Hypertension &
Left Ventricular Hypertrophy

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Pathophysiology and treatment of hypertensive left ventricular hypertrophy
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Bibliography of One Hundred Key Papers
Pathophysiology and treatment of hypertensive left ventricular hypertrophy

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At some point in the natural history of hypertension, the compensatory increase in left ventricular (LV) mass ceases to be beneficial. LV hypertrophy (LVH) becomes a preclinical disease and an independent risk factor for congestive heart failure, ischemic heart disease, arrhythmia, sudden death, and stroke. The multiple mechanisms involved, in addition to elevated blood pressure, include body size (obesity), demographics (age, gender, and race), and contributions by fibrogenic cytokines and neurohumoral factors, notably angiotensin II, which favor interstitial collagen deposition and perivascular fibrosis. These tissue changes, in conjunction with geometric abnormalities, primarily concentric hypertrophy, are responsible for the insidious dysfunction associated with LVH, beginning with decreased coronary reserve and altered diastolic ventricular filling and relaxation. The cardinal investigation is echocardiography: Doppler transmitral flow velocities expressed as the early (E) to atrial (A) wave ratio reveal LVH as a state of potential or actual myocardial ischemia. All antihypertensive drugs regress LVH, notably the angiotensin-converting enzyme inhibitors, which may also target the detrimental tissue changes. Regression enhances systolic midwall performance, normalizes autonomic function, and restores coronary reserve. The resulting improvement in prognosis has enshrined the detection, prevention, and reversal of LVH in the current guidelines of hypertension management.

Table I. Left ventricular hypertrophy (LVH) parameters measured by echocardiography.

- Left ventricular geometry, left atrium, aortic root
- Left ventricular systolic dysfunction
- Diastolic filling abnormalities
- Stroke work
- Total arterial compliance
- Myocardial ischemia (stress echocardiography)

DETERMINANTS OF HYPERTENSIVE LVH

The high prevalence of LVH in hypertension reflects the increased afterload imposed on the LV. However, other important determinants include demographic characteristics, the nature of the hemodynamic load, neurohumoral and growth factors, and underlying genetic factors.
Blood pressure

Hypertension is the fundamental trigger to the sequence of biological events leading to the development of LVH. However, the relationship between LV mass and clinic blood pressure is rather weak. LV mass is more closely related to mean 24-hour blood pressure.2

Several studies investigating the relative importance of day and night blood pressure have focused on the absence of a nocturnal dip in blood pressure.3,4 However, the dipper/nondipper classification is arbitrary and poorly reproducible. There is also the possibility that increased blood pressure is the consequence, rather than the cause, of LVH and associated vascular structural changes. Volume load, inotropy, and arterial compliance are also important determinants of the development and degree of LVH.

Demographics

Age, gender, race, and body size can all influence LV mass, possibly mediated via cardiac load. Thus, LVH prevalence increases with age, in both hypertensives and normotensives, perhaps due to the combination of age-related blood pressure elevation and declining aortic compliance. Aging also accounts for specific tissue changes, notably interstitial fibrosis and myocyte loss. Similarly, there is a gender difference in LV mass, which becomes evident in adolescence and remains constant during adult life; although the age-related increase in LV mass is greater in postmenopausal women than in men, gender is not a significant determinant of cardiovascular complications or of the prognostic impact of LVH. Hypertensive LVH is more evident in blacks than in whites at similar increases in blood pressure, certain cardiovascular complications, such as heart failure and sudden death, are also more common in blacks.

Body size, notably obesity, which compounds hemodynamic load independently of a clear-cut increase in blood pressure, is a major determinant of LV mass. With dietary sodium, it is associated with increased plasma volume and cardiac output, and may be responsible for hypertensive LVH.5

It has been suggested that by considering these measurable factors and hemodynamic load, echocardiographic LV mass could be assessed in the individual patient by deviation from the value appropriate for their gender and body size. Patients with an LV mass inappropriate to the stroke work for their gender and body size tend to cluster with metabolic risk factors. LV mass that overcompensates for hemodynamic load is associated with high cardiovascular risk. However, it is not yet known whether the morphological alteration conferring the higher risk is the presence of inappropriate LV mass or the development of LVH per se.6,7 The definition and clinical evaluation of “inappropriate” LV mass require further study.
Neurohumoral factors

Early experiments showed that the sympathetic nervous system induced LVH in a number of situations: even subhypotensive doses of norepinephrine increased LV mass. In humans, the effect is less clear-cut: if in pheochromocytoma LVH prevalence is relatively low and LV mass appears to increase proportionately to blood pressure, in essential hypertension LVH is associated with altered autonomic activity and a blunted response to β-adrenoceptor stimulation.8-10

Experimental studies also revealed the role of the renin-angiotensin-aldosterone system (RAAS) in mediating LVH. By stimulating the angiotensin receptor, angiotensin II induces hypertrophy and hyperplasia in myocytes and smooth muscle cells, and may regulate myocardial collagen synthesis. Excess angiotensin II production may regulate the expression of fibrogenic cytokine transforming growth factor-β1 (TGF-β1). Autocrine induction by TGF-β1 of the genes coding for extracellular matrix proteins determines perivascular and interstitial fibrosis. Angiotensin II may also depress collagenase activity, hence favoring interstitial collagen deposition.

Aldosterone may also stimulate extracellular collagen deposition and myocardial fibrosis.11,12 A key determinant of collagen degradation is the activation of metalloproteinases (a family of zinc-containing proteins that also includes stromalysins, collagenases, and gelatinases) and a multifunctional protein, tissue inhibitor of metalloproteinase–1 (TIMP-1), produced by connective tissue cells and macrophages, and probably regulated by angiotensin II.13

The pathogenic role of the RAAS in the development of hypertensive LVH requires confirmation, although LV mass is significantly increased in renovascular hypertension and primary aldosteronism compared with essential hypertension.14,15 There is also a correlation between LV mass and plasma aldosterone, which is independent of blood pressure.12

Insulin

Hypertensive LVH is often associated with insulin resistance and high insulin levels. Significant correlation between LV mass and insulin and insulin-like growth factor-I (IGF-I) was observed in a cohort of 101 essential hypertensives with normal glucose tolerance from the Progetto Ipertensione Umbria Monitoraggio Ambulatoriale (PIUMA); in addition, IGF-I was a main determinant of LV mass and geometry, independent of blood pressure.16 Very high LVH prevalence (>70%) has been repeatedly observed in diabetics, associated with changes in systolic and diastolic function disproportionate to the increase in blood pressure. The involvement of IGF-I may clarify the link between obesity, blood pressure elevation, LVH, and the metabolic syndrome.

Leptin is another possible neuroendocrine determinant. LVH in an animal model of leptin deficiency (the ob/ob mouse) reversed rapidly in response to exogenous leptin, suggesting that myocardial leptin receptors could be involved in cardiac remodeling.17 Other major metabolic cardiovascular risk factors, notably hypercholesterolemia and diabetes, also determine LV mass and the prevalence of LVH. Thus, low plasma high-density lipoprotein (HDL) cholesterol levels have been associated with increased LV mass, independently of blood pressure.

