Left ventricular hypertrophy in renal failure

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Left ventricular hypertrophy in renal failure. In patients with terminal renal failure, left ventricular hypertrophy (LVH) is extremely common. It is found in approximately 60 to 80% of patients starting renal replacement therapy. The main causes of LVH are increased preload from hypervolemia and increased afterload from increased peripheral resistance, giving rise to a mixture of excentric and concentric hypertrophy, but other factors (high cardiac output from anemia and arteriovenous (A-V) fistula, altered compliance of central arteries, and activation of local systems such as renin and endothelin) 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 microvascular disease and by marked interstitial fibrosis (more than seen in non-renal patients with similar degrees of hypertension). 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 hypervolemia, (near) normalization of hemoglobin and lowering of blood pressure, particularly by administration of angiotensin converting enzyme inhibitors.

EPIDEMIOLOGY OF LEFT VENTRICULAR HYPERTROPHY IN RENAL FAILURE

Left ventricular hypertrophy (LVH) is one of the major cardiovascular complications of end-stage renal failure. There is consensus that echocardiography is the gold standard for diagnosing LVH. A number of recent studies [1–4] document the high frequency of this condition in patients entering renal replacement therapy, that is, between 60% [2] and 80% [3]. Left ventricular mass increases progressively with duration of dialysis treatment even in normotensive patients [5]. Particularly in patients with incipient LVH, asymmetric septal hypertrophy (ASH) may be encountered [6]. The patient usually has a mixture of concentric and excentric hypertrophy, which reflects the variable contributions of increased preload and afterload [4].

Increased LVH persist even after renal transplantation [7], 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 end-stage renal failure. As shown in Table 1, increased septal thickness (mostly within the normal range) is found even in the earliest stages of glomerular disease, that is, in patients with IgA glomerulonephritis, non-nephrotic proteinuria and normal inulin clearance who have blood pressures within the range of normotension according to WHO criteria [8]. Even at this early stage of glomerulonephritis, cardiac remodeling is accompanied by impaired diastolic LV function as reflected by the ratio between early diastolic/late diastolic (atrial contraction) inflow velocity across the mitral valve.

CLINICAL SIGNIFICANCE OF LEFT VENTRICULAR HYPERTROPHY

In patients with essential hypertension it has been well established that LVH, independent of blood pressure, is predictive of ventricular arrhythmia [9] and cardiac death [10]. The same is true for uremic patients on maintenance hemodialysis. Silberberg et al noted that the actuarial five year survival rate is significantly higher (56 vs. 22%) in patients with normal LV mass, that is, <125 g/1.73 m², as opposed to patients with increased LV mass [11]. By multivariate analysis, LV mass emerged as a predictor that is independent of blood pressure.

LVH has a number of important clinical sequelae: (i) impaired LV compliance; (ii) increased coronary resistance; and (iii) arrhythmogenesis [12].

Left ventricular hypertrophy reduces compliance of the left ventricle

Compliance of the left ventricle is impaired in LVH. As a consequence of this action, cardiac filling is more sensitive to changes in LV filling pressure. On the one hand, hypervolemia will more readily cause an increase in left atrial pressure and thus predispose the patient to pulmonary edema. On the other hand, a decrease of LV filling pressure, for example, during ultrafiltration, will predispose the patient to an abrupt LV underfilling, reduced ejection volume, tachycardia and hypotension (or else, if LV underfilling activates the Bezold Jarisch reflex, it will predispose the patient to vagovasal syncope and bradycardia). Ruffmann et al found a very significant relationship between disturbed LV compliance, as assessed by transmirtal inflow

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velocity (E/A ratio) and the propensity to intradialytic hypotension [13]. This point is important because in a prospective study intradialytic hypotension was identified as a strong predictor of cardiac death [14].

