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Pericardial Thickening is a Major Cardiac Complication in Patients with Chronic Kidney Disease at First Presentation

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Abstract

Background and Aims: A high prevalence of pericardial effusion and low prevalence of pericardial thickening have been documented in end stage renal disease (ESRD) especially in patients undergoing dialysis. The aim of the study was to investigate the presence of pericardial disease in predialysis chronic kidney disease (CKD) patients and to determine relationship of pericardial disease with the aetiology of CKD.

Methods: This is a prospective cross-sectional conducted in Enugu, Nigeria. Eighty eight consecutive predialysis CKD patients, and forty four age and sex-matched control subjects were studied using two-dimensional echocardiography.

Results: Fifty six percent of the patients had pericardial disease while 44% did not. Pericardial disease was detected as early as stage 3 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. Majority (81.8%) were in ESRD. Systolic blood pressure, diastolic blood pressure, CKD stage, and serum phosphate correlated positively with pericardial disease. Haemoglobin concentration, glomerular filtration rate, and serum albumin correlated negatively with the presence of pericardial disease. The aetiology of CKD did not correlate with the presence of pericardial disease. Regression analysis showed that only serum haemoglobin predicted the presence of pericardial effusion.

Conclusions: Pericardial disease is common in Nigerian patients with CKD at first evaluation and occurs as early as stage 3 CKD. Pericardial thickening is more prevalent than pericardial effusion. Pericardial effusion is predicted by low haemoglobin concentration. Echocardiography to detect pericardial disease should be part of routine investigation of patients with CKD.

Keywords: Pericardial Effusion, Pericardial Thickening, Chronic Kidney Disease, Echocardiography

Introduction

Cardiovascular complications are the leading causes of death in patients with chronic kidney disease (CKD) (1). A high cardiovascular death in dialysis had been documented in the 1970s (2), and has persisted till the present time (3, 4). Left ventricular hypertrophy occurs in up to 70% to 90% of patients in uraemia as has been documented in our previous and other studies (5, 6). Although pericarditis is common in the ureamic state (7, 8), most studies have documented predominant pericardial effusion and low prevalence of pericardial thickening (9-12). Pericardial disease in CKD occurs as pericardial effusion or pericardial thickening or both (12). Ureamic pericarditis predisposes to arrhythmias, effusion, tamponade and constrictive

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pericarditis (13-15). Early detection and treatment of pericardial disease in CKD will reduce the high cardiovascular morbidity and mortality associated with this disease.

Echocardiography permits rapid and non-invasive detection of pericardial disease (16, 17). This study was designed to investigate patients with CKD at first presentation before the initiation of dialysis by two-dimensional echocardiography to determine the presence of pericardial disease and the factors associated with the condition.

Materials and Methods

The study group was drawn from the patients attending the out-patient and nephrology clinics of the University of Nigeria Teaching Hospital between January 2002 and December 2003. Ethical clearance was obtained from the Hospital Ethics Committee. Informed consent was also obtained from the study participants. The first one hundred consecutive patients who met the inclusion criteria were recruited into the study. The inclusion criteria were patients of both sexes, fifteen years and above, and the diagnosis of CKD as defined by the National Kidney Foundation Quality Outcome Initiative guidelines (K/DOQI) (18). The exclusion criteria were age less than fifteen years, acute renal failure, history and clinical features consistent with primary cardiovascular disease (cardiomyopathy, valvular heart disease, and pericardial disease), dialysis patients, and kidney transplantation. Hypothyroidism was excluded clinically by the absence of classical clinical features of the disease including bradycardia, dry coarse skin, myxoedema etc. The diagnosis of primary kidney disease was based on history, physical examination and laboratory investigations including urinalysis, imaging procedure and serology. Forty four control subjects without kidney disease drawn randomly from the general population who attended the hospital for medical examination for employment and premarital evaluation and hospital staff were recruited in the ratio of two patients to one control subject. All the control subjects had normal kidney function with glomerular filtration rate (GFR) > 90 ml/min, and without biochemical, radiological and pathological evidence of renal disease.

Biodata of the patients and control subjects were obtained. Fasting venous blood samples were taken for the determination of haemoglobin concentration, serum creatinine, albumin, calcium, and phosphate. The creatinine clearance was calculated from the Cockcroft/Gault equation (19), which has been found to correlate closely with measured creatinine clearance in Nigerians (20).

The degree of kidney disease was classified according to K/DOQI (18), classification.