Genetics

Analysis of LV mass heritability in 2624 subjects in the Framingham Heart Study showed a closer correlation between LV mass in first-degree relatives than in second-degree relatives or couples, suggesting that about 30% of LV mass variance is genetic.18 Studies of genetic influence on LV mass have focused on candidate genes, ie, gene polymorphisms that may be involved in the hypertrophic cell process, using the genomewide scan technique to screen for a large number of genetic polymorphisms associated with the phenotype.

Polymorphisms associated with the RAAS were the initial target. In 1994, Schunkert et al described an association between insertion/deletion polymorphism of the angiotensin-converting enzyme (ACE I/D) and ECG LVH.19 Attempts at confirmation brought mixed results: a 1997 meta-analysis of five case-control studies in 3285 subjects found no association between the D allele and an increased risk of echocardiographic LVH.20 The ACE I/D genotype may only have a significant effect on LV mass in particular circumstances, eg, vigorous exercise, hypertension, renal failure, or cardiac ischemia.

There is unconfirmed evidence of an association between LVH and aldosterone synthase genetic polymorphism.21 Studies are ongoing on the role of other candidate genes, including those related to α- and β-adrenoceptors and components of the signal transduction mechanisms involved in cardiac hypertrophy, ie, G proteins, and mitogen-activated protein kinase.
(MAPK) regulated by calcium-dependent phosphatase. Genomewide scans are becoming easier to perform thanks to DNA microarray technology and the increasing number of single nucleotide polymorphisms (SNP) that have been identified. Putative chromosomal quantitative trait loci (QTL) influencing the variability of cardiac mass have been described in animals, but not as yet any specific genes related to increased LV mass—nor have any similar results been obtained in humans.

**METHODS OF ASSESSING LVH**

LVH has become integral to the diagnostic workup and treatment strategy in hypertension, as recommended by the European Society of Hypertension (ESH) and European Society of Cardiology (ESC). The most common diagnostic tools are the ECG and echocardiogram. ECG remains the conventional method, despite low sensitivity compounded by increasing age and body weight. New ECG criteria in addition to repolarization abnormalities and increased voltage have been proposed in recent years, the Cornell method being the most sensitive. The ECG can also be used to detect patterns of ventricular overload ("strain") or ischemia, indicating higher risk.

Since ECG and echocardiographic LVH predict mortality independently of one another and other cardiovascular risk factors, they convey, at least in part, different prognostic information, in particular when the ECG shows a strain pattern. Echocardiography is now widely available in the industrialized world for determining LV mass. It is time- and cost-effective, specific, ideal for serial mass and function follow-up, and more sensitive than ECG.

LV mass is calculated from the LV interventricular septum and posterior wall thicknesses and internal diameter using the Penn or American Society of Echocardiography (ASE) formulas, each of which has been validated by autopsy. All studies evaluating the prognostic significance of changes in LV mass have applied one or both formulas to M-mode measures made under 2D control. Values obtained using different formulas have given superimposable results. However, despite its advantages, echocardiography is not infallible, and technical error is always possible, due to the method itself, the quality of the examination, or interpreter inexperience. An Italian Society of Hypertension study of the reliability of repeat echocardiography recordings and interpretations in 260 normotensive and hypertensive subjects in 16 centers attributed biological significance to changes in LV mass exceeding 10% to 15%. Similarly, the Prospective Randomized Enalapril Study Evaluating Regression of Ventricular Enlargement (PRESERVE) found an intraclass correlation coefficient of 0.93 between two measures (screening and randomization) of echocardiographic LV mass in 183 hypertensive patients with LVH. Changes ±35 g and ±17 g represented probabilities of biological significance of 95% and 80%, respectively.

Under normal cardiac loading conditions, body size, and in particular lean body mass, is the most important determinant of heart size. For this reason, LV mass is usually normalized to body size. Normalization to body weight or other size measures (eg, body surface area) are inaccurate when body composition is altered, as in obesity. A surrogate of lean mass, body height, with LV mass indexed to height to the allometric power of 2.7, is particularly useful when evaluating the impact of abnormal body composition on LV anatomy, as in obesity or anorexia nervosa, but it is no better than other indices for prognostic purposes. Two main definitions of echocardiographic LVH based on prognostic data are in current use: (i) LV mass indexed to height (m².7) ≥51 g in both genders; and (ii) LV mass indexed to body surface area (m²) >125 in both genders (Table II).

Echocardiography is also useful in assessing the different types of LV geometric adaptation to increased cardiac load. The characteristics of concentric hypertrophy are increased in both mass and relative wall thickness, whereas those of eccentric hypertrophy are increased mass and a relative wall thickness < 0.45. Remodeling is said to be concentric when thickness increases with respect to radius, but without an increase in LV mass. Concentric hypertrophy ap-

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</table>

**Table II. Left ventricular hypertrophy (LVH) diagnostic values.**

**Abbreviations:** BSA: body surface area; F: females; h, height; M: males.
pears to carry the highest risk and eccentric hypertrophy
an intermediate risk, while concentric remodeling is
probably associated with a smaller, albeit noteworthy
risk. Geometries also differ in their hemodynamics, with
elevated total peripheral resistance and low cardiac out-
put in concentric hypertrophy, and normal total periph-
eral resistance and high cardiac output in eccentric
hypertrophy. Whether the geometries represent struc-
tural alterations of myocardial tissue is unknown.

Geometric patterns of LV adaptation have mechanical
consequences. LV systolic performance can be mea-
sured both at the endocardium by fractional shortening,
reflecting chamber function, and at the midwall, where
circumferential fiber contraction makes a greater con-
tribution to stroke volume. Midwall fractional short-
ening has important prognostic significance. In ad-
dition, Doppler transmitral flow and LV outflow tract
studies can be used to measure several indices of dias-
tolic function, reflecting both passive filling and active
relaxation.

