



Left ventricular hypertrophy: targeting the hypertensive patient

Graham Jackson

Consultant Cardiologist, Guy's & St. Thomas Hospitals, London, UK

Correspondence: Dr Graham Jackson, London Bridge Hospital, Suite 301, Emblem House, 27 Tooley Street, London SE2 2PF, UK. Fax: +44 171 357 7408

Hypertension is one of the "big three" modifiable risk factors – the others being cigarette smoking and hyperlipidemia. It is always important not to view risk factors in isolation because it is the cumulative risk that determines morbidity and mortality. Hypertension can lead to significant target organ damage, clinical cardiovascular disease, and frequently both.

In their review Spencer and Lip provide a succinct yet comprehensive review of target organ effects and their adverse influence on prognosis. Left ventricular hypertrophy (LVH) is a well-known marker for an adverse prognosis but it is only recently that we have seen evidence that treatment aimed at regressing LVH can impact on morbidity and mortality. Given its adverse effect on prognosis it is important to accurately detect the presence of LVH.

It is now recognised that echocardiography is significantly superior to electrocardiography and should routinely be used for the detection of LVH. Takeda and Chambers provide us with a useful practical guide to the use of echocardiography and, though enthusiasts, clearly help us to understand its limitations. Magnetic resonance imaging (MRI,) whilst being more accurate than echocardiography in assessing LVH, is limited by cost, which precludes its use for serial measurement in clinical practice. In the research setting, MRI is the most accurate means of monitoring regression of LVH, with two-dimensional echocardiography an acceptable, less expensive alternative.

The metabolic consequences of LVH and their detrimental effect on contractile function are reviewed by Montessuit and colleagues, who pose a challenging cause and effect question. This interesting and thoughtful overview opens the door to the concept of metabolic

manipulation by agents such as trimetazidine, which would, from the paper by Sabouret, appear to address the metabolic abnormalities. Specific studies in this area are not yet available but the concept of adding a metabolic agent when hypertension is controlled and LVH is present may be worthy of prospective evaluation.

Translating basic concepts and research protocols into clinical practice is the ultimate end-point of any study aimed at improving patient care. As Brilla says, "The question arises whether pharmacologically mediated regression of LVH would improve patients' morbidity and mortality". His article presents a well-balanced case for antihypertensive therapy not only benefitting the patient by good blood pressure control but also by regressing LVH. The question to which we do not yet have a clear answer to is whether the regression is due to the blood pressure control itself (no matter what agents are used) or whether certain agents achieve a preferential benefit (e.g. angiotensin converting enzyme inhibitors or angiotensin II antagonists.). It could also be a combination of means of action and time, with blood pressure control the common denominator. Thus certain drugs may regress LVH inside 12 months whereas, in the presence of equal blood pressure control, others may take 18–24 months.

The "take home message" from this issue of Heart and Metabolism is that LVH is bad news. Its detection is clearly important and routine echocardiography is superior to electrocardiography and in addition offers the opportunity for serial non-invasive monitoring of the response to antihypertensive therapy. Controlling blood pressure leads to regression of LVH and reduced morbidity and mortality – we have a target and a benefit but we still need to make

progress with our understanding and treatment of LVH.

Graham Jackson
Consultant Cardiologist

FURTHER READING

Loell BH, Carabello BA Left ventricular hypertrophy: pathogenesis, detection and prognosis. *Circulation* 2000;201: 470–479.

Metabolic changes in cardiac hypertrophy

Christophe Montessuit, Nathalie Rosenblatt-Velin, René Lerch
Cardiology Center, University Hospital, Geneva, Switzerland

Correspondence: Dr Christophe Montessuit, Cardiology Center, University Hospital, 24, rue Micheli-du-Crest, CH-1211 Geneva 14, Switzerland. Tel: +41-22 372 72 16, fax: +41-22 372 72 29, email: christophe.montessuit@hcuge.ch

Myocardial hypertrophy is associated with profound changes in the cardiomyocyte phenotype, altering size, shape and function of the cells. There is now substantial evidence that hypertrophy is associated with changes in both regulation of substrate metabolism and expression of control proteins of metabolism. This results in increased glucose metabolism with reduced fatty acid oxidation. These metabolic changes have features of both adaptation and maladaptation, since although they are detrimental to contractile function they may enable survival of the cardiomyocytes in unfavorable conditions.

Introduction

Life critically depends on the beating of the heart, an energy-consuming process fueled by hydrolysis of ATP to ADP. The energy required for the resynthesis of ATP is in turn harnessed from the catabolic breakdown of metabolic substrates. In order to maintain a continuous supply of ATP to the contractile machinery, the heart has developed an omnivorous attitude and is able to use a wide variety of circulating substrates, including fatty acids, glucose, lactate and ketone bodies. However, substrate selection is not simply dictated by their relative

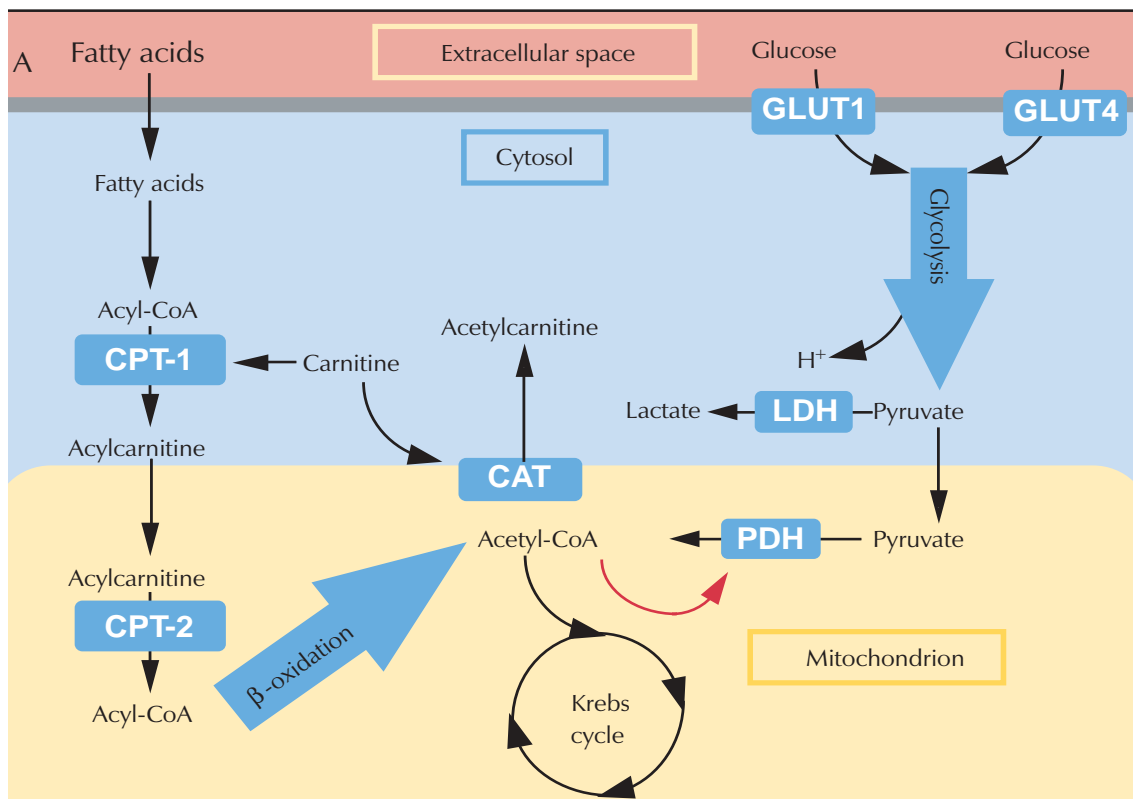


Figure 1. (A) Simplified overview of substrate metabolism in normal cardiac myocytes. CAT, carnitine acetyltransferase; CPT-1, carnitine palmitoyltransferase-1; GLUT1, non-insulin-dependent glucose transporter; GLUT4, insulin-dependent glucose transporter; LDH, lactate dehydrogenase; PDH, pyruvate dehydrogenase; LCAD, long-chain acyl-CoA dehydrogenase; MCAD, medium-chain acyl-CoA dehydrogenase; SCAD, short-chain acyl-CoA dehydrogenase.

abundance at a given time, but is submitted to regulation according to the developmental, hormonal and pathophysiological status of the organism. Cardiac hypertrophy is among the pathologies that modify myocardial substrate utilization.

Overview of fatty acid and glucose metabolism

Catabolic breakdown of glucose occurs in two stages (Figure 1A): glycolysis, an anaerobic, cytoplasmic stage with low ATP yield, followed by aerobic oxidation of glycolysis-derived pyruvate in the mitochondria (the Krebs cycle). Pyruvate is first converted to acetyl-CoA by the action of pyruvate dehydrogenase (PDH), the rate-limiting enzyme for glucose oxidation. β -Oxidation of fatty acids also takes place in the mitochondria and generates acetyl-CoA, which is further oxidized in the Krebs cycle.