Left ventricular hypertrophy also increases coronary vascular resistance even in the absence of coronary stenosis

Coronary vascular resistance is increased in LVH, even in the absence of coronary stenosis. Such an 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 dialysis patients with angina pectoris have patent coronaries upon coronarography, as documented by Roig et al [15] and Rostand, Kirk and Rutsky [16]. This tendency to underperfusion is aggravated by the fact that a mismatch between capillary supply and cardiomyocytes is found in the heart of uremic patients (Table 2) [17].

Hypertrophied hearts are predisposed to develop arrhythmia

Finally, hypertrophied hearts are predisposed to develop arrhythmia [18, 19] through various mechanisms.

PATHOMECHANISMS OF LEFT VENTRICULAR HYPERTROPHY IN RENAL FAILURE

In renal failure, both preload and afterload are increased because of hypervolemia and increased peripheral vascular resistance respectively. As illustrated schematically in Figure 1, an increase in preload, induced by hypervolemia, causes serial addition of sarcomers leading to lengthening of myofibers and concentric hypertrophy.

In contrast, increased afterload, such as, from increased peripheral resistance and increased impedance, causes 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 left ventricular hypertrophy are accompanied by interstitial fibrosis (Fig. 2). Dilated cardiomyopathy

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**Table 1.** Findings in normotensive (<140/90 mm Hg) patients with IgA glomerulonephritis with normal inulin clearance (C\textsubscript{In}) and non-nephrotic proteinuria [8]

<table>
<thead>
<tr>
<th></th>
<th>Casual BP</th>
<th>24 Hour BP</th>
<th>Septal thickness</th>
<th>Transmitral inflow E/A ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mm Hg</td>
<td>mm Hg</td>
<td>mm</td>
<td></td>
</tr>
<tr>
<td>IgA-GN (N = 20)</td>
<td>(95)</td>
<td>(93)</td>
<td>9.0</td>
<td>1.7</td>
</tr>
<tr>
<td>Matched controls (N = 20)</td>
<td>(90)</td>
<td>(81.5)</td>
<td>8.0</td>
<td>2.29</td>
</tr>
<tr>
<td>P</td>
<td>0.02</td>
<td>0.0005</td>
<td>0.001</td>
<td>0.0003</td>
</tr>
</tbody>
</table>

* Ratio of early diastolic inflow rate/inflow rate during atrial contraction

**Table 2.** Capillary density in the hearts of uremic patients [17]

<table>
<thead>
<tr>
<th></th>
<th>Length density of capillaries [L\textsubscript{V}] (mm/mm^3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls (N = 10)</td>
<td>2898 ± 456</td>
</tr>
<tr>
<td>Essential hypertension (N = 9)</td>
<td>1872 ± 243(^b)</td>
</tr>
<tr>
<td>Uremia (N = 9)</td>
<td>1483 ± 283(^bc)</td>
</tr>
</tbody>
</table>

\(^a\) Total length (mm) of all capillaries contained in one unit volume (mm\(^3\)) of heart tissue

\(^b\) P < 0.001 vs. control

\(^c\) P < 0.05 vs. essential hypertension

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**Fig. 1.** Schema of the genesis (top) and sequelae (bottom) of left ventricular hypertrophy in renal failure.
and systolic pump failure supervene when the mass of working myocardium is reduced through single cell necrosis, through patchy necrosis [12] and—as our experiments also suggest—through apoptosis [20].

PATHOMECHANISMS OF LEFT VENTRICULAR HYPERTROPHY IN RENAL FAILURE

Apart from hypervolemia and hypertension, which are undoubtedly the key factors in the genesis of LVH, several other mechanisms come into play [21]. These comprise high cardiac output as a result of anemia and the arteriovenous (A-V) fistula, disturbed elasticity of the central arteries with elevated impedance, and possibly activation of local systems, such as the renin or endothelin systems [12].