Siemens Sonoline CD echocardiographic machine was used to examine the patients by two-dimensional echocardiography from the apical four-chamber, subcostal, and parasternal long and short axes views. Two cardiologists/echocardiographers performed and read the echocardiograms to reduce intraobserver error. Pericardial effusion was defined by an echo free space between the two layers of the pericardium. The size of the effusion was graded as follows (17, 21):

- Small (echo-free space in diastole < 10 mm)
  Moderate (10-20 mm)
- Large > 20 mm

Pericardial thickening was defined by 2-Dimensional echocardiography as pericardial thickening greater than 3 mm, a cut off with a diagnostic sensitivity and specificity of 95% and 86% respectively by the transesophageal route (22).

Statistics

Data were analysed using Statistical Package for Social Sciences (SPSS Inc, Chicago, Ill) version 11.5. For continuous variables, mean values and standard deviations were calculated, and the means were compared using two sample t test. Categorical variables were compared using two sample t test . Categorical

variables were compared using the nonparametric test, the chi-square. All tests were two-tailed and P values less than 0.05 were considered significant.

The Pearson's and Spearman rho correlation were used to assess the relationship between pericardial disease and the variables: age, gender, body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), haemoglobin concentration (Hb), serum albumin concentration, serum calcium, phosphate, calcium-phosphate product, GFR, aetiology of kidney disease and stage of kidney disease.

The correlations between pericardial effusion and pericardial thickening and the variables were analysed using Pearson's and Spearman rho correlation. Linear regression analysis was used to determine the variables that could predict the presence of pericardial disease, pericardial thickening and pericardial effusion respectively.

Results

The demographic and clinical characteristics of the patients and control subjects are shown in table 1. There was no difference between the mean age of the patients and control subjects (p = 0.990). There were significant differences in the mean SBP, DBP, Hb, GFR, serum albumin, serum calcium, inorganic phosphate, and calcium-phosphate product between the patients and the control group (Table 1).

Table 1. Demographic and clinical characteristics of the study population

	Patient (N = 88)	Control subjects (N = 44)	p-value
Mean age (years) ±SD	41±15	41±14	0.990
ex: male (%)	55 (63%)	27 (61%)	0.899
Female (%)	33 (38%)	17 (39%)	
Mean BMI (kg/M^2)	24±5	26±3	0.132
Mean SBP (mmHg)	174±32	117±10	<0.001
Mean DBP (mmHg)	110±22	73±7	<0.001
Mean Hb (g/dl)	8±2	13±1	<0.001
GFR (ml/min/1.73 m^2)	10±6	100±8	<0.001
Mean serum albumin (g/L)	31±7	45±7	<0.001
Mean Corrected calcium (mmol/L)	2.4±0.4	2.6±0.4	0.013
Mean phosphate (mmol/L)	2.5±0.8	1.5±0.2	<0.001
Mean Ca^{+2} x $PO4^{-3}$	5.8±2.1	3.9±0.6	<0.001

BMI, Body Mass Index; **Ca^{+2},** Serum Calcium; **DBP,** Diastolic Blood Pressure; **GFR,** Glomerular Filtration Rate; **Hb,** haemoglobin; $PO4^{-3}$, Serum Pphosphate; **SBP,** Systolic Blood Pressure

Table 2. Pericardial disease in the study population

CKD Stage	N Pericardial disease	Pericardial disease			Total
		Pericardial effusion	Pericardial Thickening	Pericardial effusion and thickening	
Control Subjects	44	0	0	0	44
CKD Stage 3	0	0	1	0	1
CKD Stage 4	8	1	4	2	15
CKD Stage 5	31	13	21	7	72
Total (%)	83 (62.9)	14 (10.6)	26 (19.7)	9 (6.8)	132 (100)

CKD, Chronic Kidney Disease

Of the 88 patients, 72 (81.8%) were in end stage renal disease (ESRD) with GFR <15ml/min. Fifteen of them were in stage 4 CKD and one in stage 3 CKD. No patient had stage 1 or 2 disease.

Forty nine patients (56%) had echocardiographic evidence of pericardial disease while thirty nine patients (44%) had no pericardial disease. Pericardial effusion was seen in 13/72 (18%) of stage 5, 1/15 (6.7%) of Stage 4, and none in stage 3 (Table 2). The corresponding figures for pericardial thickening were 21/72 (29.2%) for stage 5, 4/15 (26.7%) for stage 4. The only patient with stage 3 CKD had pericardial thickening with no effusion. Also 7/72 (9.7%) and 2/15 (13.3%) of patients in stages 5 and 4 respectively had both pericardial effusion and thickening. Of the number of patients with pericardial effusion, 9 had small effusion, 5 had moderate effusion and none had large effusion. For the patients with pericardial thickening, the pericardial thickness ranged from 3.5 mm to 8.0 mm (mean 5.8±1.2 mm). In general, the prevalence of pericardial effusion, pericardial thickening, and effusion with thickening increased with progressive decrease in GFR and progression of disease from CKD stage 3 to 5 (Table 2). None of the control subjects had pericardial disease.

