Hypertensive heart disease

A complex syndrome or a hypertensive ‘cardiomyopathy’?

G. Y. H. Lip, D. C. Felmeden, F. L. Li-Saw-Hee and D. G. Beevers

University Department of Medicine, City Hospital, Birmingham, U.K.

Introduction

Hypertension is a major risk factor for cardiovascular morbidity and mortality. The presence of hypertension more than doubles the risk for coronary heart disease, including acute myocardial infarction and sudden death, and more than triples the risk of congestive heart failure as well as strokes[1]. Patients with high blood pressure frequently have abnormalities of cardiac structure or function, including left ventricular hypertrophy, systolic and diastolic dysfunction and in extreme cases, overt heart failure. There may also be concomitant or related coronary heart disease and an increased risk of arrhythmias and sudden death.

Many of these factors are inter-related and their individual contributions are difficult to quantify. There is, however, some debate as to whether ‘hypertensive cardiomyopathy’ exists as a separate entity specific to hypertension. The term ‘cardiomyopathy’, however, would normally be reserved for intrinsic myocardial disease, where underlying causes such as hypertension and coronary artery disease have been excluded. Therefore, the preferred term should perhaps be ‘hypertensive heart disease’, and given the many mechanisms by which the heart may be abnormal in hypertension, the term ‘hypertensive heart disease’ is probably not so controversial.

The purpose of this review is to describe the various mechanisms whereby the heart is abnormal in hypertension and to discuss the possibility of a discrete entity called hypertensive cardiomyopathy.

Left ventricular hypertrophy

Left ventricular hypertrophy has long been recognised as an important clinical prognostic entity. Epidemiological research has shown that left ventricular hypertrophy itself is associated with increased mortality and morbidity for myocardial infarction, heart failure and stroke. There is a continuous graded relationship between left ventricular mass and the development of cardiovascular disease with no distinct threshold separating the postulated ‘compensatory’ from ‘pathological’ left ventricular hypertrophy[2].

In normotensive adults, for example, left ventricular mass is directly related to the risk of developing later hypertension[3-5], raising the possibility that left ventricular hypertrophy may also be involved in the development of hypertension in the first place, as well as being a consequence of raised systemic pressure. There may also be a continuous graded relationship between left ventricular mass and blood pressure, with no critical threshold of blood pressure, beyond which left ventricular hypertrophy develops[2-4]. Left ventricular hypertrophy also has been linked to the development of atrial fibrillation, ventricular arrhythmias and sudden cardiac death[5-7]. Left ventricular hypertrophy is also associated with a three- to four-fold increase in the risk of stroke, a two- to three-fold increase in coronary heart disease (CHD) and a three-fold increase in peripheral arterial disease. However, the pathophysiological basis linking left ventricular hypertrophy with these adverse cardiovascular events has not been fully elucidated.

In several epidemiological studies, left ventricular hypertrophy is an independent risk factor for cardiovascular morbidity and mortality[2-8]. The gradient of risk factor, adjusted for age, of cardiovascular disease in men was 1.49 for each 50 g.m⁻² (corrected for height) and in women, 1.57. This graded correlation between echocardiographically determined left ventricular mass and the development of cardiovascular disease appears to be without a critical mass, separating the sometimes postulated ‘compensatory’ from ‘pathological’ hypertrophy[2]. Although a much less sensitive measure for the

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Correspondence: Dr G. Y. H. Lip, University Department of Medicine, City Hospital, Birmingham B18 7QH, U.K.
presence of left ventricular hypertrophy, the ECG is also indicative of increased cardiovascular morbidity and mortality. In the Framingham Study, for example, ECG–left ventricular hypertrophy increased the risk of cardiovascular disease from three- to seven-fold depending on age and sex of the patient[8].

**Types of left ventricular hypertrophy**

There are two common types of left ventricular hypertrophy: concentric and eccentric. The thickening of the left ventricular wall relative to the internal cavity is referred to as ‘concentric’ left ventricular hypertrophy. Less common is the disproportionate (relative to the posterior wall) thickening of the intraventricular septum, referred to as asymmetrical or eccentric left ventricular hypertrophy. These different patterns of left ventricular hypertrophy have different features, haemodynamic relations, and prognostic implications[10]. For example, concentric left ventricular hypertrophy is normally associated with moderate to severe hypertension and is more common in the middle aged and elderly than in young patients. Cardiac output is normal or low in concentric left ventricular hypertrophy, but is high in eccentric left ventricular hypertrophy. However, some investigators have reported that these geometric patterns do not add much additional prognostic information beyond that offered by the simple degree of left ventricular hypertrophy and traditional cardiovascular risk factors[8,11].

**The relationship of left ventricular hypertrophy to blood pressure**

In patients with normal blood pressure (systolic blood pressure <140 mmHg) the risk of having left ventricular hypertrophy is 1.3%–1.6%, whilst with mild hypertension (systolic blood pressure 140 mmHg–160 mmHg) the risk is 2.7%–5.6%, and with definite hypertension (systolic blood pressure >180 mmHg) the risk is 11.8%–18.8%[12]. In one series, the prevalence of left ventricular hypertrophy using the Sokolow–Lyon ECG criteria in malignant phase hypertension, which is the most severe form of hypertension, is 75.6%–82.6%[13].