Newer imaging methods such as MRI offer more accu-
rately measures of LV mass, even in ventricles with asym-
metrically increased thickness or abnormal contractility.
MRI has provided important pathophysiologic infor-
mation (midwall mechanics), but the duration, com-
plexity, and cost of the examination hinder wider use.
3D reconstruction of 2D echocardiographic images has
increased the reproducibility of LV mass measurements
and improved the display of changes in the segmental contractility of the
LV wall. However, given the difficulty of obtaining accurate orientation of the
2D planar images, their time-con-
suming planimetric reconstruction in 3D and identification of the exter-
nal border of LV walls, technologi-
cal advance is required before there

**PROGNOSTIC SIGNIFICANCE OF LVH**

Whether assessed by ECG or echocardiography, LVH
is a well-documented harbinger of morbidity and mor-
tality. In several studies the adjusted risk of cardiovas-
cular morbidity associated with baseline LVH ranges
from 1.5 to 3.5 with a weighted risk ratio of 2.3 for all
studies combined (Table III, page 8). The adjusted
risk of all-cause mortality associated with baseline
LVH ranges from 1.5 to 8, with a weighted mean risk
ratio of 2.5 for all studies combined.41

The structural remodeling of cardiomyocytes, non-my-
ocyes, and fibroblasts that occurs in cardiac hypertro-
phy contributes to perivascular fibrosis, initially around

**Figure 1. Cardiovascular events associated with concentric versus eccentric geometry.**

**Abbreviations:** LVMI: left ventricular mass index; RWT: relative wall thickness.

intramural coronary arteries and thereafter in the interstitial space. Increases in fibrillar collagen types I and III lead to progressive abnormalities of diastolic ventricular filling and relaxation, systolic dysfunction, arrhythmias, and conduction disturbances, thus greatly compounding the risk associated with LVH. Excess ventricular collagen may be due to increased collagen synthesis, but also to insufficient collagen degradation by interstitial collagenase.

The resulting pathophysiological and clinical changes accounting for increased risk in hypertensive LVH include both diastolic and systolic dysfunction, the latter being initially detected only during exercise. LV systolic function depends closely on myocardial afterload, as shown by the linear relationship between LV endocardial fractional shortening and end-systolic stress. In most cases of mild-to-moderate hypertension, LV systolic function is well preserved. Indeed, “supranormal” LV ejection fraction and fractional shortening have been found in hypertensive subgroups with mild LVH, possibly reflecting enhanced myocardial contractility. However, this contrasts not only with experimental data showing progressive impairment of contractility during gradual hypertension onset, but also with the Framingham evidence that hypertension remains, directly or indirectly, the most important predictor of congestive heart failure in the general population.

The paradox has been resolved by showing that LV fractional shortening or ejection fraction, measured at the endocardium, reflects chamber dynamics, but does not necessarily provide a direct measure of myocardial fiber shortening: the circumferential fibers responsible for LV short-axis shortening are located in the midportion of the LV walls, between two longitudinal shells responsible for long-axis shortening and twisting. Switching to a more physiologic midwall mechanics index related to circumferential end-systolic stress reveals that myocardial chamber function is often overestimated in hypertension, particularly if LV wall thickness is increased. Several studies have shown that LV midwall function is commonly reduced by 15% to 20% in hypertensive patients. The subgroup with depressed LV midwall function displays other features associated with an elevated cardiovascular risk profile, eg, concentric geometry, elevated peripheral resistance and heart rate, overweight, or obesity. Higher midwall fractional shortening is associated with female gender, in both hypertensive patients and the general population. Low midwall fractional shortening has proved an independent predictor of cardiovascular morbidity and mortality in hypertensive patients, as well as in healthy elderly subjects and American Indians in two general population–based surveys.

Diastolic dysfunction may be observed early in the natural history of hypertension and also in the normotensive children of hypertensive parents. It becomes more frequent in the presence of hypertensive LVH, and is influenced by advancing age, high heart rate and obesity. There is also a gender difference: in hypertensive LVH, impaired diastolic relaxation affects exercise capacity more severely in women, particularly if elderly, than in men.

LV diastolic dysfunction has been increasingly diagnosed in asymptomatic hypertension thanks to echocardiography, initially from measurements made on M-mode tracings and subsequently from Doppler transmitral flow velocities, corrected for a number of well-characterized determinants such as age, gender, heart rate, and blood pressure. The velocities—A wave (atrial contraction and emptying) and E wave (early LV filling)—occur in three patterns representing worsening diastolic LV filling: (i) slowed relaxation, with an inverted E/A ratio, slowed deceleration time, and increased isovolumic relaxation time; (ii) pseudonormalization,
with a preserved E/A ratio, but shortened deceleration time due to abnormalities of both relaxation and compliance, and (iii) restrictive pattern, with an increased E/A ratio (>1.5–2) associated with a very abrupt deceleration time, suggestive of elevated atrial pressure, and an abnormal pressure rise in a stiff LV. Pseudonormalization is best diagnosed by analyzing pulmonary venous filling patterns and/or the Valsalva maneuver.

The PIUMA study showed an association between E/A ratio changes and significant increases in cardiovascular events in a cohort of 1839 middle-aged hypertensives. Even more recent data come from a community survey in 2042 subjects aged 45 years or older that found diastolic dysfunction, evaluated by comprehensive transmitial, outflow tract and pulmonary flow Doppler examination, in 47% of hypertensives and 25.5% of subjects with a normal ejection fraction (>50%). The frequency of congestive heart failure increased dramatically with the severity of diastolic dysfunction.

Diastolic dysfunction is thought to precede systolic dysfunction, although evidence to this effect from longitudinal studies is lacking. Several studies using various techniques have shown that diastolic LV performance significantly influences exercise capacity in hypertensive LVH. Diastolic dysfunction (combined with incipient systolic dysfunction) is more prevalent in LVH, suggesting that it represents an accelerated transition phase from compensatory LVH to heart failure. Indeed, heart failure is diastolic in one third of cases or more. Although it may be associated with a lower mortality rate than other forms of heart failure, morbidity is high. Early recognition and appropriate therapy could help to prevent progression to diastolic heart failure and death. Although several studies have evaluated the effect of antihypertensive treatment on diastolic function, the clinical implications remain to be established.

LVH and failure are frequently associated with coronary artery disease, and hypertension is a major risk factor for coronary atherosclerosis. In ECG LVH, use of a “definite LVH” pattern comprising ST-segment and T-wave abnormalities was strongly associated with an increased incidence of acute infarction and sudden death. The association was weaker when LVH was defined by voltage criteria, suggesting that altered repolarization reflects reduced coronary perfusion.

LVH is associated with structural and functional changes in arteries, both large and small. Structural changes are particularly evident in concentric LVH. The association between LVH and extracranial carotid atherosclerosis might also explain the increased risk of cerebrovascular events (stroke and transient ischemic attacks) in ECG or echocardiographic LVH. LVH is thus a risk factor for vascular events.

The vascular changes consistently observed in LVH are largely responsible for the reduced coronary reserve. Concomitant atherosclerosis in epicardial coronary vessels and structural alterations and rarefaction of small coronary vessels limit blood supply when oxygen demand is increased by the greater tissue mass. Compensatory angiogenesis is inadequate during the development of adult LVH. Decreased subendocardial coronary perfusion leads to myocyte necrosis and reparative fibrosis, encouraging the progression to heart failure. Other extravascular mechanisms compounding the impairment of coronary reserve include changes in wall tension, heart rate, and contractility, at a time when the oxygen requirement, measured by the triple product (heart rate × LV mass × end-systolic stress), is progressively increased compared with patients with normal LV mass and geometry.