Many authors found a correlation between the hemoglobin (Hb) concentration and LV mass in dialyzed patients [2]. On the other hand, partial reversal of anemia through administration of recombinant human erythropoietin (rHuEPO) reduced left ventricular mass (LVM), but failed to normalize it [11, 22, 23]. Since Hb was not normalized, it is uncertain whether complete normalization of Hb may cause a further decrease of LVM; this issue is currently the object of several controlled studies [24].

By multivariate analysis, London et al further identified

Fig. 2. Heart of a patient with chronic renal failure. Note hypertrophy of cardiomyocytes and diffuse interstitial fibrosis (HE stain, paraffin section; magnification 1:250).

Fig. 3. Expression of endothelin 1 in the myocardial interstitium of a patient with renal failure of 20 years duration.
(Immunohistochemistry, paraffin section; magnification 1:150).
cardiac output as an important contributor to LVH [21]. It may be increased as a function of hypervolemia, anemia and A-V fistula.

Abnormal interaction (coupling) between the heart and central arteries will be discussed below [25, 26].

Recent studies in our laboratory showed that experimental uremia is associated with increased expression of renin mRNA (by in situ hybridization), endothelin-1 (by immunohistochemistry) [12], and a variety of cytokines and cytokine receptors as summarized in Table 3 [27]. It is of interest that endothelin receptor antagonists prevent interstitial fibrosis (Fig. 3) and the reduction in capillary length density, that is, capillary supply, in the heart of subtotally nephrectomized rats (Fig. 4).

ROLE OF A FAULTY INTERACTION BETWEEN HEART AND CENTRAL ARTERIES

Abnormalities of the contour of the pulse in Bright’s disease had been described as early as 1872 by Mahomed [28], and this has recently been analyzed with modern methodology by London et al [29–31]. 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, 33]. The analogies in this respect have led to the idea that to some extent uremia is a form of accelerated aging [26, 33], and there may be, at least in part, a common molecular basis through cumulation 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 LV performance. On the one hand, peak systolic pressure and by implication wall stress will be increased in the LV, augmenting the stroke work index and contributing to LV hypertrophy. At the same time, the decrease in diastolic aortic pressure is accelerated in the non-compliant stiff aorta of the uremic patient. Since coronary perfusion occurs only during diastole, low diastolic 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]. Because travel time is reduced, the wave that has been reflected in the periphery will arrive in systole (instead of in diastole). As a consequence, LV stroke work is further augmented.

In uremia, 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 and a substantial increase in collagen fiber content of the aortic wall (Table 4) [34]. At the ultrastructural level this was accompanied by a striking derangement of the normally regular bedding of elastic

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### Table 3. Immunohistological findings in the hearts of subtotally nephrectomized rats [27]

<table>
<thead>
<tr>
<th></th>
<th>Interstitium</th>
<th>Arterioles</th>
</tr>
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<tbody>
<tr>
<td>VEGF</td>
<td>ND</td>
<td>+</td>
</tr>
<tr>
<td>β1 integrin</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>PDGF-AB</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>PDGF-RA</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>TGF-β1</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>TGF-β2,3</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>TGFβRI</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

Abbreviations are: VEGF, vascular epithelial growth factor; PDGF, platelet-derived growth factor; TGF, transforming growth factor; ND, not detectible. Symbols are: (–) no difference subtotally nephrectomized vs. control; (+) P < 0.05 subtotally nephrectomized > control; (++) P < 0.01 subtotally nephrectomized > control.

### Table 4. Aortic cell hypertrophy and hyperplasia and deranged wall matrix composition in subtotally nephrectomized rats [34]