The commonest causes of CKD were chronic glomerulonephritis 38 (43.2%), hypertensive nephrosclerosis 23 (26.1%) and diabetic nephropathy 13 (14.8%). The three accounted for 74 (84.1%) of the patients.

Using bivariate correlation analysis, SBP, DBP, CKD stage, and serum phosphate correlated positively with pericardial disease, while Hb, GFR and serum albumin correlated negatively with pericardial disease (Table 3). Further bivariate correlation analysis showed that SBP, DBP, and CKD stage, showed positive correlation with pericardial thickening while Hb, serum albumin and GFR, correlated negatively with pericardial thickening (Table 3).

Also SBP, DBP, CKD stage, and the aetiology of disease correlated positively with pericardial effusion while Hb, GFR and serum albumin correlated negatively with pericardial effusion (Table 3).

Linear regression analysis with pericardial disease, pericardial thickening and pericardial effusion respectively as the dependent variable and the other parameters as independent variables showed that only haemoglobin concentration could predict the presence of pericardial effusion. All the other parameters including age of patient, gender, BMI, SBP, DBP, GFR, calcium, phosphate, calcium-phosphate product, serum albumin, stage of CKD and aetiology of disease, did not predict the presence of either pericardial disease, pericardial thickening or pericardial effusion (Tables 4-6).

Table 3. Correlation between pericardial disease, type of pericardial disease and other variables

Variables	Pericardial disease n = 88		Pericardial thickening n= 25		Pericardial effusion n = 14	
	R	p-value	R	p-value	R	p-value
Age of patient	-0.049	0.074	-0.000	0.997	-0.047	0.589
BMI	-0.071	0.421	-0.145	0.098	0.098	0.263
Gender	-0.018	0.837	-0.009	0.920	0.035	0.687
SBP	0.545	<0.001	0.345	<0.001	0.260	0.003
DBP	0.545	<0.001	0.356	<0.001	0.240	0.006
Hb	-0.466	<0.001	-0.206	0.018	-0.347	<0.001
GFR	-0.537	<0.001	-0.345	0<0.001	-0.256	0.003
Albumin	-0.321	<0.001	-0.190	0.029	-0.189	0.030
Calcium	-0.057	0.517	0.022	0.800	-0.104	0.235
Inorganic Phosphorus	212	0.015	0.092	0.292	0.086	0.326
Ca x $PO4^{-3}$	0.151	0.084	0.079	0.367	0.067	0.443
CKD stage	0.513	<0.001	0.322	<0.001	0.272	0.002
Disease etiology	0.143	0.184	-0.019	0.861	0.211	0.048

BMI, Body Mass Index; **Ca^{+2},** Serum Calcium; **CKD,** Chronic Kidney Disease; **DBP,** Diastolic Blood Pressure; **GFR,** Glomerular Filtration Rate; **Hb,** haemoglobin; **$PO4^{-3}$,** Serum Pphosphate; **SBP,** Systolic Blood Pressure

Discussion

Pericardial disease in predialysis CKD

We have demonstrated in this study that pericardial disease is highly prevalent in CKD, being present in 56% of the patients studied. More importantly, these cases were detected in patients who were not yet on dialysis and were being evaluated for the first time implying that pericardial disease in CKD starts before end stage and is present in stage 3 CKD through stage 5 CKD, and not necessarily terminally. Furthermore, these patients were asymptomatic for heart disease. In a similar study by Frommer et al (23), by M-mode echocardiography of 50 patients in ESRD just prior to initiation of dialysis, 36% were found to have pericardial effusion and apparently

Table 4. Linear regression analysis to determine relationship between pericardial disease and other variables with pericardial disease as the dependent variable

Variables	B	Std Error	Confidence interval	p-value
Constant	-0.031	0.694	-0.044	0.965
SBP	0.002	0.002	0.798	0.426
DBP	0.004	0.003	1.441	0.199
Hb	-0.027	0.021	-1.290	0.199
GFR	-0.002	0.006	-0.269	0.789
Serum albumin	0.004	0.005	0.788	0.432
Serum phosphate	-0.096	0.051	-0.879	0.063
CKD Stage	0.031	0.121	0.260	0.795

