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The Significance Mild Renal Dysfunction in Chronic Heart Failure

L'importance dysfonction rénale légère dans l'insuffisance cardiaque chronique

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ABSTRACT

BACKGROUND: **Heart failure is a major public health concern. Prediction models in heart failure have employed echocardiography and other advanced laboratory parameters in predicting the risk of mortality.However, most of the patients in the resource poor economies still do not have easy access to these advanced technology.**

OBJECTIVE: **To determine the clinical and echocardiographic correlates of patients with chronic heart failure (CHF) in the presence or mild renal disease (MRD).**

METHODS: **One hundred CHF patients were categorized based on their estimated glomerular filtration rates into either normal renal function or MRD. The clinical and echocardiographic variables of both groups were compared.**

RESULTS: **There were 38 females and 62 males with an overall mean age of 54 years. A significantly greater proportion of patients with mild renal disease presented in New York Heart Association classes 3 and 4 (82.9% vs 27.1%). Patients with MRD had echocardiographic findings of a significantly larger left atrial dimension, lower ejection fraction and fractional shortening and shorter deceleration time. A significantly greater proportion of patients with mild renal disease also had moderate- severe mitral and tricuspid regurgitation and grades 2-3 diastolic dysfunction compared to patients without mild renal disease. Patients with MRD also exhibited a significantly greater degree of deterioration in the fractional shortening and ejection fraction compared to non-MRD patients. Multivariate regression analysis indicated that a low ejection fraction and a low fractional shortening were significantly associated with MRD.**

CONCLUSION: **Identification of MRD in chronic heart failure patients using the estimated glomerular filtration rate is valuable in resource poor countries. The presence of MRD in CHF is associated with poor left ventricular function and increased deterioration of ventricular function. WAJM 2011; 30(6): 442–446.**

Keywords: **Heart failure, mild renal dysfunction, ventricular function.**

RÉSUMÉ

CONTEXTE: L'insuffisance cardiaque est un problème de santé publique. Modèles prédictifs en insuffisance cardiaque ont EMPLOI échocardiographie et des autres paramètres de laboratoire de pointe pour prédire le risque de mortality. However, la plupart des patients dans les économies pauvres en ressources Vous n'avez pas encore accès facile à ces technologie de pointe.

OBJECTIF: à déterminer les corrélats cliniques et échocardiographiques des patients atteints d'insuffisance cardiaque chronique (CHF) en présence ou légère insuffisance rénale (MRD).

MÉTHODES: Cent patients ont été classés CHF BASE de leur durée de taux de filtration glomérulaire en soit fonction rénale normale ou MRD. Les variables cliniques et échographiques des deux groupes ont été comparés.

RÉSULTATS: Il y avait 38 femmes et 62 hommes avec un âge moyen global de 54 ans. Une proportion significativement plus élevé de patients atteints de la maladie rénale légère présentée dans de nouvelles classes New York Heart Association 3 et 4 (82,9% vs 27,1%). Les patients atteints de MDR a donné des résultats échocardiographiques d'une dimension beaucoup plus importante auriculaire gauche, fraction d'éjection inférieure et la fraction de raccourcissement et de réduction du temps de décélération. Une proportion significativement plus élevé de patients atteints de la maladie rénale légère a également eu modérée à sévère régurgitation mitrale et tricuspide et Grades 2–3 dysfonction diastolique par rapport aux patients sans maladie rénale légère. Les patients atteints de MDR également preuve d'un degré nettement plus élevé de détérioration de la fraction de raccourcissement et la fraction d'éjection par rapport aux non-MRD patients. L'analyse de régression multivariée a indiqué que d'une fraction d'éjection basse et un raccourcissement faible fraction étaient significativement associés à MRD.

CONCLUSION: Identification de MRM dans insuffisance cardiaque chronique aide du taux de filtration glomérulaire estimé est précieux dans pays pauvres en ressources. La presence de mrd en chf est associé à une mauvaise fonction ventriculaire gauche ET à une dégradation croissante de la fonction ventriculaire. **WAJM 2011; 30 (6): 442–446.**

Mots-clés: Insuffisance cardiaque, DOUX dysfonction rénale, la fonction ventriculaire.

