

Aortic and mitral valve disease in patients with end stage renal failure on long-term haemodialysis

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Abstract

Objective—To identify valvar heart disease in patients with chronic uraemia by conventional and colour coded Doppler echocardiography.

Design—Case series of an unselected group of 62 patients with end stage renal failure.

Setting—Centre for haemodialysis in a referral hospital in Switzerland.

Patients—62 patients on chronic haemodialysis.

Main outcome measures—Frequency of structural and functional valve abnormalities and their relation to clinical findings.

Results—Structural changes were seen in 40 (64%) of 62 patients after 50 months (range 3–178 months) on haemodialysis. The mitral annulus and aortic cusps were thickened in 25 (40%) and in 34 (55%) patients respectively. Aortic stenosis was present in eight (mean (SD) age 60.5 (8.5) years), with a maximal instantaneous pressure gradient of 41 (14) mm Hg. Aortic regurgitation was seen in eight, mitral regurgitation in seven, and mitral stenosis in three patients. Patients with aortic stenosis had been on haemodialysis for significantly longer than the remaining patients (101 (43) v 46 (43) months, $p = 0.01$) and had significantly higher concentrations of serum alkaline phosphatase (176 (89) v 117 (47) IU/l, $p < 0.01$) and of parathyroid hormone (54 (66) v 19 (29) ng/ml, $p < 0.02$).

Conclusions—Patients on long-term haemodialysis had an increased frequency of haemodynamically relevant changes in the aortic and mitral valves. The degenerative valve disease may be related in part to the duration of haemodialysis and to alterations in calcium metabolism as indicated by increased plasma concentrations of alkaline phosphatase and parathyroid hormone.

mitral and aortic valves can occur prematurely in patients with chronic uraemia on long-term haemodialysis.^{2,3,5} The cause of premature calcification of the mitral and aortic valves are uncertain; however, secondary hyperparathyroidism, hypertension,¹² and hypercholesterolaemia¹³ are thought to be essential risk factors. There are few data on the frequency of Doppler detected haemodynamically relevant valvar complications in end stage renal disease. We examined the frequency and aetiology of calcified, haemodynamically relevant aortic and mitral valve stenosis and regurgitation and its relation to clinical findings in an unselected population of patients on long-term haemodialysis.

Patients and methods

We studied 62 patients (31 men and 31 women) aged 55 (14) years who had been receiving maintenance haemodialysis (9–12 h/week) for 50 (47) months (range 3–178). The primary cause of end stage renal disease was analgesic nephropathy in 22, glomerular nephritis in 13, polycystic kidney disease in eight, pyelonephritis in five, diabetes mellitus in five, and other or unknown underlying renal disease in nine. Conventional and colour coded Doppler echocardiographic examinations were performed just after haemodialysis on a Toshiba 160 equipment with 2.5 and 3.5 MHz transducers. The two echocardiographers were unaware of the clinical details. M mode, cross sectional, and conventional and colour coded Doppler echocardiograms and measurements were obtained by standard techniques. All video and paper records were reviewed by three cardiologists. Structural alterations in the cusps and annuluses of the aortic and mitral valves were diagnosed by thickened and bright echoes on both the M mode and cross sectional echocardiograms by established diagnostic criteria.¹⁴ Significant aortic stenosis was defined as cusp separation of less than 15 mm and a maximum aortic flow velocity greater than 2.2 m/s. Significant regurgitation was defined as a regurgitation jet on the colour and pulsed Doppler echocardiograms extending more than 2 cm behind the plane of the aortic, mitral, or tricuspid valve and pandsystolic (aortic regurgitation) or pansystolic (mitral and tricuspid regurgitation) regurgitant flow of more than 2 m/s on continuous wave Doppler. Regurgitation was classified as mild, moderate, or severe on the basis of the extent to which retrograde flow filled the atrium or ventricle (less than one third, one to two thirds, more than two

Valve disease is an under-recognised complication of chronic uraemia.¹ Calcification of the mitral annulus was more common in patients with chronic renal failure than in age-matched controls.²⁻⁵ Calcification of the mitral annulus can cause mitral regurgitation² or stenosis or both^{3,6} and is also often associated with aortic valve calcification.^{6,7} Severe aortic valve calcification can cause aortic stenosis⁸⁻¹⁰ and aortic regurgitation.¹¹ Calcification of the

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thirds). The following blood tests were done before dialysis: haemoglobin, creatinine, total cholesterol, total calcium, phosphate, alkaline phosphatase (normal value < 174 U/l), parathyroid hormone (carboxyl terminal RIA, normal value 0.4–1.5 ng/ml). The mean pre-dialysis calcium-phosphate product (mmol/l) was calculated from the monthly determinations during the 12 months before echocardiography.