In the Framingham study, after adjusting for age, diastolic blood pressure and body mass index, isolated systolic hypertension was found to be associated with a 2.6%– to 5.9-fold risk of developing echocardiographic evidence of left ventricular hypertrophy. Also increased wall thickness tended to predominate in women, whilst left ventricular dilatation predominates in men[14].

However, the correlation between blood pressures measured in the clinical environment and left ventricular mass is poor[15]. By contrast, 24 h ambulatory blood pressure monitoring provides a close correlation between average daytime arterial blood pressure and left ventricular mass[16,17]. In addition, there is normally a diurnal variation in blood pressure, with mean daytime blood pressures being at least 10% higher than mean nocturnal blood pressure (‘dipping’). ‘Non-dipping’ is arbitrarily defined as a nocturnal fall in blood pressure of less than 10% compared to mean daytime readings[19]. Non-dippers are considered to have a greater 24 h blood pressure ‘load’ when compared to dippers, as well as greater end-diastolic volumes[19] and, in some studies, more left ventricular hypertrophy[8]. However, one meta-analysis of 19 studies published before 1994 found that the left ventricular mass was only weakly associated with the day–night blood pressure difference[21]. It has also been suggested that nocturnal falls in pressure could induce myocardial ischaemia in hypertensives with left ventricular hypertrophy and impaired coronary vasodilator reserve, perhaps contributing to the so-called ‘J curve’, which has been previously observed in some retrospective studies where diastolic blood pressure was lowered below 85 mmHg, resulting in increased coronary events[22]. Kario et al.[23] also found that more magnetic resonance imaging scan evidence of silent cerebrovascular disease was present in extreme ‘dippers’, whose fall in nocturnal systolic pressure was greater than 20%. By contrast, the recent large prospective Hypertension Optimal Treatment (HOT) trial showed no evidence of a J curve in the short-term amongst hypertensive patients including those with previous coronary heart disease[24].

**Other variables associated with left ventricular hypertrophy**

The prevalence of left ventricular hypertrophy has been shown to increase progressively with age[25] and varies with ethnic group, sex and obesity. African origin patients have a larger left ventricular mass than comparable white patients. In addition, left ventricular hypertrophy may also precede the development of hypertension[26]. In general, women have a lower prevalence of left ventricular hypertrophy for a given level of blood pressure than men, even after their left ventricular mass has been corrected for body surface area or body weight. However, this gender difference only appears to hold true for pre-menopausal women, raising the possibility of a preventive role of oestrogens in the pathogenesis of left ventricular hypertrophy[27].

In left ventricular hypertrophy, increased left ventricular wall thickness causes reduced ventricular compliance (that is, the ventricle is ‘stiffer’) together with the degree of diastolic dysfunction. This also increases left atrial filling pressure, resulting in atrial dilatation, which can be detected by a biphasic P-wave in lead V1 on the ECG as well as on the echocardiogram[28]. In the absence of mitral valve disease and atrial fibrillation, the left atrial size reflects the duration of increased atrial pressures as a consequence of left ventricular diastolic dysfunction[29]. Changes in left atrial function and size also mirror the regression of left ventricular hypertrophy in response to antihypertensive treatment[30].
Diagnosis and definitions of left ventricular hypertrophy

Left ventricular hypertrophy is defined by an increase in left ventricular mass, quantified by measurements of post-mortem left ventricular weight, by ECG criteria, by echocardiography or more recently, by magnetic resonance imaging.

Postmortem

The classic studies from decades ago by Devereux and Reichek[31] and Jones[32] reported that the normal mean total ventricular weight is below 250 g: the left ventricle and the interventricular septum usually weigh less than 190 g; and the right ventricular free wall is below 65 g. Left ventricular hypertrophy exists when the left ventricular plus septal weight exceeds 225 g[31]. In hypertensive heart disease, in the absence of symptomatic heart failure, overall heart weight is often greater than 350 g, and in the presence of heart failure, values in excess of 400 g have been reported[32]. However, this may be a simplistic viewpoint as individual values for ‘normal’ and ‘abnormal’ are likely to vary by age, sex and size of the individual.

Echocardiography

For echocardiographic assessment of left ventricular hypertrophy several upper limits of normal for left ventricular mass have been suggested. Epidemiological data from the mainly white population of the Framingham study defined left ventricular hypertrophy as left ventricular mass in relation to total body surface area >131 g · m⁻² for men and >100 g · m⁻² for women[33]. In a racially mixed normotensive population, 134 g · m⁻² for men and 110 g · m⁻² for women were identified as upper limits of normal[34]. Another way of defining left ventricular hypertrophy with echocardiography is by indexation of the left ventricular mass for the power of its relationship to body height. Thus, the cut-off point for left ventricular hypertrophy normalized to height was reported by de Simone et al.[35] as 126 g · m⁻¹ and 50 g · m⁻² for men and 105 g · m⁻¹ and 47 g · m⁻² for women. Despite differing criteria, the presence of left ventricular hypertrophy still remains a powerful predictor of mortality and morbidity in hypertension[36].