Reducing power used for ATP resynthesis is extracted both at the β -oxidation and the Krebs cycle stages.¹ Long-chain fatty acids (LCFA) cannot freely diffuse into the mitochondria. They have first to be converted to acylcarnitine by the carnitine palmitoyltransferase-1 (CPT-1) reaction, a rate-limiting step for LCFA oxidation. β -Oxidation-derived acetyl-CoA inhibits the PDH and, consequently, glucose oxidation, a feedback mechanism known as the Randle cycle.²

The fetal or neonatal myocardium relies mostly on glycolysis for energy production; within a few days after birth, this substrate preference is shifted towards oxidation of fatty acids.³ This evolution is associated with changes in the expression of genes coding for metabolic regulatory proteins. After birth, the constitutively active glucose transporter isoform GLUT1 is replaced by the insulin-sensitive, regulable isoform GLUT4.^{4,5} Simultaneously, expression of enzymes of fatty acid oxidation is increased. In addition to changes in gene

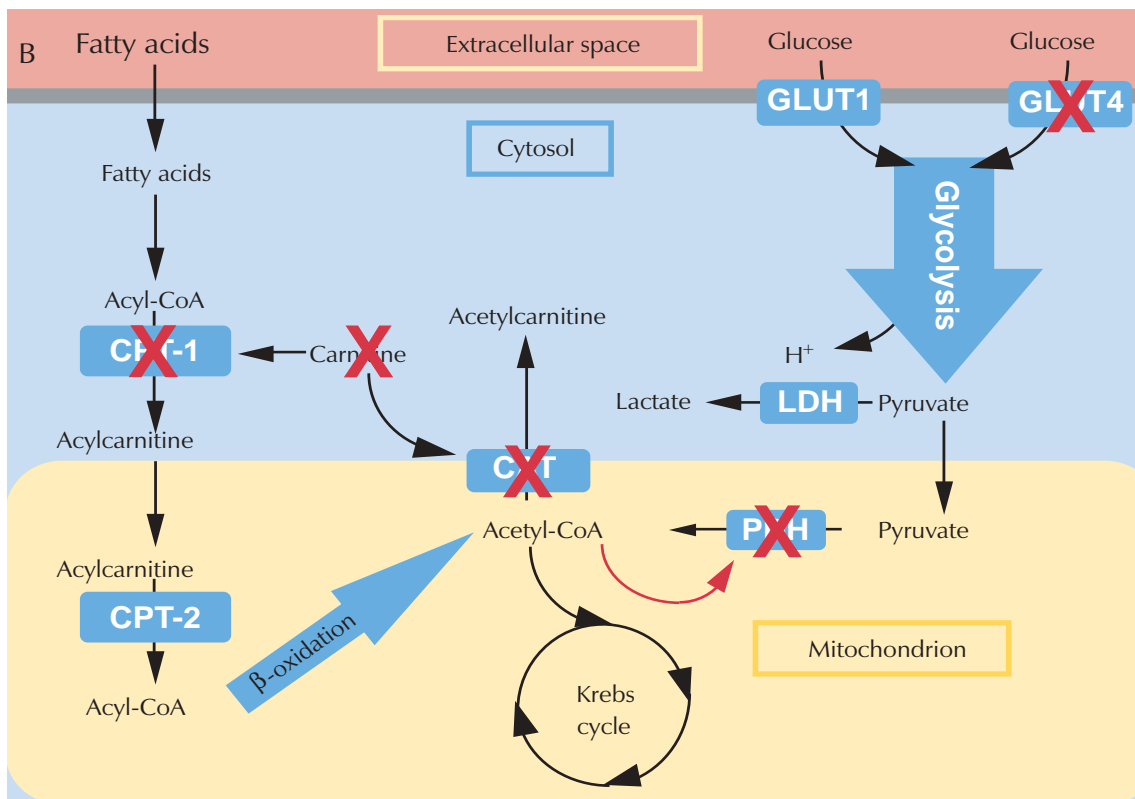


Figure 1. (B) Alterations of substrate metabolism in hypertrophied cardiac myocytes. Red crosses denote impaired steps or pathways.

expression, allosteric regulation of several enzymes is involved in the developmental maturation of fatty acid oxidation.³

Metabolism in cardiac hypertrophy

Despite the availability of methods allowing non-invasive, quantitative assessment of myocardial metabolism in humans,⁶ the bulk of information on substrate metabolism in cardiac hypertrophy comes from experiments in isolated perfused rodent hearts. This model allows for precise control of the substrate supply, the hormonal milieu and the workload imposed on the heart. Cardiac hypertrophy is induced in vivo within a few weeks by artificial generation of a pressure-overload (i.e. aortic banding) or volume-overload (i.e. aortocaval fistula) condition. Another widely used experimental model of left ventricular hypertrophy is the spontaneously hypertensive rat (SHR).

Fatty acid metabolism

Several studies using isolated perfused hearts obtained from rats with cardiac hypertrophy have documented a reduction of palmitate oxidation, associated with reduced cardiac performance.⁷⁻⁹ Reduction in fatty acid oxidation is not due to systemic alterations of substrate metabolism, since it persists in isolated cardiomyocytes.^{10,11} Replacement of palmitate with short-chain fatty acids that can freely diffuse into the mitochondria ameliorates the performance of hypertrophied hearts, suggesting that the β -oxidation pathway itself is not impaired in the heart with compensated hypertrophy.⁷ Instead, inhibition of LCFA oxidation has been attributed to the reduced availability of L-carnitine in hypertrophied hearts, leading to impaired transport of LCFA into the mitochondria (Figure 1B). Indeed, addition of L-carnitine or propionyl-L-carnitine, a naturally occurring derivative of L-carnitine, to the culture medium stimulates oxidation of palmitate

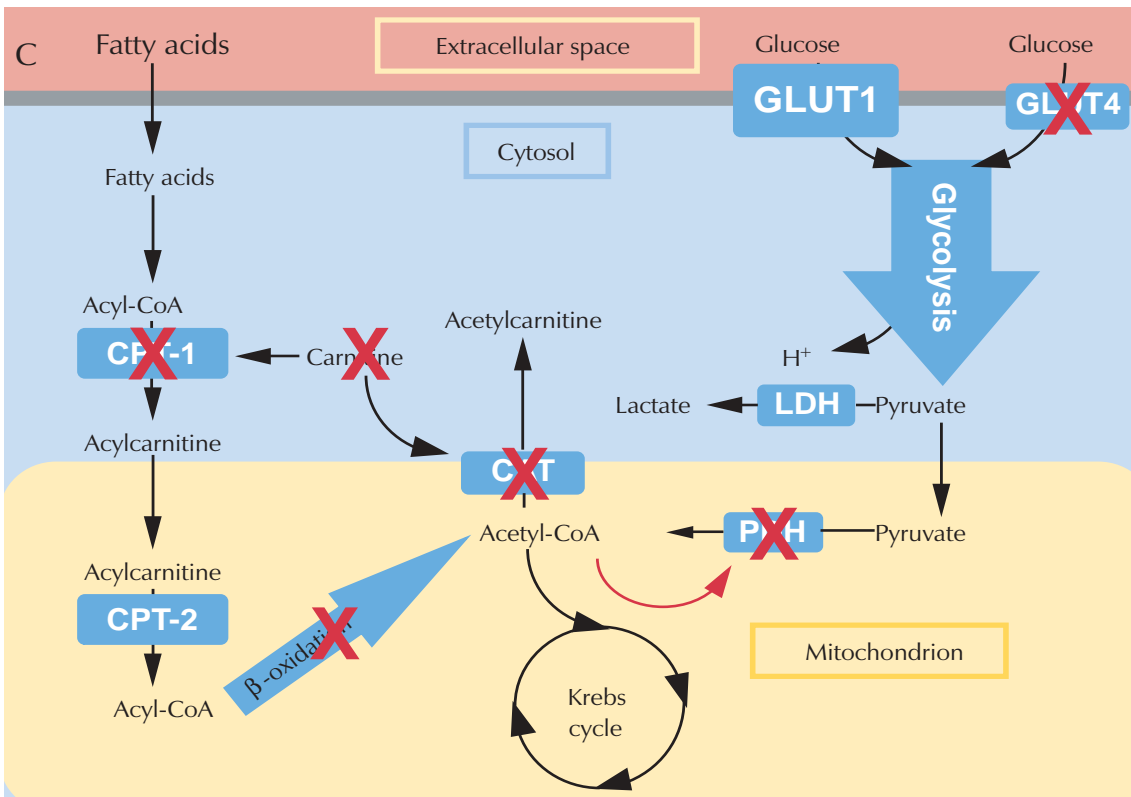


Figure 1. (C) Alterations of substrate metabolism in failing cardiac myocytes. Red crosses denote impaired steps or pathways.

in cardiomyocytes isolated from hypertrophied hearts. Similarly, administration of propionyl-L-carnitine in the drinking water during development of hypertrophy *in vivo* restores both palmitate oxidation¹² and contractile function during *ex vivo* perfusion.¹³ However, in some experiments,^{13,14} L-carnitine replenishment is not accompanied by increased LCFA oxidation. Rather, oxidative metabolism of carbohydrates is stimulated,¹⁴ possibly by export of acetyl-CoA out of the mitochondrion, relieving inhibition of PDH.

Fatty acid metabolism can also be (dys)regulated by alterations of expression of the enzymes of the pathway. We¹⁵ and others¹⁶ have observed downregulation of the mRNA coding for the medium-chain acyl-CoA dehydrogenase (MCAD), a key enzyme of β -oxidation, during development of hypertrophy. Interestingly, a deficiency in activity or protein content of this enzyme became apparent only in the failing heart (Figure 1C). This confirms that, as mentioned above, compensated hypertrophy is probably not associated with an impairment of β -oxidation. Whether downregulation of enzymes of β -oxidation is a cause or a consequence of heart failure remains to be investigated.

Glucose metabolism

In parallel with defects of fatty acid metabolism, cardiac hypertrophy is associated with alterations of glucose metabolism. The first stage of glucose catabolism, anaerobic glycolysis, has been found to be stimulated in several models of cardiac hypertrophy.^{8,12,17} The mechanism responsible for increased glycolytic flux is not well understood. In a model of right ventricle hypertrophy, Do et al.¹⁸ observed increased activity of several glycolytic enzymes. Little is known, however, about the activity of phosphofructokinase, the most important control element in glycolysis.