The ability to regulate coronary flow is weakest during exercise when oxygen demand increases. Under resting conditions, the reduction in coronary flow reserve may not have important consequences, but during the exercise-induced increase in oxygen requirement it becomes symptomatic and a factor in progressive LV dysfunction. Functional changes further weaken the vasodilator response of the coronary microcirculation. Endothelial dysfunction precedes morphological changes in the vascular wall and triggers remodeling. In summary, LVH is a state of potential or actual myocardial ischemia.

There is a predisposition to ventricular arrhythmias in hypertensive LVH, explaining the risk of sudden death. Proposed causes include repolarization abnormalities (QT dispersion) due to the concomitant increase in fibrous tissue, changes in coronary structure and function, diuretic-induced hypokalemia, and autonomic dysfunction (adrenergic hyperactivity and reduced cardiac responsiveness to β-adrenergic stimulation). Impaired ventricular filling, left atrial enlargement, and slowing of atrial conduction velocity all encourage atrial fibrillation, increasing the risk of cerebrovascular thromboembolism.

Since hypertensive LVH is an independent risk factor for cardiovascular morbidity and mortality, the possibility of reversal or even prevention by lowering blood pressure and modifying other pathogenetic factors is a major goal in antihypertensive therapy.
LV mass can be decreased by nonpharmacological intervention, notably weight loss, which is effective in obese hypertensives independently of blood pressure. The multicenter Treatment Of Mild Hypertension Study (TOMHS) monitored echocardiographic LV mass in 819 mild hypertensives annually for 4 years and found that lifestyle intervention reduced blood pressure significantly and decreased LV mass substantially in 30% of patients. However, there is still no hard evidence of an independent effect by dynamic exercise, dietary sodium, or alcohol restriction.

Multiple studies have shown that blood pressure reduction reverses LVH. The important determinants are treatment duration and the degree of blood pressure reduction. The Study on Ambulatory Monitoring of blood Pressure and Lisinopril Evaluation (SAMPLE) showed that changes in LV mass on ACE inhibitor therapy were significantly related not to changes in office blood pressure, but to the degree of mean 24-hour blood pressure control. Subsequent evidence has also shown the importance of homogeneity, or minimal daily fluctuation, in blood pressure control, as expressed in the “smoothness index.”

However, since blood pressure is not the sole determinant of LVH and fibrosis, the differing response of LV mass to different classes of antihypertensive drugs was ascribed to interference in nonhemodynamic factors such as the RAAS and sympathetic nervous system. Several meta-analyses were therefore conducted of studies demonstrating reversal of echocardiographic LVH using different antihypertensive drugs. Dahlöf et al calculated that for the same decrease in blood pressure the decrease in LV mass was greatest with ACE inhibitors, a conclusion confirmed by Cruickshank et al. Three years later, however, in a comparative review of diuretics, β-blockers, calcium channel blockers, and ACE inhibitors, Fagard showed that each reduced LV mass to a degree similar to that of the other three classes combined, and that direct comparison could not separate ACE inhibitors from calcium channel blockers. Two more recent meta-analyses, by Jennings and Wong and Klingbeil et al, confined to randomized, double-blind parallel group comparisons, have confirmed that the main determinants of LVH regression are the degree of blood pressure reduction and baseline LV mass. However, both studies also observed that ACE inhibitors, angiotensin II receptor blockers, and calcium channel blockers were more effective than β-blockers and diuretics given the same decrease in blood pressure.

Large randomized blinded studies (Table IV) comparing two or more different antihypertensive drugs have provided other data. The TOMHS results were the least instructive, due to the low prevalence of LVH and the efficacy of lifestyle intervention. The RAmipril Cardioprotective Evaluation (RACE) study showed significant LVH regression on the ACE inhibitor versus none on atenolol, at comparable levels of blood pressure reduction. Unfortunately, high dropout rendered largely inconclusive the comparison by the Department of Veterans Affairs Cooperative Study Group of 1 year’s monotherapy with six different antihypertensive agents.

### LVH REGRESSION ON ANTIHYPERTENSIVE TREATMENT

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Table IV. Studies comparing left ventricular hypertrophy (LVH) regression on different antihypertensive drugs. Study acronyms: see box on page 4.
in 587 male hypertensives. Two other randomized double-blind parallel studies employing centralized echocardiographic LVH criteria compared the effect on LV mass of an ACE inhibitor and a calcium antagonist (PRESERVE [Prospective Randomized Enalapril Study Evaluating Regression of Ventricular Enlargement]: enalapril vs nifedipine; ELVERA [Effects of amlodipine and lisinopril on Left VEntricuAR mAss and diastolic function (E/A ratio): lisinopril versus amlodipine]. Both found similar benefits with both drugs, as did the European Lacidipine Study on Atherosclerosis (ELSA) study with the calcium antagonist lacidipine and the β-blocker atenolol after treatment for 1 and 4 years.

The results of the comparative LVH regression: Indapamide Versus Enalapril (LIVE) study showed a reduction in LV mass on indapamide, suggesting that diuretics can also regress LVH. As for angiotensin II antagonists, they have been found more effective than the β-blocker atenolol, and similar to enalapril.

The Losartan Intervention For Endpoint reduction in hypertension (LIFE) trial versus atenolol in hypertensive ECG LVH confirmed the superiority of angiotensin II antagonists over β-blockers. Finally, a very recently published study (REASON, PREterax in regression of Arterial Stiffness in a contrOlled double-blinD study) found that the low-dose combination strategy, now proposed in several cases by the ESH/ESC guidelines, demonstrated superior LVH regression using perindopril/indapamide versus atenolol.

However, it should be kept in mind that interdrug differences tend to fade with time, since treatment duration is associated with progressive blood pressure control and decrease in LV mass, although β-blockers seem to be less effective in reversing LVH than other classes of drugs. In addition, blood pressure may be resistant if there is target-organ damage requiring the use of combination antihypertensive therapy. Several major intervention trials comparing the effects of single antihypertensive drugs on LV mass have in fact largely been comparisons of combination therapies in that most patients were taking more than one drug. Thus, over 50% of SAMPLE patients received lisinopril plus a diuretic, while about 90% of LIFE patients received a diuretic in addition to their β-blocker or angiotensin II blocker.

The RACE patients were also stratified by the addition or nonaddition of a diuretic to their basal therapy: LV mass was similarly reduced in each subgroup, with ramipril proving superior to atenolol both alone and in combination.

There is increasing interest in the effect of antihypertensive treatment on myocardial tissue composition, with particular respect to perivascular and interstitial fibrous tissue. Thus, for similar decreases in blood pressure after treatment for 6 months, Brilla et al showed that lisinopril decreased myocardial collagen and hydroxyproline content, and improved some diastolic function parameters, whereas hydrochlorothiazide had none of these effects, and only reduced myocyte diameter. Recent experimental and human evidence suggests that angiotensin II antagonists may also regress myocardial fibrosis.