Magnetic resonance imaging

A recently validated method of assessing the left ventricular mass is by magnetic resonance imaging, which shows a close correlation between estimated left ventricular mass compared to echocardiography[37] and post-mortem left ventricular weights[38]. Several limitations, such as the long acquisition time, expense, availability, and unsuitability for critically ill patients, restrict the use of magnetic resonance imaging in some patients.

The ECG

Left ventricular hypertrophy may also be assessed by analysing the electrocardiogram by various means. Several methods have been evaluated[39]: (i) the Romhilt–Estes Point-Score System of ≥4 has a sensitivity of 12% and a specificity of 87%; (ii) the more commonly used Sokolow–Lyon Index (SV₁ + SV₅ or V₆ ≥ 35 mV) has a sensitivity of 22% and a specificity of 79%, and a Sokolow–Lyon Index (RaVL ≥ 1·1 mV) has a sensitivity of 18% and a specificity of 92%; (iii) the Cornell system has a sensitivity of 31% and a specificity of 87%; and (iv) the Rodrigez Padial system has a sensitivity of 82% and a specificity of 84%[39].

Thus most forms of interpreting the electrocardiogram with regards to left ventricular hypertrophy are not useful as a screening tool. This can be marginally improved by multiplying the QRS voltage by the QRS duration, thus increasing the sensitivity to 96% and the specificity to about 50%[40]. Crudely speaking, the features of left ventricular hypertrophy on the ECG normally mean that true left ventricular hypertrophy is present, but its absence does not mean that left ventricular hypertrophy is absent — indeed, ECG–left ventricular hypertrophy is clearly an insensitive measure of left ventricular hypertrophy, but when present is a powerful predictor of cardiovascular events[41].

Left ventricular ‘strain’

The cardiovascular risk associated with left ventricular hypertrophy by voltage criteria is further increased when associated with ST and T wave changes (the so-called ‘strain’ pattern). For example in the age group of 65–94 years, the risk of cardiovascular disease rose from 7·4% in hypertensives without electrocardiogram abnormalities to 30·2% with ECG changes of left ventricular hypertrophy and repolarization abnormalities[41]. This strain pattern is found in approximately two-thirds of patients with normal coronary arteries and left ventricular hypertrophy on the ECG. Non-specific ST abnormalities, which may be due to relative ischaemia, are indistinguishable from those of coronary artery disease, thus potentially reducing the accuracy for the diagnosis of ischaemia on resting or exercise ECG, if pre-existing strain is already present[42].

Histopathology of left ventricular hypertrophy

One area of recent interest has been the study of the many stimuli for the ultra-structural growth of the

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myocardium\textsuperscript{[43]}, with particular reference to myocyte and fibroblast proliferation\textsuperscript{[44]}. Factors such as angiotensin II, endothelin-1 and aldosterone all have effects on fibroblast proliferation. Growth hormone, thyroxin, volume and pressure loading are other factors contributing to myocyte proliferation\textsuperscript{[45]}. The relative increase in fibroblastic activity that occurs in hypertensive heart disease may be an important factor in pathological rather than physiological left ventricular hypertrophy.

Cardiac myocytes of the left ventricle are enlarged in hypertensive heart disease\textsuperscript{[46]} and fibrosis is another feature of the adverse structural remodelling found in the myocardium in hypertensive heart disease\textsuperscript{[47]}. Coronary resistance vessels are also remodelled in hypertensive heart disease, with perivascular fibrosis of intramyocardial coronary arteries and arterioles, together with thickening of their media\textsuperscript{[48]}. Furthermore, fibrosis and myocyte changes are a feature of heart failure secondary to causes other than hypertension, and treatments such as the ACE inhibitors can beneficially affect these abnormalities\textsuperscript{[49]}.

Besides contractile disturbance of cardiomyocytes and interstitial and perivascular fibrosis, cardiomyocyte loss is now being considered as one of the determinants of the maladaptive process implicated in the transition from compensated to decompensated left ventricular hypertrophy. Involvement of apoptosis in the development of left ventricular hypertrophy was first demonstrated in rats during aortic banding induced cardiac hypertrophy (even without failure)\textsuperscript{[50]}. Recent reports have also shown an increase in apoptotic myocytes in failing hearts, although this did not indicate whether this was a cause or consequence of heart failure\textsuperscript{[51,52]}. The increased numbers of apoptotic cells present in the failing hearts of spontaneous hypertensive rats as compared to non-failing spontaneous hypertensive rats suggests that apoptosis might be the mechanism involved in the reduction of myocyte mass that accompanies the transition from compensated left ventricular hypertrophy to cardiac failure\textsuperscript{[53]}

These observations need to be translated into the clinical scenario as further work is clearly needed to assess the contribution of ultra-structural changes to the morbidity and mortality associated with hypertensive heart disease and whether they are an independent feature of hypertensive heart disease rather than simply being features of associated underlying disease.

