Nigerian Journal of Clinical Practice
March 2007 Vol 10(1): 83-90

LEFT VENTRICULAR HYPERTROPHY IN RENAL FAILURE A REVIEW

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ABSTRACT
Renal failure is becoming increasingly common in our enironment. Advances in management like availability of dialysis and transplantation is prolonging the live of patients. As a consequence complication are increasingly being encountered. Cardiovascular complication is one of the commonest; and left ventricular hypertrophy is one of the major cardiovascular complications of end stage renal failure. It is an independent predictor of survival in patients with chronic renal failure and is present in a large number of patients entering maintenance haemodialysis.
This review summarizes the occurrences of left ventricular hypertrophy, its pathomechhanism, clinical significance, evaluation and interventional strategies. This information is useful to us as we grapple with this problem.
Key words: Left Ventricular hypertrophy (LVH), Renal failure; cardiovascular

INTRODUCTION
Chronic Renal failure (CRF) is a major cause of cardiovascular morbidity and mortality in Nigeria, and most parts of Africa. [1] Even in advanced countries of the world, renal failure remains a major health problem, being an important indirect cause of congestive cardiac failure, and other cardiovascular disease particularly myocardial infarction, sudden cardiac death, hypertension and stroke. [2,3] Left ventricular hypertrophy (LVH) has been reported in essential of left ventricular hypertrophy with blood pressure level has not been uniformly documented in patients with CRF [4].Other risk factors include anaemia, hyperparathyroidism, sympathetic overactivity, recurrent volume overload and possibly uraemia per se.obesity and male sex [4,5].LVU is known to be an independent predictor of survival in patients with CRF and is present in approximately 70 % of these patients at initiation of dialysis [6,7,8] and in up to > 90% in a recent local study [9].

Occurrence of LVH in Renal Failure
Left ventricular hypertrophy is one of the major cardiovascular complications of end stage renal failure (ESRF). A number of recent studies [10,11,12] document the high frequency of this condition in patients entering renal replacement therapy that ranges from 60% [10], 80% [11] to as high as 96% [9].Left ventricular mass increase progressively with duration of dialysis treatment even in normotensive patients. [13] Particularly in patients with incipient LVH, asymmetric septal hypertrophy (ASH) may be encountered .[14] The patient usually has a mixture of concentric and eccentric hypertrophy, which reflects the increased LVH persists even after renal transplantation; [15] and a relationship between blood pressure and LVH is found even in normotensive recipients of renal grafts.
The question emerges as to whether LVH is unique to ESRF. A study carried out by stefanski A; et al [16] showed that increased septal thickness is found even in the earliest stages of glomerular disease in patients with IgA glomerulonephritis, non-nephrotic proteinuria and normal inulin clearance, who have blood pressures within the range of normotension according to World Health Oraganisation (WHO) criteria 17 Even at this early stage of glomerulonephritis, cardiac remodeling is accompanied by impaired diastolic left ventricular function as reflected by the ratio between early diastolic/late diastolic (atrial contraction) inflow velocity across the mitral valve.

Pathomechanisms of LVH in renal Failure
In renal failure, both preload and afterload are increased because of hypervolaemia and increased peripheral vascular resistance respectively, As illustrated in figure 1, an increase in preload, induced by hpervollaemia, causes serial additional of sarcomers leading to lengthening of myofibers and eccentric.
In contrast, increase afterload, such as, from increased peripheral resistance and increase impedance, cause parallel addition of sarcomers, thickening of myofibers and concentric hypertrophy. In contrast to "physiological hypertrophy" as encountered, for instance, in athletes ("athletes' heart"), pathological forms of LVH are accompanied by interstitial fibrosis.