The clinical data were collected by an experienced physician. Results were expressed as mean (SD). The data were analysed by an unpaired *t* test. A *p* value of < 0.05 was considered statistically significant.

Results

Table 1 shows the clinical features of patients with and without aortic and/or mitral valve abnormalities. Patients with structural abnormalities of aortic valve and/or mitral valve were older (59.5 (11.6) years, *n* = 40) than patients with normal valves (46 (13.5) *n* = 22). Aortic and mitral valve abnormalities were not associated with a higher incidence of hypertension. There was a history of hypertension in 30 (75%) of 40 patients with aortic and/or mitral valve abnormalities and in 49 (79%) of all patients (table 1).

The interval since diagnosis of hypertension was similar in patients with and without structural abnormalities of the valves (10.9 (6.4) *v* 8.7 (6.8) years) but there was a tendency for hypertension to have been present longer in patients with mitral valve abnormalities than in those without.

There was no association between the aetiology of end stage renal disease and aortic or mitral valve disease. No patient gave a history for previous rheumatic fever or infective endocarditis. Echocardiographically abnormal and thickened aortic and mitral valves (including the mitral annulus) with bright echoes were seen in 40 (64%) of the 62 patients (table 2). Twenty five patients (40%) had an altered mitral valve apparatus (at least thickened mitral annulus). In 34 patients (55%) one or more aortic cusps were thickened and all cusps were thickened in 17 (27%). Nineteen (76%) of the 25 patients with mitral valve abnormalities also had calcification of the aortic valve.

Seventeen (43%) of the 40 patients with structural valve abnormalities had a total of 26

Table 2 Frequency of echocardiographically confirmed aortic and mitral valve abnormalities (valve calcification) in 62 patients with end stage renal disease

Echocardiographic finding	Number of patients	Frequency of MVA/AVA (%)
No valve alterations	22	—
All valve alterations (MVA, AVA)	40	65
MVA	25	40
AVA:		
1 cusp	34	55
3 cusps	17	27
MVA and AVA combined	19	31

AVA, aortic valve abnormality; MVA, mitral valve abnormality.

abnormal Doppler echocardiographic findings associated with the aortic or mitral valve (table 3).

AORTIC STENOSIS

Aortic stenosis was present in three men and five women (8/62, (13%)). Maximal aortic flow ranged from 2.4 to 4.0 m/s resulting in a maximal instantaneous pressure gradient of 41 (14) mm Hg (range 23–64 mm Hg). Systolic blood pressure, systolic separation of the aortic valve, and fractional shortening were significantly lower and posterior wall thickness was higher in patients with aortic stenosis than in the remaining patients; there was no age difference, however (table 4).

Aortic stenosis was associated with longer duration on dialysis (*p* < 0.01), higher serum alkaline phosphatase concentrations (*p* < 0.01), and higher serum concentrations of parathyroid hormone (*p* < 0.02), but it was not associated with a higher calcium-phosphate product (table 4) or the underlying kidney disease.

AORTIC REGURGITATION

Aortic regurgitation was present in three patients with predominantly aortic stenosis and in one patient with mitral regurgitation, and in four other patients (all with structural abnormalities of the aortic valve). Regurgitation was mild in four of the eight patients and was moderate in four.

MITRAL REGURGITATION

Mitral regurgitation was present in seven patients. Six of them had mitral valve abnormalities, one had left ventricular dilatation with

Table 1 Comparison of patients with and without structural abnormalities of the aortic and mitral valves (mean (SD))

Variable	All	No AVA/MVA	AVA	MVA	AVA/MVA
<i>n</i> (%)	62	22 (35)	34 (55)	25 (40)	40 (65)
Age at study (yr)	55.2 (13.5)	46.9 (13.1)	59.0 (12.4)‡	62.9 (6.8)‡	59.5 (11.4)‡
Months on dialysis	50.4 (46.1)	35.7 (41.6)	56.8 (49.1)	71.2 (50.7)†	57.0 (48.1)
Hours on dialysis (per week)	10.0 (2.0)	9.7 (2.5)	10.3 (1.7)	10.2 (1.7)	10.2 (1.7)
History of hypertension (<i>n</i>)	49	19	26	17	30
Years of hypertension	10.0 (6.6)	8.7 (6.8)	10.3 (5.6)	13.3 (6.7)*	10.9 (6.4)
Systolic blood pressure (mm Hg)	142 (20)	144 (19)	141 (21)	140 (22)	141 (20)
Diastolic blood pressure (mm Hg)	83 (11)	83 (9)	83 (12)	82 (11)	83 (12)
Haemoglobin (g/l)	101 (1.7)	99 (1.8)	102 (1.6)	101 (1.6)	102 (1.6)
Creatinine (μmol/l)	914 (201)	975 (203)	904 (195)	821 (196)	879 (191)
Calcium × phosphate product (mmol/l)	4.4 (0.9)	4.6 (0.9)	4.3 (0.9)	4.4 (0.4)	4.3 (0.9)
Alkaline phosphatase (U/l)	129 (67)	131 (73)	134 (67)	133 (72)	129 (63)
Parathyroid hormone (ng/ml)	22 (37)	20 (34)	25 (41)	22 (40)	23 (38)

**p* = 0.05 *v* no AVA/MVA; †*p* < 0.05 *v* no AVA/MVA; ‡*p* < 0.01 *v* no AVA/MVA.

AVA, aortic valve abnormality; MVA, mitral valve abnormality; AVA/MVA, any abnormality of aortic and/or mitral valves; no AVA/MVA, neither aortic nor mitral valve abnormality.