Long-term studies thus indicate that all classes of antihypertensive drugs can lower blood pressure and regress LVH, with any initial interclass differences tending to fade with time. Differences in the reduction of LV mass for similar decreases in blood pressure are generally marginal, although there remains the possibility that drug classes differ markedly in their effect on cardiac structure and composition.

**CLINICAL AND PROGNOSTIC SIGNIFICANCE OF LVH REGRESSION**

Since LVH is such an important independent risk factor in hypertension, there is no lack of consensus as to the desirability of regression and prevention. Regression is associated with numerous benefits such as enhanced systolic midwall performance, normalized autonomic function, enhanced coronary reserve, and, possibly, enhanced diastolic filling and decreased ventricular arrhythmia. All contribute to the improved prognosis (Table V) demonstrated in several studies over

<table>
<thead>
<tr>
<th>Presence of LVH</th>
<th>Reversal of LVH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic dysfunction (midwall depression)</td>
<td>Unchanged (or improved at midwall)</td>
</tr>
<tr>
<td>Diastolic filling abnormalities</td>
<td>Unchanged or improved</td>
</tr>
<tr>
<td>Autonomic dysfunction</td>
<td>Autonomic near-normalization</td>
</tr>
<tr>
<td>Predisposition to ventricular arrhythmias</td>
<td>Fewer arrhythmias</td>
</tr>
<tr>
<td>Reduced coronary reserve</td>
<td>Improved coronary reserve</td>
</tr>
<tr>
<td>Associated vascular structural changes</td>
<td>Improved</td>
</tr>
</tbody>
</table>

*Table V. Pathophysiological and clinical consequences of left ventricular hypertrophy (LVH) regression.*
In the years using ECG measures. Normalization of ECG LVH in 524 Framingham subjects over a mean 5-year follow-up was associated with reduction in cardiovascular risk. Regression of Sokolow LVH criteria in the Heart Outcomes Prevention Evaluation (HOPE) study was similarly associated with a reduction in cardiovascular events; no change—or worsening—of this simple ECG index implied a less favorable outcome. The large long-term LIFE study showed that the greater regression of LVH with losartan was associated with fewer cardiovascular events (Table VI).

We ourselves demonstrated this for the first time in 151 uncomplicated hypertensives followed for 10 years. Cox survival analysis adjusted for conventional cardiovascular risk factors showed that LVH at the end of follow-up was the most important independent predictor of cardiovascular events.40

Moreover, regression of LVH was associated with a significantly lower cardiovascular risk not statistically different from that observed in patients who never developed LVH during follow-up. Verdecchia et al obtained similar results in a larger group of 430 patients over a shorter period (3.2 years).79 In 172 hypertensive patients followed for 11.3 years, Koren et al observed cardiovascular events in 29% with LVH at follow-up versus in 9% of those without.80

In the echocardiographic substudy of the LIFE trial that included 941 patients followed for over 4 years, the better prognosis associated with the significant decrease in LV mass from baseline to end of study was due mainly to a decrease in the incidence of stroke.81

These cumulative findings highlight the prognostic value of the LV mass response to treatment. Blood pressure was not significantly associated with cardiovascular events in these studies, although it cannot be excluded that the changes observed in the LV mass index at least partially reflected blood pressure control.

Baseline LV geometry confers differing cardiovascular risk in hypertension, concentric hypertrophy being the least favorable. We recently evaluated the relationship between prognosis and the response of LV geometry to antihypertensive treatment in 436 uncomplicated

<table>
<thead>
<tr>
<th>Reference</th>
<th>Patients (n)</th>
<th>Events (n)</th>
<th>Persistence</th>
<th>Regression</th>
<th>None</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muiesan et al.40, 1995</td>
<td>151</td>
<td>23</td>
<td>38</td>
<td>12.5</td>
<td>5</td>
</tr>
<tr>
<td>Verdecchia et al.79, 1998</td>
<td>430</td>
<td>31</td>
<td>21</td>
<td>6.2</td>
<td>5.4</td>
</tr>
<tr>
<td>Koren et al.80, 2002</td>
<td>172</td>
<td>34</td>
<td>19.8</td>
<td>8.8</td>
<td>9.6</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>753</strong></td>
<td><strong>88</strong></td>
<td><strong>26.3</strong></td>
<td><strong>9.2</strong></td>
<td><strong>6.7</strong></td>
</tr>
</tbody>
</table>
hypertensives (M: n=249; F: n=187; age 18-71 years) over 6.4 years. Persistence of LVH from baseline to follow-up was confirmed as an independent predictor of cardiovascular events. Cardiovascular morbidity and mortality were significantly greater with concentric than eccentric geometry, whether in the presence \( (P=0.04) \) or absence of LVH \( (P=0.02) \) at follow-up. Cardiovascular events were significantly more frequent with persistent concentric geometry \( (P<0.0001) \) for similar LV mass at follow-up (Figure 1).

Thus, an increase in echocardiographic LV mass in response to antihypertensive therapy, or a failure to decrease, confers a worse prognosis, while complete regression significantly reduces—indeed virtually normalizes—cardiovascular risk. In addition, the response of LV geometry to treatment may also have prognostic significance with and without LVH.

**FUTURE GOALS**

Focuses of future concern will include the biochemistry of the adaptive changes in energy metabolism and contractile proteins, notably the role of transmitters and transductional factors, as well as the timing of these responses to blood pressure changes, neurohumoral activation, and the development of structural alterations in other organs.

Techniques such as tissue characterization and non-invasive quantitative analysis of coronary flow will describe the respective contributions of perivascular and intraventricular fibrosis and myocardial ischemia to the mechanisms of LVH risk, and hopefully reveal ways in which these advances can be translated into individual patient benefit. However, we already know more than enough to realize that a major goal in the management of hypertension is the detection, prevention, and reversal of LVH.

**THREE KEY QUESTIONS**

The story of left ventricular hypertrophy (LVH) in hypertension is that of a good thing gone bad: hypertension initially triggers a potentially beneficial compensatory increase in left ventricular mass, but this ultimately evolves to a problem, becoming a disease in its own right, as well as a risk factor, endangering the heart and the patient’s life. The turning point in the pathophysiology of LVH is fibrosis, which, added to concentric hypertrophy, heralds left ventricular dysfunction. Antonello Ganau and Giuseppe Talanas take a close look at the pathogenesis of LVH, and ask: “Do coronary circulation abnormalities play an important role in the pathogenesis of hypertensive LVH?” and establish a firm link, even though the chicken-and-egg conundrum remains entire: is LVH the cause or the consequence of a defect in myocardial perfusion in hypertension? In view of the pivotal role of tissue alterations in the disease process, Javier Díez addresses the question: “How important is it to assess and attempt to control cardiac fibrosis in hypertension?” In doing so he opens up exciting preventive and therapeutic prospects. Bernhard M. W. Schmidt and Roland E. Schmieder examine another important question: “Hypertension and left ventricular hypertrophy: how much attention should we pay to the renin-angiotensin-aldosterone system?” This question is of particular relevance in view of evidence that drugs modulating the RAAS have beneficial effects that are additive to, and independent of, their blood-pressure-lowering effect. To conclude, by whichever means, LVH regression has benefits and as such detection, prevention, and reversal of LVH are now major targets in the management of hypertension.
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Left ventricular concentric geometry during treatment adversely affects cardiovascular prognosis in hypertensive patients.  
Hypertensive left ventricular hypertrophy (LVH) is a powerful predictor of coronary events. It is characterized by coronary circulation abnormalities such as impaired coronary blood flow autoregulation, decreased coronary reserve, increased minimal coronary vascular resistance, subendocardial underperfusion during exercise, and increased risk of myocardial infarction and death in the presence of coronary occlusion. These abnormalities appear to play a significant role in the pathogenesis of cardiac complications in arterial hypertension. Although the imbalance between coronary supply and myocardial needs has often been incriminated in the pathogenesis of hypertensive LVH, no convincing evidence has been provided to date that LVH is the consequence, rather than the cause, of a primary defect of myocardial perfusion in hypertensive patients.