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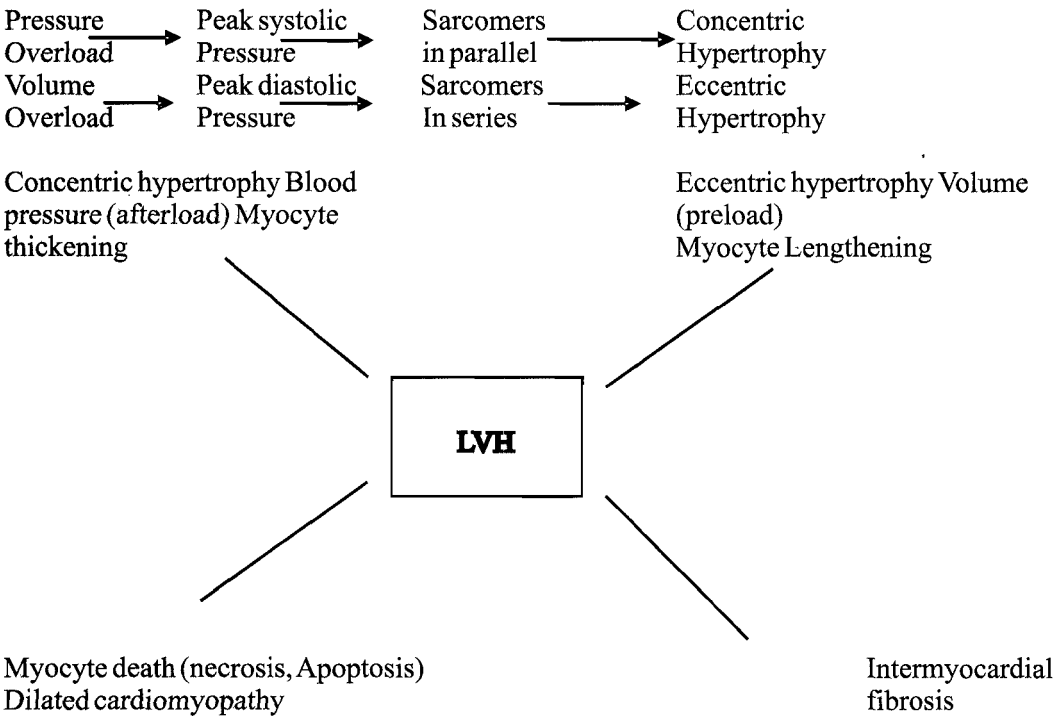
Fig. 1. **Schema of the genesis (top) and sequelae (bottom) of left ventricular hypertrophy in renal failure** [20]



Dilated cardiomyopathy and systolic pump failure supervene when the mass of working myocardium is reduced through single cell necrosis, through patchy necrosis [18] and through apoptosis. [19]. Apart from hypertension and hypervolaemia, which are undoubtedly the key factors in the genesis of LVH in renal failure, several other mechanisms come into play.[21] these comprise high cardiac output as a result of anaemia; age, disturbed elasticity of the central arteries with elevated impedance, and possible activation of local systems, such as the rennin or endothelin systems. Other putative risk factors may include aluminum overload, hyperparathyroidism, and some unknown uraemic toxins. The relative contribution of each of these risk factors in the pathogenesis of LVH has not been fully elucidated [4]. In their initial studies Harnet J. D.et al [22] were able to associated hypertension with severe LVH but a large proportion of the LVH seen could not be explained by elevations in blood pressure. They subsequently identified a cohort of dialysis patients without LVH and followed them prospectively for several years. Comparing those who subsequently developed LVH with those who did not, the two factors that independently predicated the development of LVH were age and systolic hypertension.[23]

However, it appears that factors other than hypertension are also important in the pathogenesis of LVH, since they observed substantial regression of LVH in 8 of 12 patients following renal transplantation despite no change in blood pressure levels.[24]

Many authors found a correlation between the haemoglobin (Hb) concentration and left ventricular mass (LVM) in dialysis patients [10]. On the other hand, partial reversal of anaemia through administration of recombinant human erthropoietin (rHuEpo) reduced LVM, but failed to normalize it [25,26,27]. Since haenogolobin was not normalized, it is uncertain whether complete normalization of Hb may cause a further decrease of LVM. By multivariate analysis, London et al further identified cardiac output as an important contributor to LVH [21].it may be increased as a function of hypervolaemia, anaemia and arterio-venous (A-V) fistula.

Recent studies have shown that experimental uraemia is associated with increased expression of rennin rnRNA (by insitu hybridization), endothelin 1 (by immunohistochemistry), and a variety of cytokine receptors like vascular epithelial growth factor (VEGF), platelet derived growth factor (PDGF) and transforming growth factor (TGF) [18].

It is of interest that endothelin receptor antagonists prevent interstitial fibrosis and the reduction in capillary length density, that is, capillary supply, in the heart of subtotally nephrectomized rats [20].

Role of faulty interation between heart and central arteries.

