	0	1 (3.1)	NS
Calcifications in the pericardium	3 (10.7)	2 (6.3)	NS
AS – aortic stiffness, NS – not significant			

Reduced elastic properties of the large arteries, termed aortic stiffness, contributes to the pathogenesis of atherosclerosis. Recent findings demonstrate that a chronic inflammatory process may play an important role in the pathogenesis of aortic atherosclerosis [17]. Clinical evidence shows that the worsening of aortic elastic properties in patients with ischemic heart disease represents a potent, independent risk factor for recurrent acute coronary events [28]. Decreased aortic compliance is associated with an increased prevalence of angiographically documented significant coronary artery stenosis [29]. In acute renal failure patients the aortic valve impairment is also associated with greater aortic stiffness [22]. Histologically, arteries in patients with chronic renal failure also demonstrate fibrotic or fibroelastic thickening traits, calcifications of the internal elastic membrane, the middle basement membrane, and the middle elastic fibers, as well as fissuration and duplication of the internal elastic membrane [4]. The relationship between aortic stiffness and aortic leaflet lesions, linked with available data demonstrating the coexistence of atherosclerosis of various localizations with the aortic valve impairment and aortic stiffness increase demonstrated by us, leads to a hypothesis that ESRD may be a substantial reason for this. Aortic valve degenerative alterations showed in the echocardiography and reduction in aortic elasticity parameters can therefore be used as indicators of atherosclerosis of various localizations, especially that developing in the coronary and the carotid arteries.

Mitral valve calcifications were more common in ESRD patients than in the control group. Interestingly, unlike the aortic valve leaflet calcifications, those of the mitral valve concerned mainly the annulus. Also, no association with the aortic stiffness has been demonstrated, which indicates its

pathogenesis is different. This phenomenon has not been explained yet. High blood pressure and dynamic aortic blood flow which may stimulate lesions in aortic valve leaflets have been considered, while the mitral flow is less rapid, thus less traumatizing. Calcifications of other regions of the heart; the myocardium and pericardium, were reported nearly uniquely in ESRD patients and they were not associated with the aortic elastic properties. It seems that mitral annulus calcifications are also typical of and specific for ERSD patients. These types of calcium salt deposits have been reported in ESRD patients, in various organs. They are an example of the classical consequences of calcium metabolism disorders, typical of renal failure. They may be a manifestation of ectopic calcifications, typical of renal failure [30]. The pathogenesis of vascular calcifications in ESRD patients has not been fully determined, though it is multifactorial. In ESRD patients the association of calcium and phosphorus metabolism disorders (abnormal plasma calcium and phosphorus levels) with abnormal bone tissue function (renal osteodystrophy), elevated parathormone levels (secondary hyperparathyroidism), and vitamin D metabolism disorders, is very important [31].

Our results and available data indicate a close relationship between atherosclerosis and renal failure. It may be the basis for numerous cardiovascular diseases which occur in the course of renal failure. The influence on aortic stiffness and calcification monitoring is an interesting and valuable aspect of the treatment of ESRD patients. The possibility of the assessment and modification of these factors allows for a better stratification of the cardiovascular risk and thus contributes to the decrease in cardiovascular mortality in ESRD patients.

Table 5. Aortic stiffness (AS) and selected echocardiographic parameters in patients with end-stage renal disease

Parameter	AS index		p
	below mean (n = 28)	above mean (n = 32)	
LVEDd (cm)	5.1 (±0.6)	5.6 (±0.7)	<0.05
IVSDd (cm)	1.32 (±0.15)	1.38 (±0.23)	NS
PWDd (cm)	1.28 (±0.16)	1.33 (±0.19)	NS
EF (%)	59.6 (±10.2)	52.4 (±7.8)	<0.05
FS (%)	30.1 (±6.2)	26.2 (±5.1)	<0.05
SV (ml)	96.3 (±19.2)	97.5 (±19.1)	NS
EDV (ml)	156.5 (±29.3)	181.1(±29.6)	<0.05
LA (cm)	4.2 (±0.7)	4.4 (±0.7)	NS
AoVA (cm²)	2.75 (±0.51)	2.11 (±0.43)	<0.05
MVA (cm²)	5.55 (±0.91)	5.38 (±1.14)	NS
Ao$_{min}$ (cm)	289.7 (±30.1)	314.1 (±31.5)	NS
Ao$_{max}$ (cm)	106.8 (±14.2)	109.7 (±11.8)	NS
LVET (ms)	294.5 (±30.1)	301.8 (±31.5)	NS
AoV$_{max}$ (cm/s)	102.5 (±14.2)	104.3 (±11.8)	NS
Abbreviations – see Tables 1, 2 and 4			

The conclusions of this study are as follows:

1) renal failure patients are characterized by greater aortic stiffness

2) aortic atherosclerotic plaques as well as heart and great vessels calcifications are more frequent in renal failure patients

3) there is a correlation between greater aortic stiffness and aortic valve leaflets impairment, left ventricular enlargement and left ventricular wall thickening, with heart systolic function impairment and aortic atherosclerotic plaque calcifications, in renal failure patients

4) there are no correlations between aortic stiffness and mitral valve or extravalvular calcifications

5) the correlation between aortic stiffness and aortic calcifications as well as aortic valve calcifications, and lack of such a correlation with calcifications of different localizations suggests their different pathogenesis.

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