CHARACTERISTICS OF UREMIC CARDIOMYOPATHY WITH REVERSIBLE SYSTOLIC DYSFUNCTION.

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Short Title: Reversible cardiac failure

Abstract:

Background:

There exists a sub group of patients with uremic cardiomyopathy who experience resolution of heart failure following hemodialysis.

It has been hypothesized that these patients are fluid overloaded, and following hemodialysis , show improvements in cardiac geometry and function. We wanted to study their clinical, biochemical and echocardiographic features to define any other additional characteristics.

Aim: To define characteristics of reversible systolic dysfunction.

Methods:

We studied 72 patients with chronic kidney disease on hemodialysis of whom 52 presented with congestive heart failure, over a period of 190 days. We studied their echocardiographic profile and blood biochemistry parameters including troponin I and C reactive protein.

Results:

There were 29 patients with systolic dysfunction(LVEF≤40%). Twenty three patients with preserved systolic function, had diastolic dysfunction. Of the 29 patients with systolic dysfunction, 10 patients had significant improvement in NYHA functional class , and left ventricular dimensions (LVIDd:59.8±2.6 mm to 55.9±2 mm and LVIDs:51.8±1.8 mm to 34±1.2 mm; $p<0.001$) with significant increase in left ventricular ejection fraction($30.5±5\%$ to $50.1±4\%$; $p<0.001$). These patients had the highest serum levels of troponin I ($p=0.024$) which decreased significantly with recovery of cardiac function. In

the patients with persistent systolic dysfunction and in the patients with diastolic

function, the troponin I remained high. The troponin I was significantly lesser in the

control group(p=0.002)

Conclusions:

A sub group of patients with uremic cardiomyopathy demonstrated reversible left

ventricular systolic dysfunction, and high levels of serum troponin I levels at

presentation, which regressed with recovery of ventricular function.

Abbreviations: LV:Left Ventricle, LVIDd: Left ventricular internal diameter in diastole,

LVIDs: Left ventricular internal diameter in systole, IVSd: interventricular septal

thickness in diastole, PWDd: posterior wall diameter in diastole, LVEF: Left ventricular

ejection fraction, PASP: Pulmonary artery systolic pressure, LSD: least significant

difference, NYHA: New york heart association, CAD: Coronary artery disease.

INTRODUCTION: Uremic cardiomyopathy [1,2,3,] presents as congestive cardiac failure due to systolic or diastolic dysfunction. Systolic dysfunction can be transient , due to increased pre-load , which hemodialysis can improve [4,5,6]. We studied these patients with reversible ventricular dysfunction.

METHODS:

Study Design: We studied 72 consecutive patients with chronic kidney disease , of whom 52 presented with congestive heart failure, and 20 were controls. The study period was from April 2007 to October 2007. The study was approved by the Institutional Ethics Committee, and written consent was obtained from the study patients. All patients underwent clinical examination, electrocardiogram, hematological and biochemistry tests and 2D transthoracic echocardiogram. .

Inclusion criteria: Congestive heart failure according to Framingham criteria, estimated glomerular filtration rate < 60ml/min/1.73 m2 for 3 months [7]. Presence of coronary artery disease was defined as>70% stenosis on coronary angiogram or presence of infarction documented on electrocardiogram. .

Exclusion criteria : a) acute coronary syndrome within 3 months b) chronic stable angina c) chest pain in the peridialysis period d) major cardiovascular surgery e)severe valvular heart disease f) pericardial disease and g) malignancy

Assessment methods: Pre dialysis and post dialysis weight was recorded on the same weighing machine. **Dry weight** was established for each patient on a trial and error basis; defined as the weight below which the patient suffered frequent hypotensive episodes during the latter part of the dialysis session, and experienced malaise, cramps and dizziness post-dialysis.

ASSAYS: All blood samples were drawn before hemodialysis.