**Does the left ventricular hypertrophy of hypertension differ from left ventricular hypertrophy of aortic stenosis?**

The structural changes seen in the myocardium associated with left ventricular hypertrophy, such as increased interstitial replacement and perivascular fibrosis, and myocardial scarring can be caused by both hypertension and aortic valve disease. However, there are reasons to believe that the left ventricular hypertrophy associated with hypertension may differ from that seen in association with aortic valve stenosis, with subtle morphological and histological differences\textsuperscript{[54]}

In cases of left ventricular hypertrophy secondary to aortic valve stenosis, the abnormalities of diastolic function normalize over time, and a reduction of fibrous tissue can be observed following aortic valve replacement\textsuperscript{[54]}. However, the left ventricular hypertrophy of hypertension is not only related to the amount of afterload, but also to neurohormonal factors, particularly the local and circulating renin–angiotensin–aldosterone systems\textsuperscript{[55]}. Furthermore, aldosterone is one of many potent stimulators of myocardial fibrosis. Friedrich et al\textsuperscript{[56]} infused the angiotensin-converting enzyme inhibitor, enalaprilat, into the left coronary artery and found an improvement in left ventricular diastolic distensibility and regional relaxation and filling in patients with left ventricular hypertrophy due to aortic valve stenosis. Thus, the cardiac renin–angiotensin system is also involved in patients with concentric pressure overload hypertrophy, such as aortic valve stenosis. At the cellular level, the intraventricular pressure overload of hypertension as well as aortic stenosis results in myocytic hypertrophy and increased perimyocytic fibrosis. However, intramyocardial arteriole wall-thickening and enhanced perivascular fibrosis are distinctive features of hypertension, but are not seen in aortic stenosis\textsuperscript{[49]}. These observations are suggestive of distinct, but important differences between left ventricular hypertrophy secondary to hypertension and aortic stenosis.

**Pathophysiology of left ventricular hypertrophy**

The progression from a structurally normal heart to left ventricular hypertrophy is not solely a consequence of increased afterload imposed by hypertension, with an increased total peripheral resistance. Many mechanisms are now known to be involved in the growth regulation of the heart, including neurogenic, humoral, autocrine, paracrine and possibly endocrine factors, all of which have important therapeutic implications.

**Pressure overload**

Both aortic stenosis and arterial hypertension lead to pressure overload of the left ventricle. Therefore if pressure overload was to be the sole stimulus for left ventricular hypertrophy the results should be identical. Nonetheless, different models inducing left ventricular hypertrophy showed heterogeneity of myocardial remodelling with varying quantity and distribution of fibrillar collagen, in addition to varying degrees of intramyocardial arterial adaptation\textsuperscript{[57,58]}. The intraventricular pressure overload of hypertension as well
as aortic stenosis results in myocytic hypertrophy and increased perimyocytic fibrosis. However, intramyocardial arteriole wall-thickening and enhanced perivascular fibrosis are distinctive features of hypertension that are not seen in aortic stenosis[48].

**Renin–angiotensin–aldosterone system**

Several growth factors have been implicated in initiating and maintaining myocardial hypertrophy[59,60]. In particular, the renin–angiotensin–aldosterone system is likely to have an important role in hypertensive heart disease, and both angiotensin II and aldosterone are known to cause myocardial fibrosis[55].

Hypertension-induced left ventricular hypertrophy results in increased myocardial fibrosis, but chronic pressure overload per se does not cause myocardial fibrosis, as demonstrated with experiments of infrarenal aortic banding causing left ventricular hypertrophy without fibrosis[58]. Only after activation of the renin–angiotensin–aldosterone by suprarenal banding would fibrosis be found in the hypertrophied, hypertrophied left ventricle. Similar changes can be observed after simulated renin–angiotensin–aldosterone activation with intravenous administration of angiotensin II or aldosterone, suggesting an important role of the renin–angiotensin–aldosterone in the development of left ventricular hypertrophy and fibrosis[61]. Furthermore, myocardial fibrosis is associated with increased expression of angiotensin converting enzyme and bradykinin receptor binding at sites of repair[62]. It is also recognised that there are both circulating and tissue renin–angiotensin systems. Tissue renin–angiotensin–aldosterone components are found in the lungs, myocardium, brain, kidneys, and testes, and in or around blood vessels with possible vasoconstrictive effects[63].

An important role for the renin–angiotensin system is suggested by the use of the angiotensin-converting enzyme (ACE) inhibitors, and more recently the angiotensin II receptor antagonists in causing regression of hypertensive left ventricular hypertrophy[64,65] and in preventing remodelling and improving prognosis after myocardial infarction[66,67]. Furthermore, there is a close correlation between circulating renin–angiotensin levels and left ventricular mass[68,69].

The renin–angiotensin–aldosterone may also explain some clinical observations related to the heart in hypertension. For example, patients with renal artery stenosis may develop ‘flash’ pulmonary oedema due to increased angiotensin-II levels, and correction of the renal artery stenosis may be curative[70]. The role of angiotensin II in inducing myocardial necrosis was postulated in dialysis patients but these cardiac events all occurred during or shortly after procedures, such as sodium-depleting dialysis, renal artery surgery, or diazoxide administration, which are known to cause an increase in plasma concentrations of renin and angiotensin II[71]. Experimental data also suggest that elevated levels of angiotensin II in the presence of systemic hypertension provokes predominantly left ventricular myocardial necrotic lesions[72], which may be relevant in some patients with very high endogenous levels of angiotensin II[71].