Another possible explanation for the activation of glycolysis is increased glucose transport into cardiomyocytes. As mentioned above, the adult heart mainly expresses the GLUT4 isoform of glucose transporters, the activity of which is regulated in response to insulin and

other factors. Hearts isolated from SHR rats show augmented basal uptake of glucose, insulin resistance and decreased GLUT4 expression,¹⁹ similar to observations in patients with cardiac hypertrophy.²⁰ Basal uptake of glucose is mediated by the GLUT1 isoform, which is expressed at a low level in the normal adult heart, but is increased *in vivo* during post-ischemic reperfusion²¹ during angiotensin II-induced hypertrophy²² or in isolated cardiomyocytes rendered hypertrophic *in vitro*.²³ Despite the elevated basal uptake of glucose in hearts from SHR rats, no increase in GLUT1 expression was observed,¹⁹ suggesting that stimulation of glucose uptake can occur without an augmentation of the GLUT's density at the cell surface.²⁴ Similarly, we observed in infarct-induced hypertrophy that GLUT1 expression increased only during progression to heart failure.²⁵

Because of reduced fatty acid oxidation in hypertrophied hearts, we should expect glucose oxidation to be elevated in comparison with normal hearts. This has been observed in SHR rats⁹ and in postinfarction left ventricular hypertrophy (Rosenblatt-Velin, unpublished observations). In contrast, a reduction of glucose oxidation has been observed in pressure- or volume-overload hypertrophy, despite acceleration of glycolysis.^{12,17} In these studies, however, isolated hearts were perfused with high concentrations of fatty acids (1.2 mM), which contribute to inhibition of glucose oxidation.²⁶ Consistently, activity of PDH, the rate-limiting enzyme of glucose oxidation, was reduced in hypertrophied myocardium, despite an unaffected total PDH content.²⁷ Inhibition of PDH seems to be relieved by carnitine supplementation.

The dissociation between accelerated glycolysis and reduced or unchanged glucose oxidation is likely to have detrimental consequences on cardiac function. The reason is that when glycolysis is not coupled to glucose oxidation, production of protons and lactate occurs, leading to intracellular acidosis, a major cause of contractile dysfunction.

Resumption of fetal gene program

Both repression of MCAD and overexpression of GLUT1 are reminiscent of the pattern of gene expression observed during fetal life. It is tempting to speculate that a general resumption of the fetal gene program occurs during cardiac hypertrophy. Other features of a return to a fetal program include a switch from expression of muscle- or cardiac-specific isoforms of CPT-1, fatty acid binding protein, or lactate dehydrogenase to expression of non-cardiac isoforms. Indeed, preliminary findings from our laboratory suggest that these isoform switches occur in myocardial hypertrophy (Rosenblatt-Velin, unpublished observations).

Interestingly, it seems that a common transcription factor, Sp1, governs expression of MCAD²⁸ and GLUT1,²⁹ albeit in opposite directions. Myocardial expression of Sp1 is down-regulated after birth,²⁹ but increases again in left ventricular hypertrophy.²⁸ Sp1 is therefore a candidate for a single molecular switch bringing the metabolic phenotype back to a fetal pattern. Whether Sp1 is actually responsible for overexpression of GLUT1 in hypertrophy is currently being investigated.

Metabolic changes: cause or consequence?

Because of their detrimental effect on contractile function, the changes in glucose and fatty acid metabolism described above can be perceived as maladaptive features of the hypertrophied heart. It is, however, possible that the augmentation of glucose metabolism represents an adaptation to enhance the chances of survival. First, stimulation of glycolysis is likely to help the myocytes withstand repetitive episodes of ischemia and reperfusion,³⁰ which often occurs in patients with cardiac hypertrophy. In particular, glycolytically produced ATP appears to be critical to the restoration of ion homeostasis during reperfusion.^{31,32} Second, glucose uptake and glycolytic activity seem to participate in the protection of cardiomyocytes against apoptosis.³³ Thus, enhanced glucose metabolism in hypertrophy, though at the expense of fatty acid oxidation and cardiac

function, may protect cardiac myocytes against both necrotic and apoptotic cell death.

Metabolic changes: or consequence?

Thus far, metabolic alterations observed in the hypertrophied heart have been considered in this review as part of the phenotype, i.e. as a consequence of the development of hypertrophy. However, some observations suggest the intriguing possibility that disruption of normal glucose or fatty acid metabolism may indeed be a primary factor responsible for the development of hypertrophy. In particular, mice with a cardiac-specific deletion of the glucose transport protein GLUT4 exhibit cardiac hypertrophy associated with increased basal glucose uptake, cardiac insulin resistance and increased expression of GLUT1.³⁴ Peripheral metabolism is normal in these animals. The mechanisms leading to development of hypertrophy are unknown, but it is tempting to speculate that ablation of cardiac GLUT4 was compensated by overexpression of GLUT1, resulting in increased glucose metabolism somehow leading to the development of myocardial hypertrophy. ■

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Target-organ damage in hypertension: who is at risk?

Charles G.C. Spencer, Gregory Y.H. Lip
University Department of Medicine, City Hospital, Birmingham, UK

Correspondence: Dr GYH Lip University Department of Medicine, City Hospital, Birmingham B18 7QH, UK. Tel: +44-121 507 5080, fax: +44 121 554 4083, e-mail: g.y.h.lip@bham.ac.uk

Introduction

One of the paradoxes of hypertension is that, overall, many patients have to be treated in order to prevent one cardiovascular adverse event. For example, in the Medical Research Council trial of the treatment of mild hypertension, 2000 patients with a diastolic blood pressure of 95–99 mmHg had to be treated in order to prevent one stroke.¹ However, the risks associated with hypertension are not uniform, and indeed many hypertensives continue to suffer heart attacks and strokes despite treatment to reduce their blood pressure.² There is therefore increasing emphasis on the estimation of absolute cardiovascular risk when assessing individual patients with hypertension, in order to target patients at highest risk for antihypertensive therapy.³ The recent joint recommendations published by the British Cardiac Society, British Hyperlipidaemia Association, British Hypertension Society, and British Diabetic Association⁴ emphasize risk stratification based upon a combination of age, sex, blood pressure levels, the presence or absence of diabetes mellitus, and serum cholesterol. In particular, hypertensive patients with evidence of target-organ damage are well-recognized to be at high risk of cardiovascular and cerebrovascular events, and should be targeted for aggressive management.

Hypertension causes target-organ damage by the direct physical effect of increased blood pressure, as well as the promotion of atherosclerosis and thrombogenesis, leading to a prothrombotic or hypercoagulable state.⁵ These 'target-organ' effects occur throughout the body but are particularly manifest in the heart, brain, kidney, peripheral arteries and the eye.

The heart

Hypertension damages the heart by its direct effect on the heart muscle itself and by the promotion of coronary artery disease. The heart responds to the increased afterload imposed by hypertension by developing left ventricular hypertrophy (LVH). According to Laplace's law, left ventricular wall stress is proportional to intracavity pressure and left ventricular radius, and is inversely proportional to wall thickness. By developing LVH, wall stress is maintained at the same level at the expense of increased wall thickness. This adaptation, however, significantly increases myocardial oxygen demand at the same time as decreasing coronary flow reserve.⁶

Left ventricular hypertrophy

LVH, whether measured by electrocardiography (ECG) or by echocardiography, is a marker of poor prognosis in hypertensive patients, increasing the risk of sudden death, ventricular arrhythmias, congestive cardiac failure and stroke. For example, the age-adjusted all-cause mortality for hypertensives with LVH was 43.2 per 1000 patient-years, compared with 27.6 for those with normal ECGs; furthermore, those with both LVH and ST-T changes ('strain' pattern) had their mortality doubled, with an age-adjusted all-cause mortality of 56.9 per 1000 patient years.⁷ Although LVH is causally related to hypertension,⁸ the correlation between level of blood pressure and LVH is poor, and other factors such as adrenergic stimulation, the renin-angiotensin system and various growth factors appear to be involved.⁶

Why is LVH such an adverse feature in hypertension? The presence of LVH may result in the following: (1) mismatch of blood supply and non-vascular tissue, resulting in a relatively 'starved' subendocardial region; (2) increased

basal myocardial oxygen demand due to increased mass and wall stress; (3) heightened likelihood of ventricular arrhythmias, perhaps related to fibrous tissue; and (4) markedly reduced coronary flow reserve, with abnormalities in the ability to dilate coronary arteries, resulting in increased cardiac ischaemia.⁹

The increased mortality with LVH can be graded according to the increasing voltage on the ECG. In an analysis from the Framingham study which divided those with LVH into four quartiles according to voltage, the age-adjusted odds ratio for cardiovascular disease between the highest and lowest quartiles was 3.08 for men and 3.29 for women.⁸ In this longitudinal study, subjects with a serial decline in voltage were at reduced risk, whilst there was an increase in risk for those in whom the voltage increased over time, indicating that LVH is a risk factor which is amenable to modification.⁸ Whilst the ECG is commonly used to assess the presence of LVH, for example by Sokolow-Lyon criteria (the sum of the S-wave in lead V_1 + R-wave in leads V_5 or $V_6 = 35$ mm), it is relatively insensitive at detecting LVH. Indeed, many patients with normal ECGs will have LVH when examined by echocardiography, which is probably the gold standard for assessing LVH.¹⁰ These patients are at similarly high risk, with an all-cause mortality several times that of those with normal echocardiograms.¹¹