Cardiac troponin I was measured with the IMMULITE troponin I assay (Diagnostic Products Corporation; Los Angeles, CA) .The analytical sensitivity was 0.1 ng/ml. The extended range C reactive protein was determined by a nephelometric analyzer (Dade-Behring, Newark, DE) by the particle enhanced turbidometric immunoassay technique(PETIA). The measurement range of the assay was 0.5 mg/L to 250 mg/L.

ECHOCARDIOGRAPHY: The General Electric Vivid 3 ultrasound machine (Milwaukee, Wisconsin) equipped with a 2.5 MHz frequency transducer was used. Two dimensional measurements were performed as recommended by the American Society of Echocardiography [8], prior to hemodialysis and at discharge. Values were indexed to body surface area. Systolic dysfunction was defined as LVEF≤40%. Diastolic dysfunction was defined as (E:A ratio<1, E deceleration time>220 ms) or restrictive filling (E:A >2, E:A between 1 and 2 with E deceleration time <150 ms) from the pulsed Doppler transmitral flow. Tissue Doppler imaging of mitral annular velocities with an E/Ea ratio >10 further defined diastolic dysfunction.[9]

FOLLOW-UP: All patients were followed over a period of 190 days. Routine hematological, biochemical tests ,C reactive protein and troponin I assays were done.

Dialysis Techniques: .All 52 patients were on long-term hemodialysis with 3 cycles/ week for 4-5 hours, using Baxter 1550(Deerfield, IL, USA) machine, a 1.2 to 1.7 m2 hollow fiber polysulfone dialyser and bicarbonate- buffered dialysis solution.. The patients with severe cardiac failure ie.NYHA class 4 were subjected to ultrafiltration just after hemodialysis, at a rate of 0.5-1L/hr until clinical resolution of cardiac failure.

STATISTICAL ANALYSIS:

Continuous variables were expressed as mean±SD. Categorical variables were expressed as %. There were 29 patients with systolic dysfunction based on LVEF≤40% and 23 patients with left ventricular diastolic dysfunction and preserved systolic function ie. LVEF>40%. Based on initial and repeat echocardiogram patients were assigned to 3 different groups. The first group consisted of patients who had initially presented with systolic dysfunction but demonstrated recovery of systolic function in the repeat echocardiogram. The second group consisted of patients who had consistent systolic dysfunction even in the repeat echocardiogram and the third group were patients with preserved systolic function. Age, Hb%, blood urea, creatinine, glomerular filtration rate, C reactive protein and troponin I at baseline were considered as variables that could possibly predict the group of the patients. LVIDd, LVIDs, IVSd, LVPWd, PASP and LVEF were the outcome variables that differentiated the group membership of the patients. The mean baseline predictors and outcomes as well as the change in outcome measures over the 2 assessments were compared between groups using ANOVA. Post-hoc LSD test was done whenever ANOVA was significant. The association of categorical variables and groups was examined using the chi-square test. Spearman's correlation co-efficients assessed the strength of association between the predictor

variables and the outcome variables in each group. Discriminant function analysis was used to identify variables that could differentiate the 3 groups. Further, multivariate logistic regression analysis identified the variables that increased the odds of a patient belonging to the group with reversible systolic dysfunction. The tests were considered significant if $p<0.05$. All analyses were carried out using SPSS version 13.0 (SPSS Inc, Chicago, Ill).

RESULTS:

The baseline patient clinical and echocardiographic characteristics are listed in Table:1. The mean age of the entire study group was 47.7 ± 6.53 years. There were 43(59.7%) males and 29(40.2%) females. There were 29 patients who presented with congestive heart failure, with LVEF<40%. Repeat echocardiogram identified 10 patients as belonging to group 1 with complete recovery of left ventricular function. The 19 patients who had persistent systolic dysfunction with LVEF<40% were labeled group 2, and the 23 patients with diastolic dysfunction and LVEF> 40% were labeled group 3. There was no significant difference in age between the 3 groups. None of the patients in all 3 groups were grossly edematous, with no significant difference in weight. The C reactive protein and troponin I were significantly higher for groups 1 and 2 as compared to group 3 ($p<0.001$). Post-hoc tests revealed that the left ventricular dimensions in diastole and systole were significantly higher for groups 1 and 2 ($p<0.001$) and the left ventricular ejection fraction was significantly lower for groups 1 and 2 ($p<0.001$). The interventricular septal thickness and free wall thickness were highest in group 3 as compared to groups 1 and 2, but not significantly so. The pulmonary systolic pressures were lowest in group 1 and highest in group 2. The 20 patients without heart failure were