Table 3 Results based on Doppler echocardiograms in 17 patients with important valve dysfunction (n = 26)

		Type of valve dysfunction (n = 26)			
		AS (8)	AR (8)	MR (7)	MS (3)
Total number of patients	(n = 17)				
With isolated valve dysfunction	(n = 13):				
5		X			
4			X		
3				X	
1					X
With combined valve dysfunction	(n = 4):				
1		X		X	
1		X	X	X	
2		X	X	X	X

AR, aortic regurgitation; AS, aortic stenosis; MR, mitral regurgitation; MS, mitral stenosis.

Table 4 Findings in patients with and without aortic stenosis (mean (SD))

Variable	AS (n = 8)	No AS (n = 54)	p
Months on dialysis	101 (43)	46 (43)	0.01
Systolic blood pressure (mm Hg)	125 (19)	144 (19)	<0.01
Aortic cusp separation (mm)	10 (3)	20 (3)	<0.001
Posterior wall thickness (mm)	14.3 (1.7)	12.2 (2.1)	<0.01
Left ventricular fractional shortening (%)	30.0 (1.8)	35.9 (7.0)	<0.03
Parathyroid hormone (ng/ml)	54 (66)*	19 (29)	<0.02
Alkaline phosphatase (U/l)	176 (98)	117 (47)	<0.01
Calcium × phosphate product (mmol/l)	4.3 (0.6)	4.5 (1.0)	NS

*n = 7, one patient who had had a parathyroidectomy was not included.
AS, aortic stenosis.

global hypokinesia and on a dilated annulus. Regurgitation was moderate in five and severe in two. Three patients had isolated (moderate) mitral regurgitation.

MITRAL STENOSIS

One patient had mild isolated mitral stenosis (Doppler derived mitral valve area 1.9 cm²) and two patients had moderate mitral stenosis (1.4 and 1.3 cm²) associated with mitral regurgitation, aortic stenosis, and aortic regurgitation.

TRICUSPID REGURGITATION

Mild to moderate tricuspid valve regurgitation was seen in five patients and was associated with other valve diseases in four: one with aortic stenosis, one with aortic regurgitation, one with mitral regurgitation, and one with combined aortic and mitral valve disease.

A COMPARISON OF CLINICAL AND DOPPLER ECHOCARDIOGRAPHIC DIAGNOSIS OF VALVE DISEASE

The clinical diagnosis of aortic stenosis was correct in five, falsely negative in three, and falsely positive in five, when conventional and colour coded Doppler ultrasound were used as the reference standard. Aortic regurgitation and mitral stenosis were not diagnosed clinically in any patient; mitral regurgitation was correctly diagnosed in three, was falsely negative in three and falsely positive in four patients. The clinical diagnosis was correct if valve disease was severe (both patients with aortic stenosis and pressure gradients greater than 60 mm Hg and both patients with mitral regurgitation grade III).

Discussion

In keeping with several earlier studies¹⁵⁻¹⁸ our data show a high frequency (40/62) of structural alterations of the aortic and mitral valve apparatus caused by degeneration and calcifica-

