BANTAO Journal 2012; 10 (2): 69-73

BJ
BANTAO Journal

Original article

Pericardial Thickening and Cardiac Valvular Calcification in End - Stage Renal Disease

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Abstract

Introduction. End-stage renal disease (ESRD) patients are at increased risk of tissue calcification because of deranged calcium-phosphorus metabolism. We have tested the hypothesis that pericardial fibrosis (PF) and thickness (PT) correlate with cardiac valvular calcification (CVC) in ESRD patients.
Methods. Echocardiography was performed in 23 ESRD patients. PT was measured in the parasternal long-axis M-mode at the site of the posterior pericardium and CVC-at the sites of the aortic and mitral valves. All parameters were defined in 3 grade scores. Hemoglobin, urea, creatinine, beta-2 microglobulin, C-reactive protein, calcium (Ca), phosphorus (P), CaxP product and PTH were measured.
Results. Eighteen patients (78.26%) had calcium deposits on the aortic valve and 13 patients (56.52%) had mitral calcification. All-cause 2-year mortality was 34.8% - 8 patients have died in the follow-up period. Virtually all patients had some degree of PT. The mean PT was 4.87±1.89 mm while normal values were considered below 2 mm (1.2±0.8). Correlations were as follows: 1) PT with aortic and mitral CVC score- r=0.478 ($p<0.05$) with aortic valve and r= 0.484 ($p<0.01$) with mitral valve; 2) PT score with aortic valve score - r=0.208 and mitral valve score r=0.231; 3) PT with CaxP product and HD-duration: r=0.333 and r=-0.401, and PT-score: r=0.401 ($p<0.05$) and r=0.053 respectively; 4) PT and PT score with all-cause 2-year mortality: r=0.270 and 0.407 ($p<0.05$), respectively. Pericardial Score combined with Aortic Valve Score and Mitral Valve Score had r coefficient 0.386 ($p<0.01$) with 2-year all-cause mortality.
Conclusions. The associations between pericardial thickness and valvular calcifications and all-cause mortality show weak-to-moderate correlations, but might well be yet another site for risk stratification of calcium burden deposition and prognosis in patients on HD.

Keywords: calcium-phosphorus metabolism, cardiac valvular calcification, end-stage renal disease, hemodialysis, pericardial thickness

Introduction

Cardiovascular complications are the leading cause of mortality in patients with end-stage kidney disease. Moreover, this high risk is present even in earlier stages before hemodialysis as well as in younger individuals [1,2].
ESRD-patients are at an increased risk of tissue calcification because of deranged calcium-phosphorus metabolism. Multiple studies have shown the relationship between increased calcium deposits in coronary arteries and coronary artery disease, cardiac valvular calcification and arterial calcifications and the grim prognosis in patients with ESRD [3-10]. The process of increased tissue calcium deposition is an active process where not only disturbances in calcium and phosphorus metabolism are involved but also persistent inflammation exists in hemodialysis patients. This has been proven in valvular calcification from excised bioprostheses in patients with ESRD as well as with previously reported greater C-reactive protein levels in this patient population and their increased risk of death [11-14]. The calcified regions of the cardiac valves were infiltrated with inflammatory cells, lipoproteins and calcium deposits similar with those in atherosclerotic plaques, but also expressed bone matrix proteins [15]. The associations among valvular calcification, inflammation, carotid atherosclerosis, and arterial calcification suggest that valvular calcification is a marker of atherosclerosis and arterial calcification in patients with ESRD [16]. Indeed some authors have found association between valvular calcification and intima-media thickness and atherosclerosis [17] and others have described the role of fibrosis in the enlarged left ventricular mass in patients with ESRD [18]. The presence of pericardial thickening in ESRD patients on HD was described as well [19], but its significance remains unclear [20].
In the present study we have tested the hypothesis that pericardial fibrosis and thickness (PT) correlate with cardiac valvular calcification and with all-cause mortality in ESRD-patients and thus might also be another site for risk stratification of calcium burden deposition and prognosis in patients on HD.

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Materials and methods

Twenty-three ESRD-patients (12 males and 11 females) were included in the study. Their mean age was 46.3±3.8 years, and they were on hemodialysis (HD) for 36.7±24.8 months. Seven patients were with chronic glomerulonephritis, 4with chronic pyelonephritis, 2with diabetes mellitus, 4 with polycystic kidney disease, 2with hypertension and in the rest no recognizable etiology was found.
Blood samples were obtained from arterial needle of ESRD-patients before hemodialysis session. Hemoglobin, urea, creatinine, beta-2 microglobulin, C-reactive protein, calcium, phosphorus, CaxP product and PTH were measured. Laboratory findings of examined patients are presented in Table 1.
All patients whose phosphate levels had been within the normal range received calcitriol. Patients with high levels of phosphates were treated by phosphate-binders-calcium carbonate or aluminum hydroxide as well as by dietary restriction. Dialysis solution with low calcium was administered in patients with high plasma levels of calcium.