**Aldosterone**

Aldosterone, apart from the retention of sodium, loss of potassium, and sympathetic activation, causes baroreceptor dysfunction, impaired arterial compliance, myocardial and vascular fibrosis[73]. There are synergistic effects of angiotensin II and aldosterone with regards to perivascular and interstitial fibrosis of the ventricle, but an angiotensin-independent effect of aldosterone on myocardial fibrosis in hypertension has been demonstrated in various animal models, as well as the protective effect of spironolactone[74]. Aldosterone, therefore, plays an important role in the pathophysiology of left ventricular hypertrophy.

Aldosterone may be involved in the transition from compensated to decompensated left ventricular hypertrophy. Initially, the increase of interstitial and perivascular fibrosis enhances the likelihood of diastolic dysfunction and signs/symptoms of heart failure. Cardiomyocyte loss, which can be induced by chronic aldosterone administration, may further accelerate this maladaptive process[75]. The recent RALES (Randomized Aldactone Evaluation) Study further supports a role of aldosterone in heart failure which may be independent of renin and angiotensin, as the blockade of aldosterone receptors by spironolactone, in addition to standard therapy (including ACE inhibitors), substantially reduced the risk of both mortality and morbidity in patients with severe heart failure[76]. Whilst the trial data suggest an additional benefit of aldosterone antagonists when given in combination with ACE inhibitors in heart failure, aldosterone plays an important part in myocardial fibrosis associated with hypertension and possibly in the transition from left ventricular hypertrophy to cardiac failure. Theoretically, therefore, aldosterone antagonists may offer additional benefits to ACE inhibition in the treatment/prevention of left ventricular hypertrophy and hypertensive heart disease.

In patients with Conn’s syndrome, where there is a chronic excess of aldosterone, the ratio of ischaemic heart disease is similar to cerebrovascular disease; nevertheless in this age group ischaemic heart disease should be 2–4 times commoner than stroke, suggesting either an excess of cerebrovascular disease or a reduction in the incidence of ischaemic heart disease in Conn’s syndrome[77]. It is therefore possible that some adverse effects of aldosterone on the heart require an excess of angiotensin II levels, which are clearly suppressed in Conn’s syndrome.

**Catecholamines**

The sympathetic activation present in hypertension contributes to the rise in blood pressure, but also seems to
have adverse metabolic effects, such as insulin resistance, hyperinsulinaemia and hyperlipidaemia[78,79]. There have been animal studies suggesting that sympathetic influences may exert cardiotoxic effects, thus favouring the development of myocardial hypertrophy[80]. Similar results on the sympathetic nervous system activity facilitating the development of left ventricular hypertrophy in essential hypertension in man have been observed[81]. Not surprisingly, patients with phaeochromocytoma frequently have left ventricular hypertrophy, and congestive heart failure is often one of the first presenting clinical symptoms. Antihypertensive agents that stimulate the sympathetic nervous system, such as direct vasodilators (hydralazine and minoxidil) also fail to reduce left ventricular hypertrophy despite their well-documented antihypertensive effect[82].

If a relationship between hypertensive left ventricular hypertrophy and sympathetic activation is postulated, this raises the possibility that heart failure may be part of this syndrome, especially since neuroendocrine activation is found in heart failure, with activation of the renin–angiotensin–aldosterone and the sympathetic system. Indeed sympathetic activation is well-recognised to be associated with the severity of heart failure and prognosis[83].

**Sodium**

Left ventricular mass is influenced by dietary salt ingestion. Studies in hypertensive rats have demonstrated left ventricular hypertrophy following high dietary salt intake[84]. This correlation has been confirmed in several trials with hypertensive patients[85–87]. Data from the TOHMS study also clearly indicate a blood pressure independent effect of sodium restriction on left ventricular mass regression[88]. Possible underlying mechanisms for the relationship between salt and left ventricular hypertrophy include: (i) salt-induced volume overload; (ii) increased sensitivity of cardiovascular system to noradrenaline; and (iii) angiotensin II[89].

**Insulin resistance**

Hypertension is commonly associated with the insulin resistance syndrome and diabetes. Indeed, insulin resistance has been identified as a blood pressure-independent determinant of left ventricular hypertrophy[90–92]. Hypertensive patients with glucose intolerance also have a higher degree of left ventricular hypertrophy and left ventricular diastolic dysfunction than those with normal glucose tolerance[93,94]. For example, diabetes is found in 5% to 25% of hypertensives, especially in African origin[95]. This combination substantially increases overall cardiovascular risk in hypertensive patients, and diabetes is also commonly associated with atrial fibrillation, coronary artery disease and heart failure. However, the relationship between insulin resistance and hypertensive heart disease has some inconsistencies.