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Abbreviations: ACE, Angiotensin Converting Enzyme; **ARD,** Aggravated Renal Dysfunction; **CHF,** Chronic Heart Failure; **CI,** Cardiac Index; **DT,** Deceleration Time; **EF,** Ejection Fraction; **GFR,** Glomerular Filtration Rate; **FS,** Fractional Shortening; **HF,** Heart Failure; **LAD,** Left Atrial Dimension; **MR,** Mitral Regurgitation; **MRD,** Mild Renal Disease; **NYHA,** New York Heart Association; **TR,** Tricuspid Regurgitation.

INTRODUCTION

Heart failure (HF) is a major and growing public health concern in terms of incidence, prevalence, morbidity and mortality.[1] Mortality among patients with HF has been reported to be high and comparable to many malignant diseases.[2–3] Heart failure is the only cardiovascular disease that is increasing in prevalence in the United States despite a fall in prevalence of coronary artery disease.[4] In Nigeria, hypertension remains the commonest cause of HF and with a prevalence which has risen to 14.5% from 9.3%[5–6] in less than a decade.

Over one-third of patients with HF present with renal insufficiency. The presence of renal insufficiency confers worsened outcome in patients with heart failure.[7–8] African Americans have higher mortality and hospitalisation rates compared with other racial/ethnic groups[9]. There is limited data among Nigerians regarding mortality in HF. Prediction models in HF have also employed echocardiography and other advanced laboratory parameters in predicting the risk of mortality. However, most of the patients in the resource poor economies still do not have easy access to these advanced technology. Estimation of the glomerular filtration rate (GFR) using the Cockroft Gault formula[10] can be done easily even in resource poor economies. The purpose of our study was then to classify HF patients based on the estimated GFR into those with normal renal function and those with MRD. We then explored the relationship of MRD to other clinical, demographic and echocardiographic variables.

SUBJECTS, MATERIALS, AND METHODS

The study population consisted of 100 consecutive patients admitted with a diagnosis of HF to the male and female medical wards of Obafemi Awolowo University Teaching Hospitals Complex. Heart failure was defined as the presence of symptoms and signs that fullfilled the Framingham criteria for diagnosing HF. Patients with an estimated creatinine clearance < 60ml/min were excluded from the study as were those with diabetes mellitus, primary respiratory disease and liver disease. The study was conducted from January to December 2006 at the Obafemi Awolowo University Teaching Hospitals Complex, Ile-Ife, Nigeria.

On completion of the data collection, patients were divided into two groups for analysis. Patients were categorised as having either MRD if they had an estimated creatinine clearance 60–90ml/minute or normal renal function if they had an estimated creatinine clearance > 90ml/min.Comparison was made between the two groups. Mortality was also noted at the end of the study period.

The study was approved by the local ethics committee. All participants signed a written informed consent form.

Echocardiography

Each participant underwent a transthoracic echocardiographic examination with a Siemens Sonoline G 60 S equipment according to standard protocols between January and December 2006 . Two dimensional apical four and two chamber views were used for all participants, supplemented by parasternal long and short axis views. Systolic function was evaluated by two experienced cardiologists and two specialist registrars. Left ventricular ejection fraction (EF) was expressed as the average values between observers. EF was estimated by the Teichholz method while left atrial and left ventricular dimensions were determined by M-Mode echocardiography in the parasternal long axis views.The transvalvular flow was evaluated by standard color Doppler technique and possible valvular dysfunction was further assessed by grading the valvular incompetence on a two grade scale as negligible/mild and moderate/severe. The repeat studies were carried out six months after the initial study.

Statistical Analysis

Continuous variables are expressed as mean ± SD and categorical variables as percentages. The association of the clinical and echocardiographic parameters with renal dysfunction were assessed in univariate analysis using Chi square and Students t-test respectively.