Dependable variable: pericardial disease

none with pericardial thickening. This study differs from our study because all the patients were in ESRD whereas our study included patients in stages 3 and 4 CKD. In a study by Methenge et al (24), in Kenya of 46 patients with CKD and 22 control subjects, 76% of predialysis patients had varying degrees of pericardial effusion and apparently none had pericardial thickening. The findings in that study contrast with this present study; we recorded only 15.9% (14/88) with pericardial effusion and a high percentage 29.5% (26/88) with pericardial thickening. In another study by D'Cruz et al (9), on 50 predialysis patients referred for echocardiography because of symptoms of cardiac disease, 66% had pericardial effusion while 33% had pericardial thickening. It is to be noted that these patients were symptomatic for heart disease but the patients in our study were asymptomatic. Two other studies by Wray et al (25), and Yoshida et al (14), documented prevalence of 13.6% and 62% respectively for pericardial effusion but apparently no pericardial thickening in their series. Pericardial effusion in predialysis patients appears to be highly prevalent in contrast to pericardial thickening. The high prevalence of pericardial thickening in this study is of interest. Our results show that pericardial thickening is more prevalent than pericardial effusion in our CKD patients.

This pattern of pericardial disease in CKD differs from published data in both predialysis and dialysis patients where a higher prevalence of pericardial effusion than thickening has been documented (9, 10, 12). The high prevalence of pericardial thickening in this study is difficult to explain. However, it may be related to high propensity to fibrosis in black individuals or to prior exposure of the patients to viral or tuberculosis infections. The absence of pericardial thickening in the control subjects exposed to the same environmental conditions makes this explanation unlikely. More studies are warranted in the tropical environment to clarify this finding.

Table 5. Linear regression analysis to determine relationship between pericardial thickening and other variables with pericardial thickening as the dependent variable

Variables	B	Std Error	Confidence interval	p-value
Constant	-0.735	0.648	-1.134	0259
SBP	0.001	0.002	0.504	0.615
DBP	0.002	0.003	0.678	0.499
Hb	0.035	0.020	1.745	0.083
GFR	0.000	0.006	-0.067	0.947
Serum albumin	0.001	0.005	0.227	0.821
CKD Stage	0.069	0.114	0.600	0.549

Dependable variable: pericardial thickening

Table 6. Linear regression analysis to determine relationship between pericardial effusion and other variables with pericardial effusion as the dependent variable

Variables	B	Std Error	Confidence interval	p-value
Constant	0.330	0.509	0.649	0.518
SBP	0.001	0.002	0.673	0.502
DBP	0.001	0.002	0.406	0.685
Hb	-0.050	0.016	-3.146	0.002
GFR	0.000	0.005	0.100	0.920
Serum albumin	0.002	0.004	0.473	0.638
CKD Stage	-0.027	0.090	-0.304	0.762

Dependable variable: pericardial effusion

The three commonest causes of CRF in this study were chronic glomerulonephritis 38 (43%), hypertension 23 (26%) and diabetes mellitus 13 (15%). These three accounted for 84% of the patients. This is in consonance with published data from Africa (26), but differs from data from America and Europe (4), where diabetes is currently the leading cause of end stage renal disease.

A great proportion of the patients, (81.8%) presented in advanced renal disease with creatinine clearance less than 15 ml/min. This is probably responsible for the high prevalence of pericardial disease at presentation (56%). This contrasts with experience in the Western world where CKD patients present early and intervention is planned for and instituted before patients become debilitated.

Conclusions

This study has shown that, pericardial disease was common in patients with chronic kidney disease at first presentation to a nephrology unit before the commencement of dialysis. This was evident as early as stage 3 CKD. Pericardial thickening was more prevalent than pericardial effusion. Pericardial effusion was predicted by low haemoglobin concentration. Echocardiography to detect pericardial disease should be part of routine investigation of patients with CKD.

Limitations of the Study

The study of the pericardium with 2-dimensional echocardiography has its limitations. Magnetic resonance imaging (MRI) and computed tomography (CT) give better resolution of the pericardium (27, 28), but these tests are expensive and the later may involve exposure to ionizing radiation and are not universally available. Therefore echocardiography remains a useful tool for the study of the pericardium for clinical purposes. CT or MRI is used when findings at echocardiography are nondiagnostic, or difficult to interpret or when loculated or haemorrhagic effusion is suspected and for characterization of cardiac masses detected at echocardiography (17). Trans-esophageal echocardiography has shown more promise but is limited by its narrow field of view and is relatively invasive (22). Although 3-dimensional echocardiography may provide a more accurate technique for determination of pericardial fluid volume and distribution (29), it is limited in its availability. The sensitivity of 2-dimensional echocardiography in detecting pericardial fluid is very high and allows the detection of effusion as well as the definition of the size of the effusion (17, 30). Indeed two-dimensional echocardiography has been shown to have good correlation with actual pericardial fluid measurement (31). Regardless of these limitations, 2-dimensional echocardiography will most likely under-diagnose pericardial diseases rather than

over-diagnose them. It becomes very significant when high prevalence rates are detected by echocardiography.

Conflict of Interest

None declared.

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