Left ventricular hypertrophy (LVH) is the most important preclinical manifestation of hypertensive organ damage and a strong predictor of cardiovascular events in subjects with arterial hypertension or coronary artery disease, as well as in the general population.

Cardiac hypertrophy is an adaptive response to a sustained elevation in workload (e.g., arterial hypertension or valve disease) and has the effect of decreasing ventricular wall stress compensating for the increased workload. If mechanical overload is not relieved, progressive ventricular dilatation occurs with a consequent increase in wall stress, afterload mismatch, and deterioration of left ventricular (LV) pump function.

**MYOCARDIAL HYPTERTROPHY AND CORONARY BLOOD FLOW**

There is overwhelming evidence that the compensated hypertrophied heart is characterized by increased susceptibility to subendocardial ischemia. Patients with LVH and angiographically normal epicardial coronary arteries may exhibit electrocardiographic signs of subendocardial ischemia or develop effort angina pectoris. In the normal resting awake animal, the subendocardial blood flow is greater than the subepicardial flow, reflecting higher systolic wall stress and oxygen requirements in the deepest myocardial layers, and this flow gradient is preserved during exercise. In contrast, in hypertrophied hearts, the subendocardial blood flow increases inadequately during exercise, and the ratio of subendocardial-to-subepicardial blood flow is reduced. These data explain the increased vulnerability of the hypertrophied heart to subendocardial hypoperfusion.

Perfusion abnormalities in the hypertrophied heart could be caused by an increase in the minimum coronary vascular resistance resulting from a decrease in the minimum cross-sectional area of the vascular bed per gram of myocardium. The latter can result from structural coronary alterations such as vascular rarefaction, as the number of capillaries fails to match the growth of cardiomyocytes per unit area, or from a decrease in vascular lumen due to luminal encroachment resulting from vascular medial hypertrophy. A recent study has shown that a single administration of vascular endothelial growth factor (VEGF), given intrapericardially during the compensated phase of hypertrophy, increases myocardial perfusion by promoting microvas-
cular growth, thus supporting the vascular rarefaction hypothesis. Abnormal myocardial perfusion may also be due to the increase in extravascular intramyocardial forces, e.g., the perivascular fibrosis that compresses the vasculature and hence impedes blood flow. The hypertrophic growth of cardiomyocytes and remodeling of extracellular matrix, not associated with a parallel increase in the microvascular bed, result in a decrease in capillary density and impaired coronary flow reserve, while the increased distance of diffusion reduces the supply of nutrients to the hypertrophied myocytes.

The myocyte-to-capillary mismatch is aggravated during states of high workload or ischemia, when an increased demand for substrates and oxygen occurs, and may contribute to the decline in contractile function taking place in the late phase of hypertrophy.

Alterations in coronary vasomotor tone originating from either endothelial or vascular smooth muscle dysfunction may also play a role in impairing myocardial perfusion. A recent study showed an increase in myocardial perfusion reserve and maximal coronary flow in asymptomatic patients with hypertension-induced LVH after long-term treatment with lisinopril, but not with an angiotensin II receptor antagonist. Furthermore, post-treatment hyperemic flow was not different in the group treated with lisinopril compared with the control group. Since the angiotensin II receptor antagonist did not improve maximal myocardial perfusion, the possible explanation for the augmented blood flow in the lisinopril arm might be the increased availability of bradykinin and, consequently, vasodilator prostaglandins and nitric oxide. In this experiment myocardial perfusion reserve improved in the absence of significant reduction in LV mass, suggesting that the improvement in coronary vasodilator capacity was not due to reduction in extravascular compressive forces on the coronary microvasculature (Table I).

### CORONARY FLOW IN PHYSIOLOGICAL AND HYPERTENSIVE LVH

A recent study compared resting coronary flow velocity, determinants of myocardial oxygen demand, coronary vasodilator capacity, and physiological LVH was associated with a favorable remodeling and enhanced vasodilator capacity of the epicardial vessels. In fact, the vasodilator response of the left main coronary artery to dipyridamole was 5 times higher in athletes compared with hypertensive patients. These results suggest that the pathologic nature of the hypertensive hypertrophy, rather than the increase of myocardial mass per se, modifies the relationship between resting flow velocity and determinants of resting myocardial oxygen demand. The mechanisms underlying the age-de-
coronary vascular resistance, suggesting a role of aging in impairing coronary vasodilator capacity in arterial hypertension. Morphometric studies in various animal models suggest that the growth of the coronary microvascular bed does not adequately match the magnitude of myocardial growth, and a relative decrease in microvascular density occurs in hypertensive LVH. Furthermore, hypertension-induced LVH is characterized not only by myocyte hypertrophy, but also by collagen deposition within the ventricular wall and around the coronary vessels. The myocardial fibrosis increases the stiffness of the LV chamber, impairs LV relaxation, and may interfere with coronary vasodilator capacity, which is likely to initiate and maintain a process of myocardial underperfusion and malnutrition leading to depression of myocardial performance and further increase in interstitial fibrosis.

It has been reported that hypertensive LVH is associated with a significant increase in the expression of brain natriuretic peptide (BNP) mRNA, angiotensin-converting enzyme (ACE) mRNA, and endothelin-1 (ET-1) mRNA compared with exercise-induced LV physiological hypertrophy. Pathological cardiac hypertrophy is partly induced by endothelin and angiotensin II, the latter being able to enhance collagen deposition and reduce collagen degradation by inhibiting tissue metalloproteinase-I.