A p value <0.05 was considered statistically significant. Variables considered for inclusion in multivariate models were fractional shortening (FS), EF, deceleration time (DT), left atrial dimension (LAD), moderate/severe mitral regurgitation (MR), moderate/severe tricuspid regurgitation (TR) and type of diastolic abnormality.

RESULTS

We enrolled 100 consecutive patients admitted with a diagnosis of HF and were followed up for six months. Five patients were lost to follow up while six patients died. Intra-hospital mortality from progressive pump failure accounted for five of the deaths that occurred while the last case was reported by relatives as a case of sudden death. We followed up 89 patients in all.

Demographic and clinical variables in patients with and without MRD are shown in Table 1.The mean age of the entire group was 54 ± 15 years. There was no significant difference between groups in regard to age and sex. Patients with MRD were more frequently in New York Heart Association (NYHA) class 3/4 compared to those with normal renal function. The systolic and diastolic blood pressures of patients with normal renal function were significantly higher when compared with patients with mild renal dysfunction, 140 + 20 mmHg vs 104 + 19 mmHg ($p< 0.05$) and 89 + 13 mmHg vs 72+13 mmHg ($p<0.05$) respectively.

Systemic hypertension accounted for majority (69%) of the cases of HF. This was followed by dilated cardiomyopathy (16%) and rheumatic valvular heart disease (10%). Endomyocardial fibrosis, myocardial infarction and congenital heart disease (secundum type atrial septal defect) accounted for only a few cases as shown. While 88% of our patients were treated with angiotensin converting enzyme (ACE)-Inhibitors and 95% were treated with frusemide, none was treated with beta blockers.

The echocardiographic findings are summarised in Table 2. Moderate to severe MR and moderate to severe TR occurred more frequently in patients with MRD; 80% vs 54% ($p<0.05$) and 66% vs 46% ($p<0.05$). The EF and FS of patients with MRD were significantly lower compared with those with normal renal

Table1: Socio-Demographic and Clinical Features of Study Participants

Characteristic	Mean ± SD		
	Normal Renal Function	Mild Renal Disease	P Value
N	**59**	**41**	
Age (years)	57 ± 14	51 ± 17	0.08
Weight (Kg)	66 ± 15	59 ± 14	0.04
BMI(Kg/m^2)	24 ± 5	22 ± 5	0.03
Gender (M/F)	36/23	26/15	0.80
NYHA CLASS 1–2/3–4	43 16	7/34	0.00
SBP (mmHg)	140 ± 20	104 ± 19	0.00
DBP (mmHg)	89 + 13	72 ± 13	0.00

***BMI**, Body Mass Index; **DBP**, Diastolic Blood Pressure; **M/F**, Male/Female; **NHYA**, New York Heart Association; **SBP**, Systolic Blood Pressure.*

Table 2: Comparison of Echocardiographic Variables by Renal Function Status

Variable	Normal Renal Function	Mild Renal Disease	P- value
N	**59**	**41**	
LAD	4± 1	5 ±1	0.02
LVMI	159 ± 54	190 ± 102	0.05
FS (%)	22 ± 7	17 ± 10	0.00
EF (%)	51 ± 13	40 ± 19	0.00
CI (L/MinM^2)	5 ± 3	5± 3	0.74
DT (ms)	19	165 ±51	0.03
Mod. -Severe MR (%)	54	80	0.01
Mod.-Severe TR (%)	46	66	0.01
Pseudo-normal/ Restrictive (%)	27	63	0.00
Conc/Ecc Hypertrophy (%)	71	73	0.68

***CI**, Cardiac index; **Conc**, Concentric; **DT,** Deceleration time; **Ecc,** Eccentric; **EF,** Ejection fraction; **FS,** fractional shortening; **LAD,** Left atrial dimension; **LVMI,** Left ventricular mass index; **Mod,** Moderate; **MR,** Mitral regurgitation; **TR,** Tricuspid regurgitation. .*

function; 40 ± 19 % vs 51± 13 % (p<0.05) and 17 ± 10% vs 22 ± 7 % (p<0.05) respectively. The LAD of patients with MRD was significantly larger compared with the normal renal function group; 5 ± 0.9 cm vs 4 ± 0.8cm (p<0.05). The DT was significantly shorter in patients with MRD; 192 ± 64ms vs 165 ± 51 ms (p<0.05).