Abnormalities of the contour of the pulse in Bight's disease had been described as early as 1872 by Mohamed[28],and this has recently been analyzed with modern methodology by London et al [29,30,31]. Using Fourier analysis it can be calculated that the modulus of aortic impedance is increased. As a consequence, energy is lost in pressure and flow pulsations, and uncoupling between the left ventricle and the systemic circulation is noted, in striking analogy to the changes seen in aging.[32] The analogies in this respect have led to the idea that to some extent uraemia is a form of accelerated aging.[33] and there may be, at least in part, a common molecular basis through accumulation of advanced glycation end products and oxidation. The abnormality of the pulse contour with an exaggerated systolic peak and an exaggerated diastolic trough has quite unfavorable repercussions on left ventricular performance. On the other hand, peak systolic pressure and by amplification wall stress will be increased in the left ventricle, augmenting the stroke work index and contributing to left ventricular hypertrophy. At the same time, the decrease in diastolic aortic pressure is accelerated in the non-compliant stiff aorta of the uramic patient. Since coronary perfusion occurs only during diastole, low diastole perfusion pressure will compromise coronary blood flow in the very heart, the oxygen demand of which is high because of increased stroke work. The systolic overshoot and end diastolic undershoot of pressure is explained in part also by increased pulse wave velocity [31]. In uraemia, striking structural abnormalities of the central arteries are noted. In the model of subtotally nephrectomized male Sprague-dawley rats, as early as eight weeks after the operation, Amann et al found marked smooth muscle cell hyperplasia, smooth muscle cell hypertrophy, a decrease in elastic fiber content of the aortic wall.[34] .At the ultrastructural level this was accompanied by a striking derangement of the normally regular bedding of elastic fibers. The molecular mechanism associated with remodeling of aortic structure are currently under investigation .It is of interest that rennin rnRNA expression was found to be increased in the adventitial tissue of subtotally nephrectomized rats.[35].

Clinical Signification Of LVH:

LVH has a number of important clinical sequelae:

I. Impaired left ventricular compliance
II. Increased coronary resistance,'an
III. Arrhythmogenesis 18

Compliance of the left ventricle is impaired in LVH. [35] As a consequence, cardiac filling is more sensitive to changes in left ventricular filling pressure. On the other hand, hypervolaemia filling readily cause an increase in left atrial pressure and thus predispose the patient to pulmonary oedema. On the other hand, a decrease of left ventricular filling pressure, for example, during ultrafiltration, will predispose the patient to an abrupt left ventricular under filling, reduced ejected volume, tachycardia and hypotension (or else, if left ventricular under filling activates the Bezold Jarisch reflex, it will predispose the patient to vasovagal syncope and bradycardia). Ruff-Mann et al found a very significant relationship between disturbed left ventricular compliance, as assessed by transmitral inflow velocity (E/A ration) and the propensity to intradialytic hypotension. [36] This point is important because in a prospective study intradialytic hypotension was identified as a strong predictor of cardiac death [37]

Coronary vascular resistance is increased in LVH, even in the absence of coronary stenosis. Such as increase in the so-called "extravascular component" of coronary resistance may be responsible for angina pectoris, despite patent coronaries in patients with aortic stenosis. Similarly, 30 to 50% of dislysis patients with angina have patent coronaries upon coronary angiography, as documented by Roig et al [38] and Rostand, Kirk and Rutsky.[39] Finally, hypertrophied hearts are predisposed to develop arrhythmia [40,41] through various mechanisms. Disorganized architecture with abnormal myofibre and myofibrillar alignment provides a substrate for electrical instability and contributes to arrhythmia. Hypertrophy leads to relative reduction in coronary perfusion to myocytes with resultant tissue hypoxia, ischaemia and cell death. Tissue metabolites accumulates and stimulate electrical instability of myocytes with resultant development of arrhythmia.

Evaluation of Cardiac function in Renal Failure.