**CORONARY FLOW AND LEFT VENTRICULAR GEOMETRY**

LV geometric adaptation to hypertension is heterogeneous, reflecting the interactions of pressure and volume load, inotropic state, and aging. Hypertensive subjects can be classified into four patterns based on LV mass and relative wall thickness. Patients with concentric hypertrophy are characterized by very elevated peripheral resistance and the highest risk of cardiovascular morbidity and mortality. Sekiya and coworkers have assessed the responses of coronary vasomotion to vasoactive agents in the left anterior descending artery of hypertensive patients with angiographically normal coronary arteries. This study has shown that endothelium-dependent vasodilation induced by adenosine, which reflects the vasodilator capacity of the microvessels or, in other words, coronary flow reserve, was impaired only in patients with concentric hypertrophy. Thus, both severe coronary endothelial dysfunction and abnormality of coronary microvascular dilatation coexist in hypertensive patients with concentric hypertrophy, and may contribute to the increased cardiovascular morbidity and mortality associated with LV concentric hypertrophy.

**DEVELOPMENT OF HYPERTENSIVE LVH: DOES IMPAIRMENT OF CORONARY BLOOD FLOW PLAY A PATHOGENETIC ROLE?**

While there is strong evidence that LVH may induce abnormalities of myocardial perfusion, the hypothesis has also been raised that an inadequate coronary blood flow may in turn be a stimulus for myocardial hypertrophy. Few studies have investigated the pathogenetic role of coronary blood flow abnormalities in inducing LVH. Although the association of LVH with coronary atherosclerosis and myocardial infarction has been demonstrated by necropsy studies more than half century ago, only the advent of coronary angiography and ventriculography permitted to study in vivo both the coronary vessels and LV mass. In 1973, Pech and coworkers investigated the association between coronary abnormalities and LVH in patients with chronic ischemic heart disease. The authors selected patients with angina pectoris who were free of hypertension, cardiomyopathies, or valvular disease and underwent diagnostic cardiac catheterization and angiography. Patients were subdivided into four groups according to the severity of coronary atherosclerosis. LV mass was significantly increased in patients with coronary artery disease compared with those with normal coronary angiography. Among patients with documented coronary lesions, the two groups with occlusion or with critical stenosis of a major coronary vessel had higher LV mass than the group with small plaques or less severe coronary stenosis. In the absence of apparent causes of LVH, the authors speculated that the increase in LV weight could be attributed to proliferation of connective tissue for repairing the hypoxic necroses and/or to vicious hypertrophy of the remaining myocardium. While this paper provided clear evidence that LVH and coronary artery disease can be associated, no direct action of ischemia on myocardial hypertrophy could be demonstrated.

Gould and coworkers studied 54 patients with angiographically proven coronary artery disease and observed that hypertrophy develops after myocardial infarction in proportion to LV dilatation and may result in a syndrome of massive LVH, hypokinesia, and heart failure quantitatively identical to that found in primary cardiomyopathies. Patients with mild-to-moderate degrees of ischemic injury had intermediate degrees of hypertrophy, suggesting...
that coronary atherosclerosis with myocardial infarction was causal rather than merely coexistent. The authors proposed the following sequence of events leading to cardiac hypertrophy: regional injury and cell death → increased end systolic volume → higher wall stress → hypertrophy of the remote viable myocardium. Thus, the authors identified the excess of left ventricular load due to loss of contractile tissue, rather than the reduced myocardial perfusion, as the primary stimulus for myocardial hypertrophy.

A more direct link between myocardial ischemia and myocardial hypertrophy was demonstrated by Anversa and coworkers. They investigated the growth response of myocytes after acute myocardial infarction in rats. The animals were killed 3 days after ligation of the left coronary artery. Elevated LV end-diastolic pressure and decreased first derivative of LV pressure and systolic arterial pressure indicated significant impairment of ventricular function. Absolute infarct size was determined morphometrically by measurement of the fraction of myocyte nuclei lost and averaged 57%. Hypertrophy of the surviving LV myocytes was 28%. These results showed, on a cellular basis, that myocardial hypertrophy occurred after severe ischemia. Since LVH resulted from changes in the cellular shape characteristic of a combination of pressure and volume overload hypertrophy, the authors suggested that the loss of cardiac cells and the consequent dilation of LV chamber resulted in a greater regional wall stress on the remaining myocytes, responsible for compensatory eccentric hypertrophy of the viable ventricular myocardium. This combination of necrotic tissue, chamber dilation, and remote hypertrophy is now well known as postinfarction ventricular remodeling. The authors found that the myocyte volume per nucleus increased by 21% also in the nonischemic right ventricle. They speculated that the right hypertrophy could reflect pulmonary hypertension or an increase in right ventricular pressure to maintain the pressure gradient across the pulmonary vascular bed. Once again, the authors identified the excess of left ventricular load due to loss of contractile tissue, rather than the reduced myocardial perfusion, as the primary stimulus for myocardial hypertrophy.

Table II. End-diastolic length, thickness, and cross-sectional area of a myocardial segment before and after repeated episodes of transitory ischemia due to brief coronary occlusions in 5 dogs. *P<0.05 vs control.

<table>
<thead>
<tr>
<th>Days</th>
<th>Control</th>
<th>Peak values in cross-sectional area</th>
<th>Development of collateral flow</th>
<th>Regression</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>14±5</td>
<td>20±7</td>
<td>30±8</td>
</tr>
<tr>
<td>No. of occlusions</td>
<td>123±52</td>
<td>180±66</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Length (mm)</td>
<td>10</td>
<td>10.50±0.34*</td>
<td>10.55±0.34</td>
<td>10.37±0.50</td>
</tr>
<tr>
<td>Wall thickness (mm)</td>
<td>10</td>
<td>10.45±0.22</td>
<td>10.57±0.21</td>
<td>10.07±0.38</td>
</tr>
<tr>
<td>Cross-sectional area (mm²)</td>
<td>100</td>
<td>109.7±3.4*</td>
<td>106.5±4.2*</td>
<td>104.3±4.6</td>
</tr>
</tbody>
</table>

**Figure 1.** Effects of repeated transitory ischemia on thickness, length, and cross-sectional area of the myocardial segment exposed to brief repeated coronary occlusions in 5 dogs. The left circumflex coronary artery was occluded for 2 minutes and occlusion was repeated at time intervals of 30 minutes per 8 hours a day and for 5 days a week. The functional recovery due to collateral flow development induced partial regression of hypertrophy, despite the repetition of coronary occlusions. The ischemic segment recovered almost entirely both baseline thickness and length a few days after cessation of the occlusions.


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there was no direct evidence of a cause-effect relationship between myocardial ischemia and LVH.

