therapy intended to be performed by the patient himself, would place too much of a responsible burden on these particular patients.

Our experience has shown that the establishment of a multidisciplinary team composed of psychiatrist, nephrological personnel and social workers enables the extension of chronic dialytic therapy to patients with major psychiatric illnesses. Obviously, every such patient will have to be thoroughly evaluated and his suitability for chronic dialysis individually assessed. Although this endeavour undoubtedly demands the investment of considerable time and resources by all involved, the satisfaction gained upon successful treatment is well worth the effort. It is time that both the psychiatric and nephrological communities openly address this issue.

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References


The role of non-haemodynamic factors of the genesis of LVH

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“Things are never so simple as they look”

Left ventricular hypertrophy (LVH) is a common finding in arterial hypertension. In mild hypertension, the prevalence of LVH is 20% and in severe hypertension 50% [1]. Evidence of LVH either by electrocardiography or echocardiography clearly increases the risk for myocardial infarction, cardiac sudden death, congestive heart failure and stroke. Most intriguingly, the cumulative incidence of cardiovascular events increases progressively with increasing left ventricular mass, without evidence of any threshold [2]. In other words, hypertensive patients with left ventricular mass in the upper normal range already have increased risk for cardiovascular events [2].

Although the pathogenesis of cardiac hypertrophy in hypertension is not yet completely understood, several haemodynamic and non-haemodynamic factors are of pathogenetic relevance [3]. The simplistic view that only blood pressure is the culprit of left ventricular hypertrophy has to be revised, since there are three lines of evidence that stress the pathogenetic importance of non-haemodynamic factors. First, even highly sophisticated measurements of blood pressure that claim to precisely determine the haemodynamic load imposed on the left ventricular wall cannot fully account for the variance in left ventricular mass in clinical trials [4]. LVH is more closely related to 24-hour-ambulatory blood pressure than casual blood pressure, but nevertheless leaves more than 50% of the variance of left ventricular mass unexplained [5].

Second, myocardial hypertrophy develops in the left and right ventricle. In hypertensive patients, an increase of right ventricular wall thickness has been found and

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a close relationship between left and right ventricular mass has been most recently reported [6]. The presence of right ventricular hypertrophy, although mild, underscores the effects of non-haemodynamic factors, in particular those that stimulate myocardial growth. Furthermore, the relationship that exists between haematocrit and left ventricular mass been also now found for right ventricular mass [6].

Third, the effectiveness of antihypertensive drugs to reduce LVH is different. In a recent meta-analysis ACE-inhibitors, angiotensin receptor blockers and calcium channel blockers have been found to be more effective in reducing LVH than betablockers, with diuretics in the intermediate range [7]. Consistently, in a large-scale prospective trial with more than 9000 hypertensive patients, treatment with angiotensin receptor blockers was more effective than the one with betablockers and this discrepancy remained evident throughout the whole study duration of more than 5 years, indicating that blood pressure-independent mechanisms are actively involved in the process of development and regression of LVH [8].

Several non-haemodynamic factors have been discussed to play a role in the process of myocardial hypertrophy. Amongst others, these include age, sex, race, genetic factors, interaction between vascular stiffness and the left ventricle, obesity, insulin resistance and AGE-products [3]. Neuroendocrine stimulation modifies cardiac remodelling at the very early stage of hypertensive heart disease. Measurement of sympathetic nervous activity to the heart by noradrenaline spillover methodology revealed that the sympathetic drive to the heart was significantly increased in hypertensive patients with LVH compared to those without LVH at similar blood pressure levels [9]. These findings are in accordance with previous data demonstrating that increased peripheral muscle sympathetic nerve activity as measured by microneurography is increased in hypertensive patients with LVH [9,10]. These recent data from human studies support previous experimental and early clinical data in humans that sympathetic augmentation contributes substantially to the development of LVH in hypertensive patients [9].