age and sex matched with the heart failure group. There were 11 hypertensives, 5 diabetics and 6 CAD patients. They all had LV hypertrophy, normal LV dimensions and LVEF. When the mean troponin I value for group 3 (1.13±0.53) was compared with the patients without heart failure (0.74±0.39), it was significantly higher in group 3 (p=0.002), demonstrating that the troponin I elevations are significantly higher in patients with heart failure.

The patient characteristics on follow-up are listed in Table:2.

On follow-up, there was a significant improvement in clinical signs of heart failure. The NYHA class 3 and 4 patients shifted to class1 in group 1. There was no change in groups 2 and 3. There was no significant change in dry weight post dialysis and in between dialysis cycles. ANOVA for difference in measure changes between the groups showed that in group 1, there was a significant decrease in left ventricular dimensions in diastole and systole (both at p<0.001), pulmonary systolic pressures (p=0.03) and increase in left ventricular ejection fraction (p<0.001). The reduction in pulmonary systolic pressures was significant for group 1 as compared to groups 2 and 3 (p=0.044).

  Discriminant function analysis showed that a model with just baseline troponin I could best differentiate between the groups . The correct classification based on discriminant function was 60% in group 1, 52.6% in group 2 and 87% in group 3 based on troponin I. Overall 69.2% patients were classified correctly. The sample size being small and not optimal for discriminant function analysis, multivariate logistic regression which is a more robust technique was done. Groups 2 and 3 for whom the disease state did not change were considered as a single reference group and the odds of group 1 with respect

to the baseline troponin I values was computed. Higher values of troponin I alone tended to increase the odds of belonging to group 1; odds ratio:10.94 (95%CI:0.80 - 150.0) ; p=0.073. The R^2 value for this model was 0.46. The repeat C reactive protein and troponin I assays done after 6 months were significantly lesser for patients in group 1 (p=0.002). There was a non significant decrease in group 3 and no change in group 2. There was no change in LV dimensions, LV hypertrophy , LVEF, troponin I and C reactive protein levels in the patients without heart failure on follow-up.

DISCUSSION:

Uremic cardiomyopathy is a distinct clinical entity [3]. Endomyocardial biopsies have shown severe myocyte hypertrophy, disarray and interstitial fibrosis [3,10,22] . In our patients, group 3 had maximum left ventricular hypertrophy. Group 2 had increased pulmonary pressures, persistent left ventricular dilatation and reduced LVEF. The patients in group 1 had lesser degree of left ventricular hypertrophy, lesser pulmonary pressures and lower baseline LVEF than group 2, which improved on follow-up. There are reports of improvements in left ventricular function following hemodialysis. [4,5,6] Nocturnal hemodialysis showed a sustained increase in left ventricular ejection fraction.[5] Persistent ultrafiltration during hemodialysis demonstrated regression in cardiac size and improvements in ejection fractions [6] in patients with significant fluid overload. All our

patients (groups 1,2 and 3) were subjected to prolonged ultrafiltration during hemodialysis. None of them were fluid overloaded.

The cardiac troponin I is specific for detection of myocardial injury in chronic renal failure.[12,13,15] Elevated troponin levels independently predicted increased left ventricular mass and systolic dysfunction in patients with chronic kidney disease [16,17,18] ,with high positive predictive values for left ventricular hypertrophy and high negative predictive values for systolic dysfunction [17,18,23]. All our patients in group 2 had ventricular hypertrophy , systolic dysfunction and elevated troponin I levels at follow up. Continued rise in troponin I in group 3 can be explained by persistent left ventricular hypertrophy. In reversible conditions like myocarditis [24] and septic shock [25] transient ventricular dilatation and reduced function was associated with transient rise of troponin I. The failure of continued release was due to absence of remodeling and release of structurally bound troponin, reflecting ' reversible injury'.