Drugs which worsen insulin resistance, such as thiazides, lower blood pressure and prevent more heart attacks than other antihypertensive agents, but appear less effective at left ventricular hypertrophy regression. Other agents, which improve insulin resistance, such as the biguanides, do not lower blood pressure and barely prevent cardiovascular problems in non-insulin diabetics[96]. Diabetic ‘cardiomyopathy’ probably represents a cardiac disorder with involvement of myocardial, interstitial, coronary and neural structures and it is postulated that it is due to underlying small vessel or microvascular disease with reduced coronary flow reserve[97].

**Other hormones**

Both atrial and brain natriuretic peptides are raised in the presence of left ventricular hypertrophy. In particular, brain natriuretic peptide appears to be a better index of left ventricular hypertrophy than atrial natriuretic peptide for the detection of altered left ventricular structure and function in a patient population at risk for cardiovascular disease[98].

It has also been postulated that left ventricular hypertrophy associated with insulin resistance and a hyperinsulinaemic state is associated with the presence of insulin-like growth factor-I receptors, implicating the role of growth hormones[92]. The role of the vasoconstrictor endothelin in the pathogenesis of left ventricular hypertrophy and its interaction with the renin–angiotensin system and atrial natriuretic peptide still remains to be elucidated[99].

Recently, there has been some interest in myocardial osteopontin, which is thought to contribute to the angiotensin II-induced remodelling process in cultured cardiomyocytes. Human myocardium with extensive fibrosis and cardiomyocyte hypertrophy obtained from explanted hearts was found to contain high immunoreactivity for osteopontin, suggesting induction of osteopontin expression is strongly associated with left ventricular hypertrophy[100]. Laviades and co-workers[101] recently found that systemic extracellular degradation of collagen type I (as indicated by the measurement of metalloproteinasises and tissue inhibitors of metalloproteinasises) is abnormal in patients with essential hypertension. The abnormal collagen proteolytic activities were normalized after 1 year of treatment with an ACE inhibitor, lisinopril[101]. Whilst more data are needed, these abnormalities may perhaps facilitate organ fibrosis in hypertensive patients, namely those with left ventricular hypertrophy.

Finally, other studies have shown a correlation between left ventricular hypertrophy and parathyroid hormones and between left ventricular hypertrophy and growth hormone[102,103]. These findings clearly attest to the role of various hormonal systems and the multifactorial pathogenesis of left ventricular hypertrophy and in particular, the hypertensive heart disease syndrome.
ACE genes

As illustrated above, the renin–angiotensin–aldosterone system plays an essential part in the pathophysiology of left ventricular hypertrophy. ACE is responsible for the generation of angiotensin II, which is closely related to left ventricular mass. Indeed the insertion/deletion polymorphism of the ACE gene has been shown to account for up to 50% of the variance in the plasma ACE concentration[104,109]. Not surprisingly, there is also a close relationship between left ventricular hypertrophy and a deletion polymorphism of the ACE gene.

For example, the DD genotype, which increases plasma ACE activity, is associated with the development of left ventricular hypertrophy[106]. In hypertensive patients without any additional risk factors, the risk of left ventricular hypertrophy increased 3.8-fold with homozygosity for the D allele of the ACE gene[107].

Another study showed increased left ventricular mass in hypertensive males with non-insulin-dependent diabetes mellitus, indicating that the ACE gene polymorphism is crucial in the pathophysiology of left ventricular hypertrophy[108].

Thyroid disease

Thyroid disease causes significant changes in the cardiovascular system, particularly the heart. Thyroid hormones interrelate with the sympathetic nervous system by modifying the sensitivity to sympathetic stimuli. There is now also increasing evidence of direct effects of thyroid hormones on the myocardium, causing an increase of protein synthesis. Therefore, the association of hyperthyroidism with left ventricular hypertrophy may be related to either thyroxin-induced increase of cardiac workload or to direct thyroid hormone-induced stimulation of the myocardial cells[109].

Microproteinuria

Microalbuminuria, a subclinical increase in urinary protein excretion, is established as an indicator of target organ damage in hypertension. Recent studies have shown a positive correlation between urinary albumin excretion and thickness of the left ventricular wall, which was independent of blood pressure[110].

Hypercoagulability

There is increasing evidence that patients with hypertension demonstrate abnormalities of haemostasis, platelets and endothelial function, in keeping with a hypercoagulable or prothrombotic state[111]. This may explain why despite the blood vessels being exposed to high pressures, the complications associated with hypertension (heart attacks, stroke) are paradoxically mainly thrombotic rather than haemorrhagic. In addition, patients with hypertension and left ventricular hypertrophy have higher plasma fibrinogen levels, which compared to those without left ventricular hypertrophy[112].

Nevertheless, the processes of thrombogenesis and atherogenesis are intimately related. Many patients with atherosclerotic vascular disease demonstrate similar abnormalities, where they may have independent prognostic implications. For example, in patients with hypertension, some markers such as prothrombin fragment F1 + 2[113] and von Willebrant factor[114] are associated with subsequent adverse cardiovascular outcomes.