tion of valve structures in patients with progressive renal failure. Furthermore 43% of our patients with structural valve changes also had Doppler echocardiographic evidence of functional abnormalities. Four patients had combined aortic and mitral valve diseases. Most importantly, aortic stenosis was present in eight of the 62 patients. This is more than expected from the estimated frequency of valve disease in the general population.^{19,20} Despite the more stringent diagnostic criteria for aortic stenosis in our study the frequency in patients with chronic renal failure and long term haemodialysis was higher than reported by others.¹ The mean age and duration of haemodialysis resembled the findings in a comparable study by Maher *et al.*²¹ One fourth of our patients with calcified aortic valves—the same proportion as reported by Bryg *et al.*¹¹—had mild aortic regurgitation of no or little clinical relevance. Our finding that 40% had abnormal mitral valves accords with other reports^{7,12}; however, the frequency of regurgitation (24% of mitral valve abnormalities) differs from the report by Bryg, who found that 37% of patients with calcification of the mitral annulus had mitral regurgitation.¹¹ Labovitz *et al.* reported that 55% of patients with a calcified mitral annulus had mitral regurgitation.²² This discrepancy may be partly explained by the fact that in our study Doppler echocardiography was performed after haemodialysis—that is, without or at a reduced volume overload. Degeneration and calcification of tricuspid aortic valves without rheumatic changes is an unusual cause of aortic stenosis in patients under the age of 70.^{23,24} The mean (SD) age of our study population was 55.2 (13.5) years. Though our patients with abnormal aortic or mitral valves were older than patients without (table 1), those with functional abnormalities were almost the same age as those with only structural changes (61.4 (6.8), n = 17 v 59.5 (11.4) n = 23). However, we found a strong correlation between the duration of haemodialysis treatment and the development of aortic stenosis. Patients with aortic stenosis had been more than twice as long on haemodialysis as those without (p < 0.001). Duration of haemodialysis was also an independent predictor of structural abnormalities of the aortic and mitral valves in another study and was associated with premature valve calcification.²¹ The duration of renal failure and subsequent haemodialysis may cause mechanical stress on valves mainly through hypertension and increased cardiac output (anaemia, arteriovenous fistula) causing further valve changes. In addition, slight inequalities in cusp size, which Roberts suggested may contribute to the development of senile tricuspid aortic stenosis,²³ may also contribute to aortic valve calcification and to aortic stenosis in patients on long-term haemodialysis.

We also found that serum alkaline phosphatase and parathyroid hormone concentrations were increased in our patients with aortic stenosis, suggesting altered bone tissue metabolism and metastatic calcification as a probable cause of premature valve calcification. This accords with a report linking aortic

sclerosis with renal osteodystrophy.⁴ Nevertheless, the ranges for alkaline phosphatase and parathyroid hormone were too wide to predict the risk of aortic stenosis developing in individual patients with high serum concentrations. In addition, we used a C-terminal parathyroid hormone assay, which because it also measures the inactive metabolites of parathyroid hormone, is not very specific.

An increased calcium-phosphate product caused by secondary hyperparathyroidism and the failure to control hyperphosphataemia have been associated with premature calcification of the aortic valve and mitral annulus.^{15 21 25} Maher *et al* found that the calcium-phosphate product was greater in patients with aortic calcification than in those without.²¹ This finding contrasts with our patients who did not show a significant increase in the calcium-phosphate product despite the increase in parathyroid hormone concentrations. This discrepancy is not easy to explain but might be related to good control of phosphataemia in our patients, at least during the last 12 months on dialysis. Furthermore, others have reported similar findings to ours.⁴

The sensitivity of the clinical diagnosis of heart valve disease in the current study was low: 60% for aortic stenosis and 40% for mitral regurgitation. This accords with other studies.^{13 22} Aortic stenosis was clinically diagnosed in only two out of five patients in a comparable study by Maher.²¹ In a study by Labovitz 17 of 28 patients with known mitral regurgitation and calcification of the mitral annulus (out of a total of 51 patients with mitral annulus calcification) had an apical murmur. Of the 17 found to have a moderate to severe mitral regurgitation by Doppler, only 11 (65%) had a murmur consistent with mitral regurgitation. None of the four patients with Doppler echocardiographic evidence of mitral stenosis had a diastolic rumble or an opening snap.²² Moreover, a systolic murmur may be caused by calcium in the mitral annulus itself (vibration of the mitral valve ring) independent of mitral regurgitation.²² The clinical diagnosis of degenerative aortic stenosis in elderly patients is known to be difficult.^{8 10} Maher noted that systolic murmurs are commonly attributed to flow murmurs and other signs of aortic stenosis may be masked by hypertension and increased cardiac output.²¹ Selzer and Roberts proposed factors influencing clinical diagnosis such as a different configuration of a usually tricuspid valve, calcium deposits limited to the aortic aspects of the valve, unfused commissures, and additional calcification of the mitral annulus in most patients^{10 13}; these causes may also be relevant in patients with end stage renal disease on long-term haemodialysis.

Conclusions

Degenerative calcification of the aortic and mitral valves was more common in patients with end stage renal failure on long-term haemodialysis than that reported in patients of similar age with normal renal function. Unlike patients with normal renal function and valve disease there was no preponderance of female patients: the association between calcification of

the mitral annulus and aortic valve was equally common in both sexes. The proportion of patients on long-term haemodialysis with important disease of the aortic and mitral valves was much higher than would have been predicted by clinical examination. The duration of haemodialysis and altered bone metabolism may be aetiological factors in the development of aortic stenosis. Prevention or early treatment of secondary hyperparathyroidism might be important. Because aortic stenosis can progress rapidly^{26 27} and can lead to severe hypotension during haemodialysis, Doppler echocardiography at regular intervals is recommended in order to assess haemodynamically important valve lesions, even in the absence of clear cardiovascular symptoms.

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