In our study, raised troponin I which regressed at follow up increased the odds of the patient having reversible systolic dysfunction. . The levels of C-reactive protein which predict cardiovascular morbidity and mortality in chronic kidney disease was 6mg/L [11,19] . The levels in our patients reflect low grade inflammation. The regression of C reactive protein levels in parallel with troponin I levels in group 1 patients, with recovery of left ventricular systolic function may generate a hypothesis that reversible myocardial injury exists in a subgroup of uremic cardiomyopathy, requiring large scale studies to explore this interesting finding

STUDY LIMITATIONS:

As the sample size is small, we have not been able to define a predictive value of troponin I for left ventricular dysfunction.

We have also not performed endomyocardial biopsies in our patients due to logistic constraints.

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CONCLUSIONS:

In patients dilated uremic cardiomyopathy, there exists a sub-group with reversible left ventricular systolic dysfunction characterized by an absence of significant remodeling, and significantly higher levels of serum cardiac troponin I, which regress with recovery of cardiac function.

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Table 1 BASELINE PATIENT CHARACTERISTICS

	Group1 (n=10)	Group2 (n=19)	Group3 (n=23)	P value
Predictor Variables				
Age(Yrs)	44.5±8.5	47.7±5.4	49.3±6.2	NS
Sex(M/F)	6/4	11/8	14/9	NS
BP(mmHg)	141±10.0	144±10.8	152±12.0	NS
	86±7.0	88±6.0	90±8.0	NS
Weight(Kg)	66±3	69±2	69±4	NS
NYHA3/4(%)	100%	99%	86%	NS
CRP(mg/L)	3.0±0.7	2.8±0.84	1.3±0.43	<0.001
TropI(ng/ml)	2.3±0.35	2±0.28	1.2±0.52	<0.001
Outcome Variables				
LVIDd(mm)	59±2.7	59±3.2*	53±2*	<0.001
LVIDs(mm)	51±4.5	49±6.4*	36±5.5*	<0.001
IVSd(mm)	12±0.8	12±0.9	13±1.2	NS
LVPWd(mm)	12.0±0.8	12.0±0.9	12.9±1.2	NS
PASP(mmHg)	43.8±5.3	45.3±4.5	44.0±3.4*	NS
LVEF(%)	30.5±5.5	35.3±5.8*	52.7±5.4*	<0.001
LVDD(%)	10.0	89.5	91.3	<0.001

P = level of significance from ANOVA for comparison of means between groups

Table 2 **CLINICAL AND ECHOCARDIOGRAPHIC CHARACTERISTICS ON FOLLOW-UP**

	Group1 (n=10)	Group2 (n=19)	Group3 (n=23)	P value
Predictor Variables				
BP(mmHg)	120±8	122±7	124±6	
	80±4	82±6	82±7	0.04
NYHA1/2(%)	99.3	0	15	<0.001
Weight(Kg)	64±2	68±3	66±2	NS
CRP(mg/L)	1.2±0.2	1.9±0.7	1.1±0.5	0.004
TropI(ng/ml)	0.2±0.01	1.8±0.3	0.5±0.05	<0.001
Outcome Variables				
LVIDd(mm)	55±2.1	59±3.7*	54±2.7*	<0.001
LVIDs(mm	34±2.5	48±8*	37±6.1*	<0.001
IVSd(mm)	11±1	12±0.9	13.5±1.5	NS
LVPWd(mm)	11.5±0.9	12.5±0.8	13±1.4	NS
PASP(mmHg)	40.8±4.6	43.8±3.7	44.4±3.1*	0.04
LVEF(%)	50±3.1	37±7.2*	50±9*	<0.001

P = level of significance from ANOVA for comparison of means between groups
* mean difference between baseline and follow up significantly different from Group 1 by post hoc test