Coronary heart disease

Epidemiological data have shown a strong association between hypertension and atherosclerosis, but only a quarter of the risk for development of coronary artery disease can be attributed to hypertension[115]. Nevertheless, some of the features attributed to hypertensive heart disease may simply be attributable to associated myocardial ischaemia. The reduction in coronary reserve seen with left ventricular hypertrophy makes the heart more susceptible to ischaemia when demand increases or when the perfusion pressure drops[116]. Furthermore, hypertension is associated with other factors that accelerate coronary artery disease, such as acceleration of atherosclerosis of larger coronary arteries[117] and impaired endothelium-dependent vasodilatation[118]. Indeed, specific associations have also been noted between left ventricular hypertrophy and other atherothrombotic disease, such as carotid atherosclerosis[119] and stroke[120].

Underlying coronary artery disease in a patient with hypertensive heart disease may be difficult to distinguish from left ventricular hypertrophy with the so-called 'strain pattern' with ST depression on the ECG. The diagnostic accuracy of the ST segment response in patients with baseline ECG abnormalities due to left ventricular hypertrophy of 59% compared to 90% in patients without resting ECG changes is poor[121]. These ST changes particularly reduce the specificity of an exercise tolerance test in hypertensive patients with chest pain, whereas the sensitivity is only marginally affected[122]. Alternative methods such as stress echocardiography or thallium perfusion scanning have been shown to be more accurate in assessing hypertensive patients with abnormalities of their baseline ECG than the exercise tolerance test[123].

Hypertension is also associated with myocardial perfusion abnormalities even in the absence of symptomatic coronary heart disease[124]. Indeed, myocardial ischaemia may result from the left ventricular hypertrophy itself because of an associated increase in coronary vascular resistance, a reduction in the number of capillaries per gram of muscle tissue and a rise in coronary vascular resistance[125,126]. Left ventricular
hypertrophy is also associated with impaired coronary reserve even in the absence of epicardial coronary disease. Underlying causes of impaired coronary reserve include arteriolar rarefaction, medial wall thickening of arterioles, perivascular fibrosis, endothelial dysfunction, and myocyte hypertrophy\(^{127}\). The presence of underlying cardiac ischaemia may also explain the increased incidence of atrial fibrillation, ventricular arrhythmias, myocardial infarction and sudden cardiac death, which have otherwise been simply attributed to hypertensive heart disease.

**Alcoholic heart disease**

It has been shown that left ventricular hypertrophy is more common in patients with essential hypertension who regularly drink 50 g or more of alcohol per day, where the left ventricular mass index is proportional to the amount of alcohol\(^{128}\). This is important, as patients with alcohol-induced hypertension and left ventricular hypertrophy are at particularly high risk of developing supraventricular arrhythmias, particularly atrial fibrillation\(^{129,130}\). Indeed, hypertensive patients with marked left ventricular hypertrophy should be carefully questioned on their alcohol intake, particularly if it seems inappropriate to the height of the blood pressure.

**Arrhythmias and sudden cardiac death**

The increased risk for sudden cardiac death in hypertensive heart disease has been attributed to increased ventricular ectopic activity\(^{131}\). However, Pringle and co-workers\(^{132}\) argued that the presence of left ventricular hypertrophy did not cause an increased propensity for re-entrant arrhythmias but rather the arrhythmias are simply markers of myocardial ischaemia. Studies in cats showed increased vulnerability to inducible polymorphic ventricular fibrillation after aortic banding induced left ventricular hypertrophy; these abnormalities disappeared with left ventricular hypertrophy regression after removal of the aortic band, whereas cats with persistent left ventricular hypertrophy remained vulnerable to arrhythmias\(^{133}\). The role of hypokalaemia, due to thiazide diuretic therapy for hypertension, in the causation of arrhythmias remains controversial\(^{134}\). Indeed, most studies showed that diuretics are very effective in preventing coronary heart disease in hypertension\(^{135}\).

Nevertheless, it is known that electrophysiological changes associated with left ventricular hypertrophy are not uniform throughout the hypertrophied tissue and this could form a substrate for cardiac arrhythmias\(^{136}\). Alternatively, myocardial fibrosis could cause local variations in the conduction velocities precipitating ventricular arrhythmias.

Supraventricular arrhythmias such as atrial fibrillation are commonly associated with hypertension and left ventricular hypertrophy\(^{137,138}\). This is of significance as the transition from sinus rhythm to atrial fibrillation in a patient with left ventricular hypertrophy and diastolic dysfunction may result in loss of stroke volume and heart failure consequent upon the loss of atrial transport. Furthermore, the presence of atrial fibrillation and hypertension are additive to the risks of stroke and thromboembolism. Left atrial dilatation also occurs in association with left ventricular hypertrophy, which may predispose to atrial fibrillation. Finally, alcohol also contributes to both hypertension and atrial fibrillation.

**Heart failure**

Hypertension, according to Framingham data, is the commonest cause of heart failure. In recent community- and hospital-based studies, however, coronary artery disease was the number one cause of heart failure in Western countries and indeed the importance of hypertension as an underlying cause has been declining\(^{139}\). Hypertension still increases the risk of heart failure four- to eight-fold when associated with ECG defined-left ventricular hypertrophy\(^{140}\), but many of these patients may have underlying coronary heart disease, which may be asymptomatic. The presence of cardiomegaly, as defined by the chest X-ray in hypertensive patients (usually related to left ventricular hypertrophy), also significantly increases the risk of heart failure\(^{140}\). However, it is often difficult to dissect out the unique influence of hypertension on the myocardium and cardiac function per se in the absence of age, as well as accompanying obesity, coronary disease and diabetes.