The following investigations are recommended for uraemic patients with cardiac problems: chest radiography, treadmill exercise electrocardiography (ECG), ambulatory ECG, exercise dipyridomole thallium scan, exercise radionuclide angiography, exercise dipyridamole echocardiography, cardiac

catheterization and coronary angiography. Mnay of these investigations are not done locally. However chest radiography, ECG, and echocardiography are available and are being used in evaluation of patients with cardiac problems. General and systemic examination of the patient is however crucial before other investigations. The chest radiograph is relatively inaccurate in detecting LVH. Electrocardiography is better with a specificity of 95% but the sensitivity is less than 60% 42. There is consensus that echocardiography is the gold standard for diagnosing LVH [8,43,44,45,46] and furthermore it is non-invasive-mode echocardiography (echo) is used to directly measure left ventricular wall thickness and internal dimensions. Calculation of LVH can be done using the Penn convention (which excluded endocardial echoes during measurement of wall thickness) or using the standard convention [47] Penn convention method is superior in detecting LVH [47]. Two-dimensional echocardiography can be used to assess global left ventricular functions.[48] It can also be used to determine LVH. This method has been shown to be superior to M-mode in determination of LVH.[49] The upper limit of normal for LVH is 125b/m^2 body surface ares.[50] Left ventricular mass index (LVMI) can be calculated by dividing the LVH by the body surface area. LVH is defined in absolute terms as LVMI>134B/M2 in men and >110g/m2 in women.51 Doppler echocardiography can detect left ventricular filling abnormalities which result from diastolic dysfunction, a possible consequence of chronic renal failure.[52] Left ventricular diastolic dysfunction may even precede the development of echocardiographically detectable LVH.[53]

Interventions to Reverse or prevent LVH:

In contrast to essential hypertension ,[54] there is little information on reversal of LVH in dialysis patients. It is plausible to assume that reducing blood pressure will ultimately result in reduction of LVH, or at least will prevent its increase. In dialysis patients canella et al observed reduction of LVH by echocardiography after 2 months of treatment including the ACE inhibitor Lisinopril.[55] It is uncertain whether this due to a specific effect of ACE inhibition or the non-specific effect of blood pressure lowering. Calcium channel blockers appear useful in reduction of LVH in non uraemic subjects. Angiotensin 11 antagonist valsartan was also showed to produce a significant regression of LVH in predominantly previously untreated patients with essential hypertension [56]. However the long-term benefit in terms of risk reduction has still to be evaluated in further trials. At this time however, there is insufficient data to recommend the use of a particular class of antihypertensive in the dialysis patient with LVH. However, ACE inhibitors, Angiotensin 11 antagonists and calcium channel blockers appear to be most promising agents. Reversal of hypervolaemia through reduction of dietary intake of sodium and ultrafiltration is important as it caused reduction of LVH in some dialysis patients even with no further use of antihypertensive agents [57]. Treatment of anemia may also lead to a reduction in LVH [25,27,58]. However, inadequate control of blood pressure in patients receiving Erthropoietin (EPO) may prevent the potentially beneficial effects of EPO on LV mass [59,60]. The issue arises as a whether the reversal of LVH is beneficial with respect to patient survival. While there is some information on this point in patients with essential hypertension, [54] controlled information is hardly available in dialyzed patients. Nevertheless, clinical common sense makes this assumption plausible, particularly in view of the fact that in observational studies LVH is an independent predictor of cardiac death.[25] Considering the findings of Stefanski et al, however, it would appear to be a rational strategy not to wait for LVH to occur before trying to reverse it.[16] It would be more logical to prevent its appearance by preemptive treatment.

CONCLUSION

Various types of cardiac involvement are potentially major complications in uraemic patients.[26,61-65] In patients with terminal renal failure, LVH is common .It is found in approximately 60-96% of patients stating renal replacement therapy .The main causes of LVH are increased preload from hypervolaemia and increased afterload from increased peripheral resistance, giving rise to a mixture of eccentric and concentric hypertrophy, but other factors high cardiac output from anaemia and arteriovenous (A-V) fistula, altered compliance of central arteries, age, aluminum overload, hyperparathyroidism, unknown uraemic toxins and activation of local system such as rennin and enothelin) also play a role .The clinical importance of LVH derives from the fact that LVH is a predictor of cardiac death in dialyzed patients independent of blood pressure.LVH is accompanied by microvacular disease and by marked interstitial fibrosis (more than seen in non-renal patients with similar degrees of hypertension)[20]. Recent findings suggest that LV remodeling starts early and is seen even in normotensive patients with glomerulonephritis when GFR is still normal. The strategies to reduce LVH include reduction of hypervolaemia, (near)

normalization of haemoglobin and lowering blood pressure, particularly by administration of ACE inhibitors ofAngiotensin antagonists.

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