Hypertensive LVH is responsible for increased cardiovascular morbidity and mortality by a number of mechanisms. These patients have an increased risk of cardiovascular events, heart failure and cardiac dysfunction, atherosclerotic vascular disease, arrhythmias and sudden death. For a given level of blood pressure, and if LVH is present, the prognosis is three or four times worse, especially for cardiac failure and stroke. The presence of LVH is also a risk factor for the development of cardiac arrhythmias, the commonest of these being atrial fibrillation and ventricular arrhythmias. The presence of atrial fibrillation is important, as this arrhythmia is associated with a fivefold increase in mortality and may often require long-term antiarrhythmic and antithrombotic therapy. In addition, ventricular arrhythmias have important implications for the risk of sudden death in these patients.¹² The mechanisms for sudden

death are complex, and may include malignant cardiac arrhythmias, including increased ventricular ectopics and non-sustained ventricular tachycardia.^{13,14} Indeed, non-sustained ventricular tachycardia has been shown to occur in 28% of hypertensive patients with ECG evidence of LVH compared with 8% of those with a normal ECG. There is evidence of myocardial ischaemia in LVH even in the presence of normal coronary arteries, and in the event of coronary artery occlusion there is an increase in infarct size and infarct-related death.¹⁵ However, the risk of sudden death is independent of arterial pressure.⁹ Electrophysiological mechanisms for arrhythmogenesis in LVH include the following: re-entry mechanisms related to myocardial fibrosis in LVH; myocardial ischaemic areas, perhaps related to reduced coronary reserve (as coronary artery disease is often not present); ventricular myocyte stretching and arterial wall tension in the hypertrophied heart; and, finally, increased sympathetic nervous system activity.⁹

Coronary artery disease

Given that hypertension is a major cause of coronary artery disease,¹⁶ it is inevitable that many patients with angina and myocardial infarction will have hypertension. These patients are at very high risk of further events, as illustrated by the Multiple Risk Factor Intervention Trial, which found a 15-year coronary heart disease mortality of 32% in middle-aged men with prior myocardial infarction and systolic blood pressures above 160 mmHg.¹⁷ Hypertensive patients with specific ECG abnormalities suggestive of coronary artery disease, such as Q-waves, are also at high risk.¹⁸ Analysis of the large treatment trials suggests that adequate treatment of hypertension reduces heart attack risk by approximately 25%, although this analysis is based on blood pressure reduction using thiazides and beta-blockers rather than the newer antihypertensive drugs.

Heart failure

Convincing evidence from prospective epidemiological studies suggests that heart failure may be caused by high blood pressure and be prevented by its control. For example, the Framingham study suggested that high blood pressure was the principal cause of heart failure.¹⁹ Furthermore, hypertension increases the risk of coronary heart disease and subsequent myocardial infarction which can lead to damaged ventricles and heart failure. The relative importance of hypertension alone and of hypertension-associated heart attacks in causing heart failure is probably influenced by the availability of diagnostic techniques and the criteria for diagnosing hypertension employed in different studies. Finally, LVH is also a powerful predictor of cardiac failure.¹⁹ The development of atrial fibrillation, especially if hypertensive LVH and diastolic dysfunction are present, can precipitate heart failure.

The brain

Despite its capacity for autoregulating its blood supply over a wide range of blood pressures, the brain is highly vulnerable to the effects of hypertension. Hypertension causes cerebrovascular disease by promoting aortic and carotid atherosclerosis, by causing arteriosclerosis and/or thrombosis of small penetrating cerebral end-arteries, by predisposing to heart disease (such as atrial fibrillation) that may lead to stroke, and finally, by predisposing to intracranial haemorrhage.²⁰ Hypertension is also well-recognized as an important cause of dementia.²¹

Patients with a history of stroke or transient ischaemic attack are at high risk not only of further stroke but also of coronary artery disease, and this risk is related directly to blood pressure.²² The presence of a carotid stenosis or increased carotid artery intima and media thickness on ultrasonography are indicators of high cardiovascular risk, even in the absence of previous stroke.^{23,24}

Peripheral arterial disease

Considering the role of hypertension in the development of atherosclerosis, it is not surprising that many patients with peripheral arterial disease have hypertension. Like those with coronary artery disease, patients with severe symptomatic peripheral artery disease are at very high risk of cardiovascular death, with a 15-fold increase in cardiovascular mortality and coronary heart disease.²⁵ Even those with asymptomatic peripheral arterial disease diagnosed by the simple clinical measurement of ankle/arm systolic blood pressure index, have a relative risk for cardiovascular mortality of 3.2.²⁶

The kidney

There is controversy as to whether renal disease in hypertension truly represents target-organ damage. Although renal dysfunction in the form of raised serum creatinine is often found in hypertension, conclusive evidence that it is actually caused by elevated blood pressure in patients with non-malignant essential hypertension is lacking.²⁷ There is, however, a substantial body of evidence that renal disease can cause hypertension. Certainly the number of patients in the large hypertension trials who developed new renal disease during follow-up is very small compared with those developing myocardial infarctions or strokes.²⁷

Nevertheless, hypertensive patients with evidence of renal dysfunction are at high risk. Those with a raised serum creatinine²⁸ and overt proteinuria²⁹ have a particularly poor prognosis in both cardiovascular and renal terms. In patients with malignant-phase hypertension, the presence of renal dysfunction is an independent prognostic risk factor.³⁰ Much interest has also been aroused by the possibility that microalbuminuria might be a marker of early renal damage and cardiovascular risk in hypertension. Indeed, a number of studies have shown a relationship between microalbuminuria and cardiovascular risk in the general population,³¹ as well as markers of target-organ damage³² and endothelial dysfunction³³ in

hypertensives. Nevertheless, convincing evidence of its usefulness as an independent marker of risk in treated non-diabetic hypertensives awaits further trial evidence.

The eye

Funduscopy provides a unique opportunity to directly visualize the blood vessels in hypertensives in order to assess target-organ involvement in the eye. Nearly all forms of retinal damage are common in people with high blood pressure and these include retinal haemorrhage and both venous and arteriolar central retinal vascular occlusion, all of which may lead to blindness. The most widely used classification of fundus changes in hypertension is that of Keith, Wagener and Barker³⁴ (Table 1). The strength of this classification is the correlation between clinical findings and prognosis, although there is only a significant difference in

prognosis between the top two grades indicative of malignant hypertension and the bottom two grades (non-malignant). For everyday clinical practice this is the only useful prognostic information to be obtained from funduscopy, thus Dodson et al.³⁵ have proposed a simpler classification of hypertensive retinopathy into 'malignant' (incorporating Keith, Wagener and Barker grades III and IV) and 'non-malignant' grades (grades I and II).

Conclusion

We have seen that the presence of target-organ damage makes a dramatic difference to prognosis in hypertension. All hypertensives should be assessed for target-organ damage by history, physical examination and other appropriate investigations where necessary. These patients deserve concerted action to reduce not only their blood pressure but also their overall level of cardiovascular risk. ■

Table 1. The Keith, Wagener and Barker classification of essential hypertension and prognosis according to hypertensive retinopathy categories.³⁴

<ul style="list-style-type: none"> • Grade I (benign hypertension) Mild narrowing or sclerosis of the retinal arterioles No symptoms Good general health • Grade II (more marked hypertensive retinopathy) Moderate to marked sclerosis of the retinal arterioles; exaggerated arterial light reflex; venous compression at arterio-venous crossings Blood pressure higher and more sustained than in Grade 1; asymptomatic; good general health • Grade III (angiospastic retinopathy, or 'accelerated' hypertension) Retinal oedema, cotton-wool spots and haemorrhages; sclerosis and spastic lesions of retinal arterioles Blood pressure often high and sustained; usually symptomatic • Grade IV (malignant hypertension) All the above and optic disc oedema Cardiac and renal functions may be impaired; reduced survival 				
Years of follow-up	Patient survival (%)			
	Grade 1	Grade II	Grade III	Grade IV
1	90	88	65	21
3	70	62	22	6
5	70	54	20	1

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Clinical relevance of left ventricular hypertrophy regression

Christian G. Brilla
Division of Cardiology, Philipps University, Marburg, Germany

Correspondence: Prof. Dr Christian G Brilla, Division of Cardiology, Philipps University of Marburg, Baldingerstr, D-35033 Marburg, Germany. Tel: +49-6421-2864980, fax: +49-6421-2868954.

Introduction

According to the Framingham Heart Study, left ventricular hypertrophy (LVH) is a primary risk factor associated with the appearance of all major cardiovascular events, including the development of heart failure.^{1,2} In the presence of LVH determined by electrocardiographic criteria, the risk of developing heart failure is increased, for men and women alike, 6- to 18-fold. A prospective, longitudinal community-based cohort study, similar to that of the Framingham Heart Study, consisted of 459 subjects aged 75–85 years.³ Electrocardiograms obtained at baseline and on an annual basis over 10 years revealed that 9.2% of subjects had LVH on electrocardiogram at baseline and a mortality rate of 11.7/100 person-years versus 4.9/100 person-years for subjects without LVH. Therefore, the question arises whether pharmacologically mediated regression of LVH would improve patients' morbidity and mortality. Before addressing this important clinical question, the growth process leading to the development of LVH needs to be characterized.

Cell population of the myocardium: myocyte and non-myocyte cells

The myocardium is composed of different cells. Cardiac myocytes are the largest of these cells and occupy 75% of the structural space of the myocardium. These parenchymal cells, however, comprise only one-third of all cardiac cells.⁴ Two-thirds of all myocardial cells are non-myocyte cells: endothelial cells, vascular smooth muscle cells, cardiac fibroblasts including pericytes, myofibroblasts and interstitial fibroblasts, which are responsible for both producing and degrading the structural components of the myocardial extracellular matrix including types-I and -III collagen, the major fibrillar collagens of the myocardium.^{5,6} These

collagens are involved in the interstitial and perivascular fibrosis of the myocardium⁷ and the replacement scarring that follows cell death.⁸ Finally, macrophages and mast cells involved in inflammatory processes during a wound healing response to any injury, i.e. hypertension, myocardial infarction, or infective heart disease, are present in the myocardium.