The proportion of patients with MRD who had pseudo-normalised and restrictive left ventricular filling pattern was significantly greater when compared with those with a normal renal function; 63% vs 27% (p<0.05). There was no difference in the cardiac index (CI) and proportion of patients with concentric/ eccentric hypertrophy when both groups were compared: 5 ± 3 L/minM^2 vs 5 ± 3 L/ minM^2 (p>0.05), and 71 vs 73% (p>0.05).

Table 3 shows that the deterioration in EF: (8 ± 14% vs. –1 ± 13 % (p<0.05) and FS: 5 ± 9% Vs –1 ± 6 % (p<0.05)) in six months was significantly greater in the MRD patients compared with the normal renal function group. When the diastolic function of both groups were compared after follow up, there was no significant difference in the isovolumic relaxation times, deceleration times and mitral E/A ratios.

Table 4 shows the multivariate association of the study variables with MRD. Only echocardiographic variables that had a univariate association with the groups at P<0.05 were considered for inclusion in the multivariate regression analysis.The presence of MRD was found to be significantly associated with systolic dysfunction (a low EF and low FS). A low EF was most predictive of renal dysfunction.

At the end of the study period, five patients were lost to follow up while six died during the study period. Overall mortality was 6% at six months.The mechanism of death was reported to be sudden in one instance (presumably arrhythmic) and the others were cases of intra-hospital mortality due to disease progression (progressive pump failure). All deaths occured in patients with MRD. Seven patients were readmitted. Four of the six who eventually died were cases of readmision.

DISCUSSION

We found that advanced HF (NYHA 3/4) and moderate to severe MR occured in a significantly greater proportion of patients with MRD compared to those with a normal renal function. Other studies have also confirmed this independent association between mitral regurgitation and renal dysfunction.[11–12] Studies have shown that NYHA 3/4 and MR is associated with renal dysfunction.[11]

Retrospective analyses of large HF trials have shown that even mild renal insufficiency has powerful negative predictive power in patients with both mild and severe HF.[13] In addition, cardiovascular morbidity and mortality are significantly increased in patients with mild chronic renal insufficiency. The mechanisms by which decreased renal function is correlated with cardio-vascular diseases are unknown. It is unclear if cardiac pump failure leads to progression of functional renal deterioration or vice-versa. What is clear however is that these interactions between the heart and the kidney can lead to poor outcomes in patients with CHF.

In a systematic review of 16 published studies by Smith *et al*[14] characterising the association between renal impairment and mortality in HF patients, mortality worsened incrementally across the range of renal function,with a 7% increase in risk for every 10ml/min decrease in estimated GFR. They concluded that renal impairment is the rule rather than the exception among HF patients and confers excess mortality.

Multiple risk factors have been found to contribute to a decrease in renal blood flow. Related haemodynamics may contribute to a decrease

Table 3: Comparison of Changes in Echocardiographic Findings at Six Months of Follow-up

Variable	Mean ± SD		
	Normal Renal Function	Mild Renal Disease	P Value
Change in EF (%)	8 ± 14	–1 + 13	0.05
Change in FS (%)	5 + 9	–1+ 6	0.00
IVRT (ms)	101 + 32	105 +35	0.75
DecelerationTime(ms)	228 + 50	212 + 71	0.46
Mitral E/A ratio	2 + 1	1 +1	0.81

EF, *Ejection Fraction;* ***FS,*** *Fractional Shortening;* ***IVRT,*** *Isovolumic relaxation time;* ***MS,*** *Milliseconds*