Table 1. Laboratory findings of examined patients (mean±SD)

	ESRD patients	Reference limits	
Hemoglobin [g/L]	106.956±11.4 n=23	♂:130-180 ♀:120-160	
Urea [mmol/L]	21.322±4.908 n=23	2.8-7.2	
Creatinine [µmol/L]	899. 692±252.346 n=23	♂:72-127 ♀:58-96	
Beta-2 microglobulin [mg/L]	24.196±8.184 n=15	0.8-2.4	
C-reactive protein [mg/L]	15.529±9.258 n=9	0-5	Within reference limits – 6 patients Above reference limits – 9 patients
Ca [mmol/l]	2.03±0.26 n=23	2.2-2.65	
P [mmol/l]	2.17±0.62 n=23	0.81-1.45	
CaxP	4.39±1.09 n=23	1.782-3.842	
PTH intact [pg/ml]	734.179±563.975 n=14	12-65	Within reference limits – 1 patient, under 250 – 3 patients, between 352 and 1696 - 10 patients

Echocardiography was performed by means of Aloka SSD 4000 SV ultrasound equipment. Pericardial thickening was measured in the parasternal long-axis M-mode at the site of the posterior pericardium in absolute numbers and was later graded also semiquantatively in 3 graded scale scores: 2-3.9 mm as grade I; 4-5.9 mm as grade II and over 6 mm as grade III. The upper limit of pericardial thickness (2 mm) was chosen from the literature [13]. Valvular calcifications at the sites of the aortic and mitral valve were defined in 3-graded scale scores as well: *grade I*- bright, spotlike calcifications less than 3 mm, on one or more cusps of the aortic valve, mitral valve or mitral anulus; *grade II*- multiple bright echoes over 3 mm; *grade III*- extensive calcification of the valvular structures.

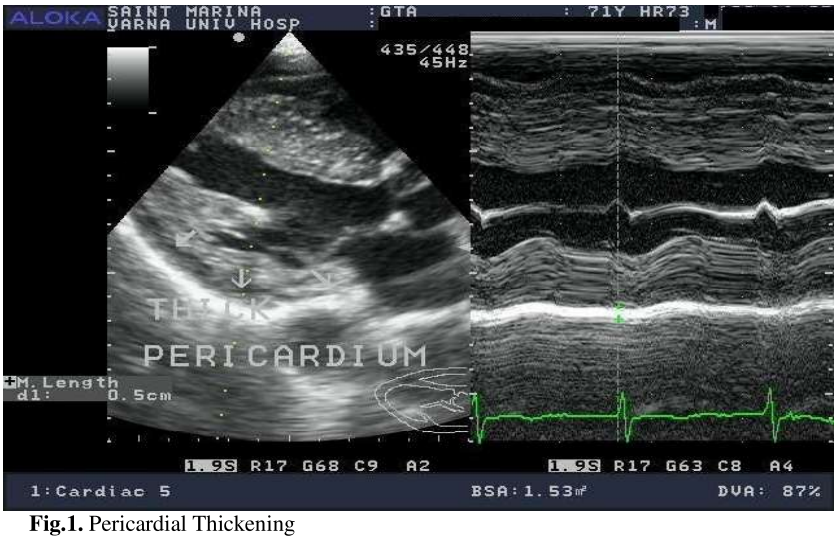

Fig.1. Pericardial Thickening

Statistical analysis

Data were analysed using the Statistical Package for Social Sciences (SPSS Inc, Chicago, Ill), version 11.5. For continuous variables, mean values and standard deviations were calculated. The Pearson's and Spearman rho correlation were used to assess the relationship between pericardial thickness and the variables. Values of $p<0.05$ were considered to be statistically significant.

Table 2. Pericardial thickening in ESRDpatients

Pericardial Thickening	Pericardial Thickness	Number Of Patients
Grade I	2-3.9 mm	9
Grade II	4-6 mm	8
Grade III	over 6 mm	6

Results

The mean pericardial thickness was 4.87±1.89 mm while normal values were considered bellow 2 mm 1.2±0.8 [13].

Virtually all patients had some degree of pericardial thickening.
Pericardial thickening is presented in Figure 1. The distribution of patients with various grades of pericardial thickening can be seen in Table 2.Eighteen patients (78.26%) had calcium deposits on the aortic valve and 13 of them had also mitral calcification (56.52%) while five patients had only aortic valve calcification. Five patients had no cardiac valve calcification.
Grades of valvular calcification are presented in Table 3. None of the patients were in Grade III valvular calcium deposition state.

Table 3. Valvular Calcifications in ESRDPatients

	Aortic valve	Mitral valve
Grade I	14	10
Grade II	4	3
Grade III	0	0
Total	**18/23 (78.26%)**	**13/23 (56.52%)**

Valvular calcifications are presented in Figure 2.
All-cause 2-year mortality was 34.8% - 8 patients have died in the follow-up period.
Correlations are presented in Table 4.