<table>
<thead>
<tr>
<th></th>
<th>Sham operated (N = 8)</th>
<th>Subtotal Nephrectomy (N = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP</td>
<td>117 ± 9</td>
<td>119 ± 9</td>
</tr>
<tr>
<td>mm Hg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aortic media cells per μm</td>
<td>281 ± 60</td>
<td>470 ± 110*</td>
</tr>
<tr>
<td>aortic segment (x10³)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Volume of aortic media</td>
<td>85.5 ± 14.7</td>
<td>97.7 ± 5.8*</td>
</tr>
<tr>
<td>smooth muscle cells μ³</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elastic fiber volume</td>
<td>63.9 ± 3.9</td>
<td>52.3 ± 2.5*</td>
</tr>
<tr>
<td>density [Vv] %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Collagen fiber volume</td>
<td>31.9 ± 4.0</td>
<td>41.4 ± 2.3*</td>
</tr>
<tr>
<td>density [Vv] %</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*P < 0.05 vs. sham operated control
fibers (Fig. 5). The molecular mechanisms associated with remodeling of aortic structure are currently under investigation. It is of interest that renin mRNA expression was found to be increased in the adventitial tissue (unpublished studies) of subtotally nephrectomized rats.

INTERVENTIONS TO REVERSE OR PREVENT LEFT VENTRICULAR HYPERTROPHY

In contrast to essential hypertension [35], 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 24 months of treatment including the ACE inhibitor lisinopril [36]. It is uncertain whether this is due to a specific effect of ACE inhibition or the nonspecific effect of blood pressure lowering. The importance of reversing increased preload is illustrated by the observation of Özkahya et al, who showed that reversal of hypervolemia through reduced dietary intake of sodium and ultrafiltration caused a reduction of LVH in dialysis patients even with no further use of antihypertensive agents [37].

The issue arises as to whether the reversal of LVH is beneficial with respect to patient survival. While there is a wealth of information on this point in patients with essential hypertension [35], no controlled information is 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 [11].

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 [8]. It would be more logical to prevent its appearance by preemptive treatment.

DIALYSIS PATIENTS WITH LEFT VENTRICULAR HYPERTROPHY

As shown in Table 5, some aspects of hemodialysis may cause adverse effects in the patient with LVH [12].
On the one hand, ultrafiltration (and if acetate is used, vasodilation) will reduce LV filling pressures, which reduces the stroke volume and thus predispose the patient to intradialytic hypotension.

Second, sympathetic activation as a consequence of ultrafiltration will reduce the duration of diastole. Since coronary perfusion occurs exclusively during diastole, shortening of the diastole in patients with tachycardia will compromise coronary perfusion and expose the patient to the risk of cardiac ischemia.

Furthermore, compensatory sympathetic activation in response to ultrafiltration is definitely undesirable. In patients with cardiac failure, catecholamines are a strong predictor of cardiac death [38]. Indirect evidence also points to a potentially adverse role of sympathetic overactivity in dialed patients, where sympathetic tone is high to begin with as a consequence of stimulatory afferent signals emerging from the kidney [39, 40]. In a prospective trial in dialed diabetic patients, it was found that beta blockers were less frequently used in patients who subsequently died from cardiac causes than in patients who survived [14]. Based on these and other observations, Zuanetti et al recently castigated the infrequent use of beta blockers in dialed diabetic (and non-diabetic) patients [41].

Finally, with the use of conventional dialysate calcium concentrations (7 mg/dl) the plasma ionized calcium concentration increases, thus increasing inotropy as documented in controlled studies [42]. This effect is clearly unwanted, because it increases myocardial oxygen demand.

What consequences can be drawn from the above considerations?

As recently summarized by Wizemann, in the patient with cardiac failure (and with LVH), the dialysis procedure should be adapted in such a fashion that slow rates of ultrafiltration are selected. This implies longer or more frequent dialysis sessions or both, and also that anemia is corrected, tachycardia is avoided by slow ultrafiltration or administration of beta blockers, and a dialysate calcium concentration is selected that avoids an increase in cardiac inotropy during dialysis sessions [43].

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36. Özkanay M, Ok E, Cirit M, Aydm S, Akçiçek F, Mees EJD: Regression of left ventricular hypertrophy in hemodialysis patients by volume control without antihypertensive drugs. *Nephrol Dial Transplant* (in press)