The renin angiotensin aldosterone system (RAAS) emerged as an additional pivotal modulator of LVH. The activity of the RAAS significantly modifies the development and regression of LVH in essential and secondary arterial hypertension. Stimulation of the angiotensin type 1 receptor exerts growth stimulating effects as indicated by the association between angiotensin II levels and increased left ventricular mass which appeared to be independent of ambulatory blood pressure, body mass index, sodium excretion, and other clinical factors [11]. Stimulation of the angiotensin type 2 receptor also exerts modulating effects on the left ventricle, although data in humans are rare due to the fact that no angiotensin type 2 receptor agonist or antagonist is available for human use. However, we can demonstrate that genetic variance in the angiotensin type 2 receptor coding gene profoundly influences left ventricular wall thickness in hypertensive patients thereby pointing to a modifying role of angiotensin type 2 receptor stimulation [12]. Clinically more important are the observations that inadequate suppression of angiotensin II and hyperresponsiveness to angiotensin II are related to cardiac structural adaptation in hypertensive subjects [13]. Similarly, inadequate suppression of the renin angiotensin system in relation to the dietary salt intake is related to exaggerated LVH [14]. The latter supports the notion that salt restriction and/or blockade of the renin angiotensin system counteracts growth-stimulating effects of angiotensin II.

Epidemiologic data clearly indicate that dietary intake modifies the process of LVH in hypertensive subjects [15]. This has been reported irrespective of whether dietary salt intake has been assessed by measuring 24 h urinary sodium excretion in clinical stable conditions or by directly measuring the salt ingested with food [16]. Of note, this relationship has been found to be independent of blood pressure even if assessed over 24 h, body weight and other clinical determinants of LVH according to several clinical trials in untreated hypertensive patients and epidemiologic studies (i.e. Framingham Heart Study) [16,17]. In experimental settings, the underlying mechanisms have been investigated [18]. In normotensive and hypertensive rats, high salt intake not only induces myocardial hypertrophy but also myocardial fibrosis (most likely related to increased cardiac aldosterone synthesis). Although high salt intake decreased plasma renin activity and lowered plasma aldosterone concentration in the systemic circulation, angiotensin type 1 receptor mRNA level, aldosterone synthase mRNA level, aldosterone synthase activity, and production of aldosterone have been found to be increased [19]. Thus, high salt intake may lead to increased cardiac aldosterone production thereby provoking the hypertrophic and fibrotic response to high salt intake. Moreover, most recent trials have indicated that increases in intracellular sodium leads to an upregulation of growth-stimulating genes thereby directly inducing growth-stimulating effects. Thus, in clinical terms, in addition to the increase in afterload and preload, direct effects of dietary salt intake on protein syntheses of myocardial cells, upregulation of cardiac aldosterone synthesis in the myocardium and upregulation of angiotensin type 1 receptors in myocardial cells explain the deleterious effects of high dietary salt intake in hypertensive subjects.

In conclusion, both haemodynamic and non-haemodynamic factors are of pathogenetic relevance for the development of LVH. Most evidence stems from experimental data but has recently been supported by several clinical trials. Increased sympathetic drive to the heart, inadequate downregulation of the renin angiotensin system in the presence of high dietary salt intake, and also high salt intake per se substantially modulate the development of LVH. Nevertheless, it should not be overlooked that the level of blood pressure is the predominant determinant of LVH.
In the VALUE-trial, new development of LVH (defined by the Cornell-voltage QRS product index) occurred in 477 subjects [20]. These patients with new development of LVH are clinically characterized by older age, female gender, smaller height, history of coronary heart disease, type 2 diabetes and blood pressure control (although those patients with new development of LVH had a higher blood pressure of only 3–4 mmHg systolic) [20]. Since several prospective trials have documented that changes in LVH, in particular reduction in left ventricular mass, are associated with a lower rate of cardiovascular events, left ventricular hypertrophy in arterial hypertension needs to be treated aggressively [21]. In addition to blood pressure control, non-haemodynamic measures such as weight reduction, restriction of dietary salt intake, and treatment with antihypertensive agents that block the renin angiotensin aldosterone system are of additional beneficial value.

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