Myocardial growth during cardiovascular disease

Myocardial growth that leads to LVH involves all cellular compartments, i.e. myocyte and non-myocyte cells. It is the hypertrophic growth of cardiac myocytes with increased expression of contractile proteins that accounts for any increment in myocardial mass and, therefore, for the development of LVH. This is the case for all etiologies of LVH, including arterial hypertension, myocardial infarction with hypertrophy of the remote viable myocardium, valvular heart disease with chronic pressure and/or volume overload of the left ventricle and dilated cardiomyopathy. The major physiologic stimulus for myocyte hypertrophy is the hemodynamic load.⁹ Why the growth of these muscle cells would prove either adaptive, as in the athlete's heart, or pathologic, as in hypertensive heart disease, has remained an enigma. One reason could be the potential occurrence of pathologic myocyte phenotypes with, for example, decreased density of sarcoplasmic Ca²⁺ pumps leading to reduced pump function of the left ventricle due to impaired intracellular Ca²⁺ cycling.¹⁰

Another line of reasoning has suggested that it is not the hypertrophic growth of myocytes that is responsible for pathologic LVH.¹¹ Instead, pathologic LVH has been attributed to the growth and altered behavior of non-myocyte cells. Medial wall thickening of intramyocardial resistance vessels due to prolif-

eration and/or load-dependent hypertrophy of vascular smooth muscle cells may occur and leads to a decrease in coronary reserve.¹² Indeed, in patients with hypertensive heart disease suffering from angina pectoris, normal coronary angiograms but abnormal medial wall thickening of intramyocardial resistance vessels examined by endomyocardial biopsies have been reported.¹³ Non-myocyte cells also include cardiac fibroblasts, the growth and enhanced collagen synthesis and/or suppressed collagen degradation of which are responsible for the accumulation of collagen within the cardiac interstitium, where type-I collagen is the major fibrillar component of the extracellular matrix that accounts for myocardial stiffness.

Myocardial collagen matrix remodeling and left ventricular function

The structural remodeling and accumulation of fibrillar collagen that occurs in different disease states have been examined in various species^{7,14} and the following identified: (1) signals mediating fibroblast and cardiac myocyte growth are largely independent of one another;^{12,14} (2) fibrous tissue accumulation occurs as either a reactive or a reparative process,¹⁵ based on whether or not there is parenchymal cell loss (i.e. myocyte necrosis); and (3) activation of the renin-angiotensin-aldosterone system (RAAS) with elevations in circulating and/or local angiotensin II and aldosterone is related to the abnormal fibrous tissue response in acquired or genetic arterial hypertension and in congestive heart failure.^{12,14} The subsequent remodeling of myocardial structure with progressive reactive fibrosis alters its mechanical behavior. During early remodeling, diastolic stiffness of the left ventricle is increased¹⁶ while systolic function (e.g. ejection fraction) is preserved. During late remodeling, in addition to diastolic dysfunction at rest with elevated left ventricular filling pressure, systolic dysfunction with chamber dilatation and reduced ejection fraction appears.¹⁷ In patients with hypertensive heart disease due to primary hypertension, myocardial stiffness measured by the stiffness constant correlates with collagen volume fraction but not with myocyte

hypertrophy of endomyocardial left ventricular biopsies. Thus, the accumulation of fibrillar collagen is a major determinant of myocardial stiffness and pump dysfunction and its progressive accumulation accounts for ventricular dysfunction that first appears during diastole and subsequently involves systole.

Collagen concentration remains normal in the hypertrophied myocardium seen in low-renin states, i.e. in arteriovenous fistula, atrial septal defect or chronic anemia, as well as with thyroxine or growth hormone administration.¹⁸⁻²¹ This is also the case when arterial hypertension is created by infrarenal aorta banding, when renal perfusion is not impaired and therefore RAAS is not activated.¹⁴ Therefore, mechanical factors would not appear to account for the disproportionate accumulation of collagen that occurs with LVH in some conditions but not in others, despite comparable elevations in wall stress due to ventricular pressure or volume overload. Instead, in cultured adult rat cardiac fibroblasts, the effector hormones of RAAS, angiotensin II and aldosterone, have shown to directly stimulate collagen synthesis under serum-free conditions.²² In addition, angiotensin II inhibits the activity of matrix metalloproteinase I, which is the key enzyme for interstitial collagen degradation.²² The net effect is excessive collagen accumulation. Furthermore, chronic administration of aldosterone in uninephrectomized animals receiving enhanced dietary sodium, is associated with increased cardiac expression of types-I and -III collagen mRNAs²³ and fibrosis in the myocardium of the right and left ventricles¹⁴ while fibrosis has also been found in the pancreas, adrenals and other organs.²⁴ When subhypotensive doses of the angiotensin converting enzyme (ACE) inhibitor lisinopril or the aldosterone antagonist spironolactone were used in genetic or aldosterone/salt hypertension, respectively, myocardial fibrosis could be either reversed or prevented, while myocyte hypertrophy remained until larger, i.e. antihypertensive doses, were applied.^{12,25} Thus, trophic factors which mediate myocyte and non-myocyte cell growth in the myocardium can be independent of one another (Table 1).

Table 1. Myocardial fibrosis in various experimental rat models with and without systemic hypertension and cardiac hypertrophy.

Model	Fibrosis	HT	LVH	Ang II	ALDO
RHT	+	+	+	↑	↑
IRB	-	+	+	→	→
AL/1K/high Na ⁺	+	+	+	↓	↑
AL/1K/high Na ⁺ + S (low)	-	+	+	↓	↓
AL/1K/high Na ⁺ + S (high)	-	-	-	↓	↓
Vehicle/1K/high Na ⁺	-	-	+	→	→
SHR	+	+	+	↑	→
SHR + L (low)	-	+	+	→	→
SHR + L (high)	-	-	-	→	→
WKY	-	-	-	→	→

HT, hypertension; LVH, left ventricular hypertrophy; Ang II, plasma or myocardial (SHR) angiotensin II concentrations; ALDO, plasma aldosterone concentration; RHT, renovascular hypertension (2-kidney-1-clip model); IRB, infrarenal aortic band;¹⁴ AL, aldosterone infusion via subcutaneously implanted osmotic minipumps; 1K, uninephrectomy; high Na⁺, enhanced dietary sodium; S, spironolactone in either a low dose that did not prevent hypertension or LVH in hyperaldosteronism, or in a high dose that did;²⁵ SHR, spontaneously hypertensive rat; L, lisinopril in either a low dose that did not affect blood pressure or in a high dose that normalized blood pressure;¹² WKY, Wistar-Kyoto rat; ↓, aldosterone receptor blockade.

Homogenous versus heterogenous regression of LVH

There is now broad evidence that regression of LVH can be achieved. In various meta-analyses of antihypertensive drugs it appeared that ACE inhibitors are particularly capable of reversing LVH while other antihypertensive drugs such as diuretics may work as well.²⁶ In prospective clinical trials, such as the Treatment of Mild Hypertension Study, diuretics were even more powerful at reversing myocyte hypertrophy that determines LVH.^{27,28} Since the remodeling of the myocardium during various disease states is a complex process involving all myocardial tissue and cellular compartments, any approach to reversing LVH appears to be a complicated matter. For instance, it would not be meaningful to reverse myocyte hypertrophy while fibrotic tissue remains in the myocardium. The functional

outcome would be even worse. Therefore, we would need to differentiate the effects of various antihypertensive agents on myocardial tissue because any disproportionate growth between myocyte and non-myocyte cells would set the stage for abnormal myocardial function.

Based on the diverse effects of antihypertensive agents on the various tissue compartments in the heart, three classes of antihypertensive agents may be considered (Table 2): (1) drugs with no evidence of reversing LVH and fibrosis (direct vasodilators);²⁹ (2) drugs with clear effects on LVH, i.e. regression of myocyte hypertrophy (diuretics, α- and β-adrenergic receptor antagonists and verapamil);^{28,30,31} and (3) agents with proven effects on regression of LVH and fibrosis (ACE inhibitors, angiotensin II type 1 receptor or aldosterone antagonists, dihydropyridine Ca²⁺ channel blockers and centrally acting antiadrenergic agents).^{25,28,30,32,33} Removal of reactive myocardial fibrosis represents a means by which myocardial failure due to collagen accumulation would be reversible.

Table 2. Antihypertensive drugs and myocardial structure.

- ◇ No regression of LVH
 - hydralazine
 - minoxidil
- ◇ LVH regression with no effect on myocardial fibrosis
 - diuretics
 - verapamil
 - α-adrenergic receptor antagonists
 - β-adrenergic receptor antagonists
- ◇ Regression of LVH and myocardial fibrosis
 - ACE inhibitors
 - angiotensin II type 1 receptor antagonists
 - aldosterone antagonists
 - dihydropyridine Ca²⁺ channel blockers
 - centrally acting antiadrenergic agents

Reversal of LVH and patient prognosis

Several medium-sized clinical trials have been performed to answer the question whether regression of LVH is associated with improved clinical outcome. In 430 patients with primary hypertension and during an observation period of 1217 patient-years, those with an echocar-

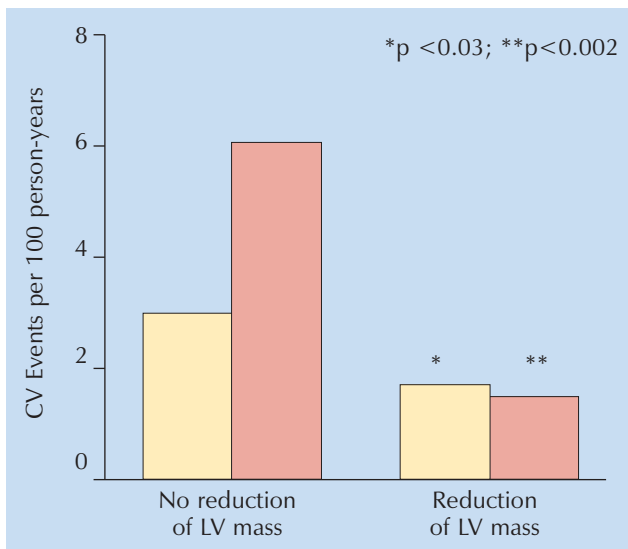


Figure 1. Cardiovascular (CV) morbid events per 100 person-years in 430 patients with primary hypertension during anti-hypertensive treatment;³⁴ a significant clinical improvement, i.e. reduction in CV events, was found in all patients if left ventricular (LV) mass could be reduced compared with patients where no change occurred (yellow), which was even more impressive in patients with left ventricular mass >125 g/m^2 (26% of subjects) at baseline (red).