Fig.2. Valvular Calcifications (Aortic valve)

Table 4. Correlation coefficients of pericardial thickness and pericardial thickness score

	Aortic Valve Score	Mitral Valve Score	CaxP product	HD duration	2-year all-cause mortality
Pericardial Thickness	0.478 (p<0.05)	0.484 (p< 0.01)	0.333	0.401 (p<0.05)	0.270
Pericardial Thickness Score	0.208	0.231	0.401 (p<0.05)	0.053	0.407 (p<0.05)
Pericardial Thickness Score + Aortic Valve Score + Mitral Valve Score					0.386 (p< 0.01)

Discussion

To our knowledge, the presence of pericardial thickening in ESRD patients on HD was not used until now as a marker of risk and was not correlated with valvular calcifications and its significance remains undetermined to a great extent.
In the study of Ijoma *et al*. [19] pericardial disease was detected as early as stage 4 CKD. Of the 88 patients studied

15.9% had pericardial effusion only, 29.5% had pericardial thickening only and 10.2% had a combination of both and the majority (81.8%) were in ESRD [19].

Pericardial thickening in our study was found in all studied hemodialysis patients and it was much higher than presented by other authors. Differences in the incidence of pericardial thickening in ESRD could be partly explained by the different methodological approaches. For example, in the study of Ijoma *et al*. [19] upper normal limit for pericardial thickness was 4 mm. If we apply this approach we should have established pericardial thickening in 60.87% of our patients (grade II and III PT), but the frequency would have still remained high.

The presence of pericardial thickening in ESRD is not surprising, as pericardial thickening was found also in predialysis patients. In the study of D'Cruz *et al*. [21] on 50 predialysis patients referred for echocardiography due to symptoms of cardiac disease, 66% had pericardial effusion while 33% had pericardial thickening. In studies of predialysis patients pericardial effusion was prevailing, while pericardial thickness was not mentioned or measured. [22-25].

Cardiac valve calcification is a common finding in end-stage renal disease patients. It has been shown recently that cardiac valvular calcification is an independent predictor for all-cause and cardiovascular mortality in peritoneal dialysis patients. In hemodialysis (HD) patients, cardiac valve calcification was also associated with all-cause and cardiovascular mortality, although statistical significance was lost after adjusting. In one study [26] echocardiographic examination in 65 HD patients revealed valve calcifications in 32 (49 %), mitral valve calcifications in 10 (15.3 %), aortic valve calcifications in 9 (13.8 %), and both valves calcifications in 13 patients. Patients with valve calcifications were older, duration of HD therapy was longer, systolic and pulse pressures were higher and left ventricular mass was also higher. In another study [27] 90 ESRD-patients on HD were examined by echocardiography where thirty-six patients (40%) presented with valve calcifications. Patients with valve calcifications were older and showed higher levels of serum calcium, phosphorus, Ca x P product. Ribeiro *et al*. [28] found a greater prevalence of valvular calcifications in dialysis patients than in normal individuals: aortic and mitral valve calcification: 52% versus 4.3% and 44.5% versus 10%, respectively. In the study of Braun *et al*. [6] with electron beam computed tomography (EBCT) 59% of patients on HD had mitral valve calcifications and 55% had aortic valve calcifications.

The frequency of aortic valve calcification in our study (78.26%) was similar to that found in the study of Ventura [29], but higher than that in other studies [6,26,27]. The frequency of mitral valve calcification in our study (56.52%) was also higher than that found in other studies [26,27], but was very close to the results of EBCT of Braun [6]. It is also known that although cardiac valve calcifications predict all-cause and cardio-vascular mortality in HD patients in unadjusted analyses, these associations are not evident in models adjusting for background cardio-vascular complications, left ventricular mass or other risk factors [30].

The results of the laboratory tests (presented in Table 1) show a high prevalence of secondary hyperparathyroidism, disturbances in calcium and phosphorus metabolism and presence of a chronic inflammation in our patients. Probably these are the combined underlying reasons for the high incidence of valvular calcification as well as for the high mortality rate in our patient group.

Pericardial thickening in our study was present in virtually all examined hemodialysis patients. There was a correlation between pericardial thickness and aortic and mitral valvular calcification, duration of dialysis and pericardial score plus calcification scores correlated with 2-year all cause mortality.

For the first time in our study pericardial thickness has been used as a morphological marker for cardiovascular risk stratification of patients with ESRD on hemodialysis. Only several attempts have been made to quantify pericardial thickness by means of echocardiography, although much more has been done now for pericardial imaging by the newer techniques-CT and MRI [14,31,32].

Prospective observational studies and clinical trials aimed at elucidating and modifying the excessive calcification and inflammation are necessary to better understand the cardiovascular outcomes in ESRD and to determine whether renal disease, dialysis, or both, are responsible for the excessive and accelerated damage of vessels and cardiac structures in this population.

Study limitations

No data from our population was undertaken for normal values of pericardial thickness and the upper limit of normal 2 mm of pericardial thickness was chosen from the literature [13]. Unadjusted model was used and the number of patients was limited.

Conclusions

The associations between pericardial thickness and valvular calcifications and all-cause mortality show weak-to-moderate correlations, but might well be yet another site for risk stratification of calcium burden deposition and prognosis in patients on HD.

Acknowledgements

We thank Miss Tsvetelina Vateva for her linguistic assistance.

Conflict of interest statement. None declared.

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