Hypertension may lead to heart failure due to systolic dysfunction, in association with underlying coronary heart disease and heart attacks, but in hypertensive left ventricular hypertrophy, heart failure due to diastolic dysfunction may also occur. The latter is related to delayed ventricular relaxation and impaired filling, associated with the ultrastructural changes of left ventricular hypertrophy\(^{141}\). Indeed the normal concentration of fibrillar collagen in the myocardium is an important determinant of its stiffness\(^{142}\). A two- to threefold increase in collagen concentration is associated with an increase in diastolic stiffness, whilst resting systolic stiffness and ejection fraction are preserved\(^{143,144}\). A further rise in myocardial collagen raises the diastolic stiffness even further, eventually leading to systolic dysfunction\(^{145}\). left ventricular hypertrophy is also associated with an impaired coronary reserve, which may lead to myocardial ischaemia, even in the absence of epicardial coronary artery disease, leading to impaired left ventricle relaxation\(^{147}\).

However, diastolic dysfunction is also commonly associated with coronary artery disease, valve disease and increasing age. Therefore the development of heart failure in hypertension is less likely to be related to hypertensive heart disease per se in many patients,
especially in elderly hypertensives with underlying coronary artery disease. It should be noted that whilst well-trained athletes develop physiological left ventricular hypertrophy, the parameters of diastolic and systolic function are be within normal range.[148]

**Regression of left ventricular hypertrophy**

There is now evidence both from experimental animal studies and from clinical studies that left ventricular mass can be reduced with control of blood pressure via pharmacological or non-pharmacological means.[147,148] Problems encountered in earlier studies include inadequate number of patients with left ventricular hypertrophy and lack of standardization of the techniques for measurement of left ventricular mass in different laboratories.[149]

Recent recommendations by Devereux and Dahlöf[149] state that a minimum of 40 subjects are needed when investigating the underlying pathophysiology of left ventricular hypertrophy; however, 300–400 subjects should be studied for the detection of left ventricular mass reduction between different agents (for at least a year); and for long-term prognosis in left ventricular hypertrophy regression studies, 1200 subjects or more should be followed over a period of at least 4 years. This raised several issues over whether previously published studies, some of which were smaller and of shorter follow-up, were adequate to answer the question(s) posed.

The published meta-analyses suggest that ACE inhibitors promote the greatest amount of regression of left ventricular hypertrophy, followed by calcium antagonists.[82,150,153] The evidence for beta-blockers and diuretics is variable, but in a recent meta-analysis, there are few little differences between diuretics and beta-blockers in left ventricular hypertrophy regression, although diuretics tended to do so by reducing left ventricular internal dimensions[152]. Recently published data also suggest that antihypertensive treatment with angiotensin-II antagonists results in significant regression of left ventricular hypertrophy, perhaps greater than that seen with the beta-blockers[153].

Does treatment of hypertensive heart disease by the regression of left ventricular hypertrophy (if present) confer a benefit on the patient, which is independent of blood pressure reduction? As yet there are only limited data with regard to morbidity and mortality available. One observational study showed a reduction in cardiovascular events in the group with a decrease in left ventricular mass as compared to the group with an increase in left ventricular mass[89]. During the observational period there were no fatal cardiovascular endpoints, presumably due the short duration of follow-up and the fairly low cardiovascular risk of the patients. To address these unresolved questions, there are now several large observational studies underway, as well as outcome trials comparing different antihypertensive treatment regimes investigating the possible prognostic implications of left ventricular hypertrophy regression[154–158].

In the absence of major end-point data, it is necessary to consider surrogate end-points that may indicate a benefit to patients in terms of regression of left ventricular hypertrophy. For example, there is now evidence that systolic ventricular function is maintained and diastolic ventricular function, both at rest and during exercise, improves with regression of left ventricular hypertrophy[159–161]. Furthermore, Iriarte et al.[162] found that regression of left ventricular mass through antihypertensive treatment with enalapril appeared to reduce microvascular ischaemia and the subsequent development of angina pectoris, with associated improvement in exercise tolerance. Finally, there is also good experimental animal evidence that treatment (with ACE inhibitors) causes a parallel regression both in myocytes and in fibrous tissues.[163]

**Conclusion**

Hypertensive heart disease is probably part of a (very) wide syndrome that includes underlying left ventricular hypertrophy, coronary artery disease, neuroendocrine activation and possibly the insulin resistance syndrome. Many of the features associated with hypertensive heart disease, such as heart failure, may be explained by activation of the renin–angiotensin–aldosterone system, catecholamine excess, diastolic dysfunction and coronary artery disease. The combination of the variety of underlying mechanisms in hypertension results in cardiac abnormalities, which are comparable to those seen in other pathophysiological circumstances. Nonetheless, distinctive dissimilarities in hypertension, particularly when comparing with aortic stenosis, require a differentiation as a separate entity, which can perhaps be referred to as a hypertensive cardiomyopathy.

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