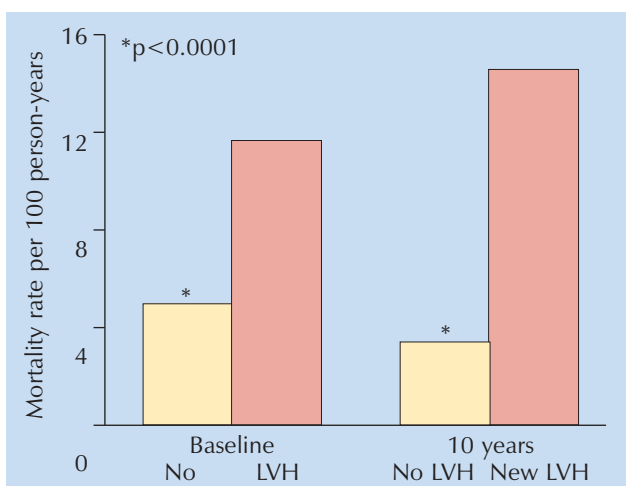


Figure 2. Total mortality rate per 100 person-years in the Bronx Longitudinal Aging Study³ in which 459 elderly subjects (mean age 79 years) were followed over 10 years in a prospective trial. In the presence of left ventricular hypertrophy (LVH) at baseline, mortality was significantly increased compared with subjects with no electrocardiographic evidence of LVH. After 10 years, subjects without LVH showed a significantly improved prognosis compared with those in whom LVH developed.

diographically determined decrease in left ventricular mass during follow-up showed a significantly ($P < 0.03$) decreased rate of cardiovascular morbid events (1.8/100 patient-years) compared with those whose left ventricular mass increased (3.0/100 patient-years) (Figure 1).³⁴ In a 10-year follow-up study of 151 patients with uncomplicated arterial hypertension, the incidence of cardiovascular events was significantly greater ($P < 0.01$) in patients without an echocardiographically determined reduction in left ventricular mass (relative risk 3.5) than in patients with LVH regression (relative risk 1.4) after adjusting for traditional risk factors.³⁵ In the Bronx Longitudinal Aging Study,³ subjects in whom the electrocardiographic LVH pattern disappeared over time had fewer cardiovascular mortality and morbidity events than those with persistent or newly developed LVH (Figure 2). Persistent LVH from baseline was an independent predictor of myocardial infarction, overall cardiovascular disease and total mortality. In the Framingham Heart Study, 524 subjects with electrocardiographic evidence of LVH were free of cardiovascular disease at baseline. During follow-up there were 269 new cardiovascular events. Subjects with a serial decline in voltage were at lower risk for cardiovascular disease than were those with no serial change.³⁶

These findings strongly indicate that the lack of decrease in left ventricular mass following antihypertensive treatment is associated with a higher risk for cardiovascular events that is markedly improved by regression of LVH. Such improvement in patient prognosis has been achieved even with unselected antihypertensive agents. Based on the diverse myocardial tissue findings following treatment with various antihypertensive drugs we may speculate that patient prognosis with LVH can be even further improved by choosing agents which lead to a homogenous reversal of LVH associated with improved cardiac function, termed cardioreparation.^{28,32} Various prospective, randomized clinical trials are underway (PRESERVE, LIFE) to prove whether ACE inhibitors or angiotensin II type 1 receptor antagonists are particularly capable of improving the prognosis of patients with LVH. ■

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Critical evaluation of diagnostic techniques to assess left ventricular hypertrophy

Scott Takeda, John Chambers
Cardiothoracic Centre, St Thomas's Hospital, London, UK

Correspondence: Dr John Chambers, Cardiothoracic Centre, St Thomas's Hospital, London SE1 7EH, UK.
Tel: +44-20 7928 9292, fax+44-20 7969 5680, e-mail: johnchambers@dial.pipex.com

Introduction

Left ventricular hypertrophy is an independent risk factor for stroke, myocardial infarction, congestive heart failure and sudden death¹ in patients with hypertension or aortic stenosis,² but also in apparently normal people with no evidence of pressure overload.³ This article assesses the techniques available for estimating left ventricular mass in clinical practice.

Echocardiography

M-mode echocardiography is still the most widely used method in clinical practice, despite several limitations. Dimensions measured at the base of the heart can only be used to generalize to the whole heart in the presence of symmetrical geometry. Non-uniformity of any wall as a result of myocardial infarction or localized hypertrophy invalidates the technique. The M-mode cursor must be placed perpendicular to the posterior wall and septum. This was not possible in up to 34% of patients^{4,5} until the relatively recent introduction of movable or 'anatomical' M-mode, although measurements from two-dimensional echocardiography could be substituted. In at least 10% of patients, adequate images used to be unobtainable because of a poor 'window'. Image quality has now improved as a result of new technologies, particularly second harmonic imaging, although preliminary experience suggests that wall thickness may be slightly larger using second harmonic than fundamental imaging.

The widely used Devereux formula⁶ treats the left ventricle as a cube so that the myocardial volume is the difference between the outer margin of the left ventricle and the cavity. The cavity diameter is the left ventricular diastolic dimension (LVID), and the outer diameter is the LVID plus the septal width (IVS) plus the posterior wall width (PWT). Mass is derived from volume after

multiplying by the density of cardiac muscle, 1.04 g/cm³. By correlating calculated left ventricular mass with angiographic and postmortem findings, Devereux et al.⁶ derived a correction factor of 13.6 g, giving the formula:

$$\text{Left ventricular mass} = 1.04 \times [(LVID + IVS + PWT)^3 - (LVID)^3] - 13.6 \text{ g}$$

The 'Devereux formula' requires the measurements to be made using the Penn convention in which the endocardial echoes are excluded from the septal and posterior walls. However, dimensions are usually measured using the convention of the American Society of Echocardiography (ASE) from 'leading edge to leading edge'. Use of the ASE convention in the cube-function formula consistently overestimates left ventricular mass by about 15–25%^{6,7} and in a recent comparison with magnetic resonance, by up to 37%.⁸ Furthermore, the formula was derived in only 34 patients and comparison with necropsy findings was by regression equations. It is well known that strong correlations are possible even in the absence of adequate agreement.⁹

There is potentially major intra- and interobserver variability in M-mode measurements which can be minimized by averaging at least 3–5 cycles and by meticulous care in obtaining optimal image quality and orientation. In the PRESERVE trial¹⁰ using M-mode or linear two-dimensional measurements according to ASE recommendations, the between-study standard deviation in left ventricular mass was only 6 g/m². However, standard deviations may sometimes be as high as 30 g,^{11,12} which is of the same magnitude as expected changes in left ventricular mass. This means that M-mode measurements should rarely be used for quantifying a change in left ventricular mass over serial studies except in a large population of several hundred patients.¹³

Two- and three-dimensional echocardiography

There are two frequently used methods for quantifying myocardial mass by two-dimensional echocardiography, the area/length and the truncated ellipsoid methods. Both correlate well with anatomic left ventricular mass,^{14,15} provided that care is taken to avoid foreshortening the left ventricular cavity. Correlations are better ($r = 0.93$, standard error of estimate error [SEE] 31 g) than by M-mode ($r = 0.86$, SEE = 59 g), especially in hearts with abnormal geometry,¹⁶ and reproducibility is also better.¹⁷ Despite this, these two-dimensional methods are seldom used, mainly because they are more time-consuming and partly because so much experience with M-mode already exists.

Three-dimensional techniques are expected to describe the heart better than M-mode or two-dimensional echocardiography. Early comparisons with magnetic resonance imaging have shown good correlations in volume estimates ($r = 0.91$, SEE = 28 ml)¹⁸ and it is possible that a transpulmonary contrast agent may further improve volume estimates using transoesophageal three-dimensional echocardiography.¹⁹ Early commercial transthoracic three-dimensional systems are now available, but are not yet widely used.

What constitutes left ventricular hypertrophy?

Left ventricular mass is related to body habitus. It is therefore conventional to index mass to body surface area taken from Dubois nomograms, although in some circumstances, especially in the morbidly obese, it may be more appropriate to normalize to height.²⁰ Left ventricular mass is a continuous variable in terms of cardiovascular risk, but it is still useful to have a bipartite division into normal or abnormal for clinical characterization. The specific criteria proposed by Hammond et al.²¹ are widely used: $>134 \text{ g/m}^2$ for men and $>110 \text{ g/m}^2$ for women. However, left ventricular mass is dependent on several factors other than body habitus, including age, gender, level of physical activity, race and possibly angiotensin-

converting enzyme genotype.^{22,23} For research studies, particularly with small population sizes, a carefully matched control population may be needed to determine thresholds of abnormality for left ventricular mass.