Table 4: Regression Analysis of Significant Variables

Variables in the Regression Equation	B	SE	Wald	Df	Significance
Fractional Shortening	0.868	0.325	7.419	1	0.007
Ejection Fraction	–0.508	0.178	8.181	1	0.004
Deceleration Time	–0.002	0.006	0.087	1	0.768
Left Atrial Dimension	–0.868	0.545	2.533	1	0.112
Moderate/Severe Mitral Regurgitation	1.507	0.885	2.900	1	0.089
Moderate/Severe Tricuspid Regurgitation	–0.225	0.697	0.104	1	0.747
Change In Ejection Fraction	–0.046	0.123	0.143	1	0.705
Change In Fractional Shortening	–0.070	0.224	0.099	1	0.753
Grade of Diastolic Dysfunction	0.997	0.877	1.293	1	0.256
Constant	7.817	3.554	4.837	1	0.028

in renal blood flow including elevated renal vein pressure caused by elevated right atrial pressure and tricuspid regurgitation.[15–16] This may explain our finding of a significantly larger proportion of patients with renal dysfunction having moderate to severe TR.

Solomon and colleagues[17] found in the VALIANT Echo study group that ejection fraction, infarct segment length,right ventricular function, and mitral deceleration time were not influenced by renal function. Our findings are in contrast to those findings. We found that the EF and FS were both significantly lower in the group with MRD compared with the group with preserved renal function and that the mitral deceleration time was significantly shortened in patients with MRD compared to those without normal renal function.

These differences may be related to the aetiology of HF. We found that longstanding hypertension accounted for 69% of the cases of HF while myocardial infarction was the aetiology of HF in the other studies sited. Longstanding hypertension tends to cause diastolic dysfunction initially but eventually will cause systolic HF if untreated. Patients with myocardial infarction are likely to have presented earlier and treated promptly compared to patients with hypertension thus reducing the incidence of systolic dysfunction in patients with ischemic heart disease.

Glomerula Filtration Rate is maintained in many patients despite a reduced renal blood flow (RBF) by the increase in efferent glomerular arterial resistance mediated by angiotensin II.[18] As RBF is further reduced, however, GFR may also fall .This implies that a mild reduction in GFR represents a state of more advanced impairment in renal blood flow. Our results however compare with findings of the VALIANT Echo study group with respect to significantly larger left atrial volume and higher left ventricular mass index found in patients with MRD as compared with patients with a normal renal function. During the 20 months of follow up of the VALIANT Echo study group, there was no significant difference in the magnitude of change in left ventricular EF. However, in our study with a follow up for only six months, we found there was a significant improvement in the EF at the end of the study period.

Weinfeld *et al*[18] found no significant difference when the left atrial dimension of HF patients with aggravated renal dysfunction (ARD) was compared with those without ARD. Aggravated renal dysfunction was defined as ≥ 25% increase in serum creatinine concentration to ≥ 2mg/dl during the treatment of decompensated HF. Their findings on left ventricular dimension and EF however were similar to previous findings by the VALIANT Echo study group. They found no significant difference in CI in patients with and without ARD.This finding compares with what we also found when we compared CI in patients with and without MRD. A significantly larger number of patients with MRD had grades 2–3 diastolic dysfunction compared with those with normal renal function.This finding is in keeping with that of the VALIANT Echo study group researchers.

Increased left atrial volume and left ventricular mass in patients with impaired renal function suggest that diastolic function might be an important mediator of increased risk of HF development and cardiovascular mortality in patients with renal impairment after myocardial infarction -the researchers concluded.[17]

Study Limitations

Our study is limited by our inability to determine the true incidence of re-admission since many of the patients who needed to be re-admitted had financial constraints. This study was hospital based and it was probable that not all patients in the region would have presented to our health care facility or to even any other hospital. Finally, though HF is a final common pathway to a number of disease entities, we acknowledge that the presence of multiple aetiologies may be a confounding factor in renal function assessment.

Conclusion

The presence of MRD based on estimated GFR in chronic HF is associated with poor left ventricular function and increased deterioration of ventricular function during a six month period. This simple classification method thus identifies those that may benefit from a more aggressive line of treatment. Renal function should therefore be considered in risk stratification and evaluation of therapeutic strategies for HF patients.

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