Left ventricular geometry

According to the law of Laplace,²⁴ left ventricular wall stress (S) is directly proportional to intracavitary pressure (P) and chamber radius (R) and is inversely proportional to wall thickness (Th):

$$S = P \cdot R/Th$$

Left ventricular hypertrophy tends to reduce wall stress by increasing wall thickness and reducing cavity size. However, the relationship between left ventricular mass, cavity size and pressure is not fixed. Three different geometric responses can be defined by the relative wall thickness ratio, which is the thickness of the posterior wall divided by the left ventricular

Table 1: Left ventricular geometry.

• Concentric hypertrophy	Increased left ventricular mass and increased relative wall thickness ratio (>0.45)
• Eccentric hypertrophy	Increased left ventricular mass and normal relative wall thickness ratio (<0.45)
• Concentric remodelling	Normal left ventricular mass but increased wall thickness ratio (>0.45)

Key points

- Left ventricular hypertrophy is a strong independent determinant of death, stroke, heart failure and myocardial infarction
- For clinical use an indexed mass of 134 g/m^2 in men or 110 g/m^2 in women or a septal width $>1.3 \text{ cm}$ are guides to hypertrophy
- The normal wall thickness ratio (posterior wall thickness/cavity radius) is <0.45
- Concentric remodelling in which the left ventricular mass is normal but the wall thickness ratio is increased is associated with an increased risk of cardiovascular events
- Two-dimensional methods of estimating left ventricular mass are more reproducible than M-mode methods
- For serial research studies, echocardiography can be used if the population size is large; otherwise magnetic resonance imaging is probably the technique of choice

radius in diastole: (1) concentric hypertrophy defined by increased left ventricular mass and a high relative wall thickness ratio (>0.45); (2) eccentric hypertrophy defined by increased left ventricular mass and normal relative wall thickness ratio (<0.45); and (3) concentric remodelling defined by normal left ventricular mass with a high wall thickness ratio. Concentric remodelling is associated with an increased risk of morbid events (2.39 per 100 patient-years) compared with normal geometry (1.12 per 100 patient-years)²⁵ (Table 1).

Other techniques for estimating left ventricular mass

Ultrafast computed tomography provides higher image resolution than echocardiography and allows truly tomographic assessment of the left ventricle.²⁶ It does not rely on geometric assumptions and has been anatomically verified in dogs.²⁷ It has also been shown to have excellent reproducibility in serial studies,²⁸ but is limited by the use of ionizing radiation and the need for intravenous contrast.

Nuclear magnetic resonance imaging has superior image quality compared with echocardiography, and truly tomographic images with little reliance on geometric assumptions. Magnetic resonance imaging has been validated against anatomic mass in cadaver hearts ($r = 0.99$, $SEE = 6.8$ g)^{29,30} and in dogs' hearts compared with subsequent postmortem assessment ($r = 0.98$, $SEE = 6.1$ g).³¹ It is accurate in assessing asymmetric hearts, for example in dogs with experimentally induced myocardial infarction³² or in humans with hypertrophic cardiomyopathy.³³ The standard error in estimating left ventricular mass is about one-third that of echocardiography, and so magnetic resonance imaging is more accurate for serial estimates of left ventricular mass.^{34,35}

Magnetic resonance imaging also has advantages over ultrafast computerized tomography in that it does not require ionizing radiation and is therefore better suited for serial studies.³⁵ A number of patients cannot be scanned because of claustrophobia or the presence of implanted metallic devices such as pacemakers or some mechanical heart valves. A previous drawback

was the unacceptably long scan times of up to 45–60 min, but newer techniques using single-phase cardiac magnetic resonance imaging have reduced scan times to about 12 min.³⁶

Conclusion

Left ventricular hypertrophy is one criterion for beginning treatment in patients with borderline hypertension, and there is evidence that regression of left ventricular hypertrophy is associated with a reduction of risk in hypertension. For routine clinical work the simple and quick M-mode methods are probably adequate. However, more than one method of assessing the ventricular response should be quoted, including septal width, indexed left ventricular mass, diastolic function and, possibly, geometry. For research studies addressing regression of left ventricular hypertrophy, it is necessary to use either large population sizes or a technique with a lower variability such as two-dimensional echocardiography or magnetic resonance imaging. ■

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Trimetazidine: a new metabolic approach in angina.

Effective and safe, even in polymedicated patients and those with concomitant disease

Dr Pierre Sabouret

Department of Cardiology, Hôpital Pitié-Salpêtrière, Paris, France

In line with current enthusiasm for the metabolic approach to improving the treatment of ischemic heart disease, the use of trimetazidine has been endorsed in the latest recommendations of the task force of the European Society of Cardiology¹ (Table 1) and of the American College of Cardiology/American Heart Association² (Table 2). This follows recent publications on its efficacy and safety, in monotherapy or combination therapy, in ischemic heart disease. Furthermore, growing interest has been aroused as to how trimetazidine's mechanism of action could explain its efficacy and acceptability.

Table 1. New guidelines of the European Society of Cardiology: lifestyle and therapeutic goals for patients with stable angina pectoris.

- Lifestyle
 - Stop smoking, make healthy food choices, be physically active and achieve ideal weight
- Other risk factors
 - Blood pressure <140/90 mmHg
 - Total cholesterol <5.0 mmol/l (190 mg/dl); LDL cholesterol <3.0 mmol/l (115 mg/dl)
 - When these risk factors are not achieved by lifestyle changes, blood pressure and cholesterol lowering drug therapies should be used.
- Other prophylactic drug therapies
 - Aspirin (at least 75 mg) for all patients (without contraindications to aspirin)

Table 2. The American College of Cardiology/American Heart Association/ACP-ASIM guidelines.²

- Other antianginal agents and therapies

'Metabolic agents such as trimetazidine ... have been observed to produce antianginal effects in some patients'

Despite the extensive progress that has been made in its prevention and treatment during recent decades, ischemic heart disease is the primary cause of mortality worldwide today. It is expected to become the world's leading cause of disease burden (which represents aggregate mortality and morbidity) by 2020.

Faced with this worrying perspective, the metabolic approach has been developed to provide new therapeutic solutions to improve on the unsatisfactory efficacy and tolerability of classic hemodynamic antianginal drugs.

A newly identified mode of action

Trimetazidine has been shown to modify energy metabolism in the heart. This mode of action has been recently determined by Kantor et al.,³ who demonstrated that the antianginal effects of this metabolic agent may occur because of the inhibition of a mitochondrial enzyme: long-chain 3-ketoacyl-CoA-thiolase, which results in a reduction of fatty acid oxidation and a stimulation of glucose oxidation (Figure 1). Previous randomized clinical studies have shown that inhibition of fatty acid oxidation, combined with stimulation of glucose oxidation, can protect the ischemic heart.

Evidence-based medicine: clinical data on trimetazidine

The growing interest in metabolic agents in the treatment of angina pectoris is due to the results of clinical studies with trimetazidine, which has been proven to be an effective antianginal agent.

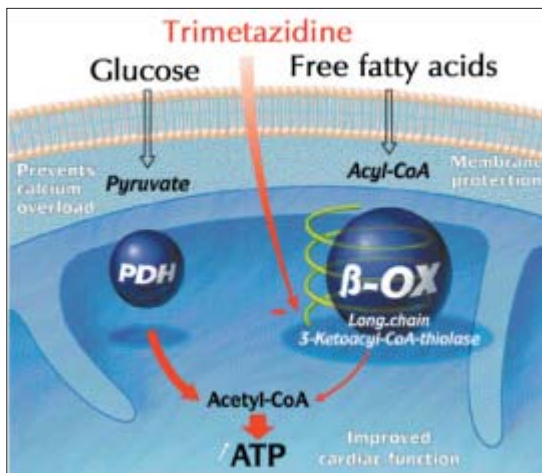


Figure 1. Mode of action of trimetazidine. PDH, pyruvate dehydrogenase; β -OX, beta-oxidation.

Trimetazidine in monotherapy

In several double-blind trials, trimetazidine significantly improved the ergometric capacity and total work output of patients with effort angina,^{4,5} reduced the frequency of attacks and nitroglycerin requirements in patients with chronic stable angina,⁶ and increased their effort tolerance.⁷ A European collaborative working group has demonstrated that the antianginal efficacy of trimetazidine is comparable to that of a beta-blocker (propranolol) but without reducing the heart rate-pressure product nor the coronary

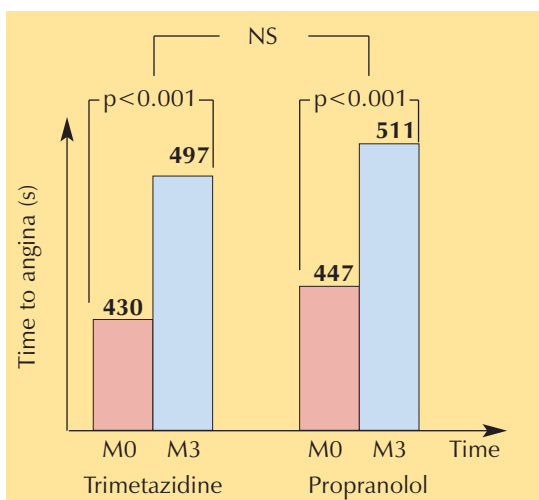


Figure 2. Effect of trimetazidine on time to onset of angina in comparison with propranolol. NS, not significant.

blood flow⁸ (Figure 2). The absence of alteration of hemodynamic parameters to the same extent as nifedipine confers trimetazidine with an attractive safety profile.⁹

Trimetazidine: a suitable choice for combination therapy

In combination, trimetazidine provides additive benefits with beta-blockers or diltiazem, and superior efficacy to isosorbide dinitrate, without adding any side effects.¹⁰⁻¹³

The efficacy and safety of trimetazidine have also been confirmed in at-risk patients.

Trimetazidine in at-risk populations

Trimetazidine delayed the ischemic threshold in patients with left ventricular dysfunction and coronary artery disease on stress echocardiography.¹⁴ In diabetic patients, trimetazidine significantly improved clinical symptoms, exercise duration, time to onset of angina, and time to 1 mm ST-segment depression. The tolerability of trimetazidine in this polymedicated population was assessed as good or excellent in 98% of patients¹⁵.

In a recent study, the same beneficial effects, with remarkable safety, were extended to an elderly population.¹⁶

Conclusion

The management and treatment of ischemic heart disease remains a challenge. The angina population is aging, the percentage of hypertensive patients is high and the number of diabetic patients is increasing dramatically; epidemiological studies have revealed that the quality of life of the angina population is fair or poor (Figure 3).¹⁷

Recently published studies on trimetazidine provide a cluster of evidence about the efficacy, safety and good quality of life achieved with this new metabolic agent.

Further studies are needed to detail the role of this promising metabolic approach to cardiovascular disease. ■

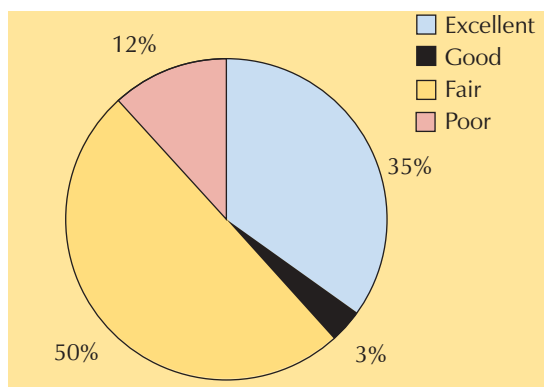


Figure 3. Quality of life of an outpatient cohort with chronic stable angina pectoris.¹⁷

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Extreme left ventricular hypertrophy complicating hypertension without evidence of myocardial disarray

Jonathan Hill, David Begley

¹London Chest Hospital, London, UK; ²Western General Hospital, Edinburgh, UK

Correspondence: Dr Jonathan Hill, London Chest Hospital, London, UK, e-mail: jono@nih.gov

Introduction

A case is presented of a 67-year-old woman with a history of mild hypertension who presented to our hospital with chest pain and shortness of breath following a holiday in the Caribbean. She was referred with a diagnosis of severe aortic stenosis requiring urgent valve replacement. Subsequent investigation showed that she had gross left ventricular hypertrophy with features of hypertrophic cardiomyopathy (HCM). Her clinical course deteriorated and she developed signs of cardiac failure and required inotropic support and ventilation. She died after 3 days of ventilation. Autopsy findings were not consistent with the clinical diagnosis.

This case illustrates an extreme presentation of hypertensive heart disease and highlights important considerations required for accurate diagnosis and targeted treatment for patients with hypertension.

Case

This 67-year-old patient of Afro-Caribbean origin first became unwell in St Lucia where, following an episode of shortness of breath and angina, a diagnosis was made of critical aortic stenosis. She was commenced on a beta-blocker, aspirin and digoxin. On return from her holiday she presented to the emergency department of our hospital following a further episode of severe pain and markedly reduced exercise tolerance. She had been experiencing pain at rest and on slight exertion.

Her medical history was unremarkable and she had no risk factors for coronary artery disease although at one routine medical visit 6 years previously she was noted to have mild systolic hypertension and was commenced on furosemide.

On initial examination her heart rate was

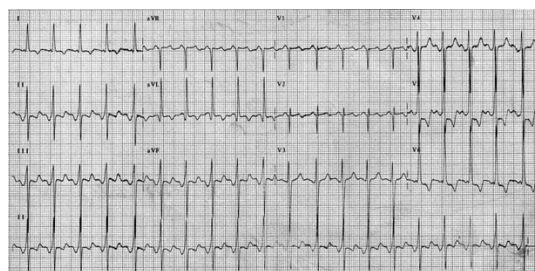


Figure 1. Left ventricular hypertrophy ECG: 12-lead electrocardiogram taken on admission to hospital showing gross changes consistent with voltage criteria for left ventricular hypertrophy with lateral repolarization abnormalities.

normal, blood pressure 100/50 mmHg, apex beat was prominent with a double impulse. Her venous pressure wave was noted at 4 cm above the aortic area. The murmur radiated to the carotids. An ECG showed large voltage complexes with marked lateral ST repolarization abnormalities (Figure 1). A provisional diagnosis of severe aortic stenosis with myocardial ischaemia was made. She was commenced on a low dose of a beta-blocker; intravenous heparin and intravenous nitrate were given as blood pressure allowed.

Initial biochemistry revealed normal liver and renal function and no elevation in cardiac enzymes. She was found to be mildly anaemic with a haemoglobin of 10.5 g/dl and a normocytic picture. ESR was markedly abnormal at 105 mm/h. CRP was also increased.

An echocardiogram showed gross biventricular hypertrophy with systolic anterior motion of the mitral valve and left ventricular outflow tract obstruction.

Within 24 h of admission the patient was symptomatically much improved with complete resolution of chest pain and dyspnoea. Arrangements were made for further invasive cardiological investigation including left and right heart catheterization. Unfortunately she developed further severe chest pain associated



Figure 2. Hypertrophy: a transverse section at mid-cavity level showing extreme left and right ventricular hypertrophy with visible areas of myocardial fibrosis.

with profound dyspnoea. Examination revealed bilateral coarse crepitations at the lung bases. Nitrates were recommenced and she was given diamorphine. There were no new changes on her ECG. She continued to develop further pain despite intravenous therapy and became dramatically more unwell, with hypotension and pulmonary oedema. Arterial blood gases revealed severe respiratory failure with PCO_2 of 7.7 kPa and PO_2 of 5.0 kPa despite high flow oxygen. There was a severe acidosis with pH of 7.16. She was intubated and ventilated and adrenaline infusion was started. She did not respond and died despite inotropic support and ventilation with 100% oxygen. The cause of death was recorded as cardiac failure secondary to severe HCM. The possibility of massive pulmonary embolus had been considered. No explanation at that time could be given for the raised ESR and mild anaemia. A post-mortem examination was carried out.

Autopsy findings revealed gross macroscopic changes in the heart consistent with HCM (Figure 2). There was striking massive hypertrophy of the left ventricle virtually obliterating the chamber. The right ventricle was also hypertrophic. Both atria were dilated. There were numerous areas of ischaemic fibrosis particularly in the interventricular septum. The coronary vasculature was normal and there was no evidence of atheroma. The thoracic and abdomi-

nal aortae were also notably free of atheromatous change. There was dilatation of the pulmonary outflow tract and vasculature in the lung peripheries, indicative of long-standing pulmonary hypertension. There was no evidence of pulmonary thromboembolism, but there was intense pulmonary oedema. Histological examination of the heart did not show myocardial disarray, which was an unexpected finding. There was severe myocyte hypertrophy and fibrosis alone.

Discussion

In view of the finding of no myocardial disarray the diagnosis of classical HCM becomes less certain. It is well known that patients of Afro-Caribbean origin do develop left ventricular thickening, which can simulate HCM, including the development of left ventricular outflow tract obstruction, in response to a mild hypertensive stimulus. This case appeared to be an extreme form of this. The exaggerated hypertrophic response may be genetically determined but the gene is not known. The alternative explanation is that there are cases of HCM due to one of the eight genes known to cause HCM (beta-myosin heavy chain, troponins T¹ and I, alpha-tropomyosin, myosin binding protein-C, essential and regulatory light chains of myosin and cardiac actin) that do not develop disarray. This is thought to be unlikely as the pathogenesis of HCM results from the mutant gene product interfering with myofibril alignment.

Considerable interest has focused on the importance of modifying factors in explaining the variability of phenotypic expression in HCM.² Similar modifying factors may play a role in the development of myocyte hypertrophy in response to hypertension. Modifying factors could be variety of possibilities including growth factors, or vascular hormones such as angiotensin II and endothelin-1. Alternatively, polymorphisms in the genes encoding for these hormones may affect function, or the polymorphism may be in a regulatory site affecting transcription. The simple insertion/deletion I/D polymorphism in intron 16 of the angiotensin-I converting enzyme (ACE) gene consists of a 287 bp repeat.³ The DD genotype is associated

with elevated levels of circulating ACE and accounts for a small but significant proportion of the phenotypic variability observed in HCM. Other genetic polymorphisms have similarly been shown to account for phenotypic variability.⁴ It is likely that a combination of these polymorphisms will increase the risk of developing left ventricular hypertrophy in response to increased afterload.

The mechanism of cardiac failure was profound diastolic dysfunction⁵ of the grossly thickened left ventricle, leading to severely impaired filling.^{6,7} The use of nitrates may also have increased the left ventricular outflow tract obstruction, interfering with coronary flow, leading to more ischaemia and worsening diastolic function.^{8,9} The left ventricle's reduced compliance was caused by replacement of myocardium with non-distensible fibrous scar tissue.¹⁰ With the added insult of myocardial ischaemia¹¹ caused by outflow tract obstruction and reduced coronary flow the failing ventricle is unable to compensate.

Conclusions

This patient had extreme hypertrophy without the typical histological features of myocardial disarray found in HCM. The cycle of events which resulted in her rapid clinical demise may not have been preventable but led to questions regarding the use of inotropes and vasodilator drugs in a patient with severe diastolic heart failure. The genetic implication for the families of patients with this pattern of cardiac hypertrophy is not clear but suggests the existence of further as yet undiscovered cardiac mass-modifying genes. ■

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