In 1988, Fujita and coworkers investigated whether brief repeated coronary occlusions induced changes in regional myocardial geometry in dogs. In this study, 5 conscious dogs were instrumented with ultrasound crystals for measurements of subendocardial segment length and transmural wall thickness in the ischemic area, subendocardial segment length in the normally perfused area, coronary flow, and LV pressure. After recovery from surgery, 2-minute occlusions of the circumflex coronary artery were repeated at 30-minute intervals for 8 hours, 5 days a week, over an average period of 20±7 days. The end-diastolic segment length did not change significantly in the normal area throughout the experiment. By contrast, in the ischemic area, the end-diastolic regional cross-sectional area (product of segment length and wall thickness), measured daily in the preocclusion state, was increased by 9.7% \((P<0.05)\) after 14 days of repeated coronary occlusions. After 10 days of functional recovery, the myocardial thickness in the ischemic zone was different from the baseline value, whereas myocardial segment length and volume remained increased, revealing the persistence of regional hypertrophy after removal of the ischemic stimulus (Table II; Figure 1).36

These data indicate that regional myocardial hypertrophy may occur in response to repeated episodes of ischemia. However, the lack of histology did not allow to assess whether the regional increase in myocardial volume was attributable to myocyte hypertrophy or rather to interstitial edema or fibrosis. In this experimental model, the stimulus for regional myocardial hypertrophy might be either the repeated hypoxia or the increase in regional wall stress secondary to the ischemia-induced systolic wall thinning.

**CONCLUSIONS**

In summary, up to now there is no conclusive evidence that the mismatch between coronary blood flow supply and myocardial metabolic needs is important in the pathogenesis of LVH in hypertension. Other stimuli appear to be more relevant, such as hemodynamic pressure or volume load and neurohumoral factors. The development of LVH is associated with myocyte-capillary mismatch, which increases the vulnerability of the hypertrophied myocardium to ischemia and predisposes the cardiac muscle to a higher risk of infarction and to more extensive hypoxic necroses compared with patients without LVH. These abnormalities of myocardial perfusion and metabolism may play an important role in the transition from the compensated phase of hypertrophy to progressive left ventricular dilation and heart failure, eliciting the vicious circle of ischemia → chamber dilation → increase in wall stress → LVH → further ischemia. Normalization of the coronary reserve with antihypertensive drugs might slow down or interrupt the progression of the hypertensive heart disease.

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How important is it to assess and attempt to control cardiac fibrosis in hypertension?

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Keywords: arterial hypertension; collagen; echoreflectivity; fibrosis; hypertensive heart disease; left ventricular hypertrophy; peptide

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Fibrous tissue accumulation is an integral feature of the adverse structural remodeling of myocardial tissue following a cardiac insult. Given the importance of fibrous tissue in leading to myocardial dysfunction and failure, noninvasive assessment of fibrosis could prove a clinically useful tool, particularly given the potential for cardioprotective and cardioreparative pharmacological strategies. This approach represents an exciting and innovative strategy, and available data set the stage for large-scale and long-term trials, where this noninvasive assessment of myocardial fibrosis in patients with hypertensive heart disease and other cardiac diseases could prove useful.

Research over the past several decades has identified the dynamic nature of collagen turnover in normal and diseased tissues and an ever-expanding array of matrix functions that include the initiation and modulation of tissue growth and repair. In kidneys, lungs, and liver, fibrosis is considered a final common pathway to organ failure. This holds true for the heart as well. Given the important role of fibrous tissue in leading to cardiac failure, noninvasive methods are being developed to address fibrous tissue formation and degradation in patients with chronic cardiovascular diseases. In addition, the concept is emerging that management of these patients must target the adverse structural cardiac remodeling associated with these diseases.

**Fibrous tissue accumulation is an integral feature of the adverse structural remodeling of myocardial tissue following a cardiac insult.**

**MYOCARDIAL FIBROSIS IS PRESENT IN THE HUMAN HYPERTENSIVE HEART**

A number of studies performed in postmortem human hearts and endomyocardial human biopsies have shown that myocardial collagen volume fraction, a morphometric measure of the amount of tissue collagen, is consistently increased in hypertensive patients with left ventricular hypertrophy compared with normotensive controls. Furthermore, immunohistochemical analysis shows exaggerated accumulation of fibrillar collagen types I and III within the myocardial interstitium and surrounding intramural coronary arteries and arterioles (Figure 1). Hypertensive myocardial fibrosis is the result of increased collagen type I and III synthesis by fibroblasts and unchanged or decreased extracellular collagen degradation by matrix metalloproteinases. Hemodynamic and nonhemodynamic factors are involved in this disequilibrium in collagen metabolism that occurs in hypertension. In this regard, various lines of evidence suggest that, besides hypertension, angiotensin II also plays a major role in the development of hypertensive myocardial fibrosis.

**MYOCARDIAL FIBROSIS HAS A DETRIMENTAL CLINICAL IMPACT IN HYPERTENSION**

Although several other risk factors for congestive heart failure have been identified, arterial hypertension is the most common risk factor in the general population. Several arguments support the concept that myocardial fibrosis has a particularly important influence in the transition from compensated left ventricular hypertrophy to heart failure in patients with hypertensive heart disease. Firstly, interstitial fibrosis compromises the rate of relaxation, diastolic suction, and passive stiffness, contributing to im-
paired diastolic function. Secondly, since neither the collagen network nor the fibroblasts contribute to systolic contraction, increased collagen deposition and fibroblast volume means that systolic work is being performed by a smaller proportion of the cardiac mass, thereby contributing to systolic dysfunction. Although microscopic examination of cardiac biopsies is the most reliable method for documenting and measuring myocardial fibrosis, it is an invasive methodology unadapted to large-scale application, and that may be subject to sampling error. Thus, the development of noninvasive methods to document the presence of myocardial fibrosis in hypertensive patients would have broader application.

Tissue characterization by ultrasound refers to the detailed evaluation of the entire reflected ultrasound signal in an effort to extract information regarding actual tissue character. A correlation between alterations in echorefractivity, namely, diminution in the cyclic variation (CV) in returning ultrasound signal or backscatter signal, and histologically assessed collagen volume fraction was recently shown in the heart of hypertensive patients, suggesting that in these patients collagen content is the major determinant of regional echo intensity. Furthermore, as shown by the receiver operating characteristics curve (ROC) analysis, CV in the apex is a highly sensitive and specific parameter in the identification of severe myocardial fibrosis in patients with hypertensive heart disease (Figure 2 and Table I). In addition, changes in serum PICP induced by antihypertensive treatment have been shown to correlate directly with changes in collagen volume fraction in patients with hypertensive heart disease. Thus, measurement of PICP may provide indirect diagnostic information on both the extent of myocardial fibrosis and the ability of antihypertensive treatment to diminish collagen type I synthesis and reduce myocardial fibrosis in hypertensive patients. Interestingly, in a recent study, we demonstrated that the CV of back-
The scatter signal is abnormally diminished in those patients with hypertensive heart disease and abnormally high serum concentrations of PICP. Furthermore, the association of these two parameters predicted with great accuracy the presence of severe myocardial fibrosis in hypertensive patients (Table I). Thus, the combination of these two methodologies may be useful for the non-invasive assessment of cardiac fibrosis in hypertensive heart disease.

**MYOCARDIAL FIBROSIS CAN BE REDUCED IN HYPERTENSIVE PATIENTS**

Recent biopsy-based clinical studies provide evidence that other goals beyond reduction in blood pressure should be set in hypertensive patients, such as repair of cardiac fibrosis. Schwartzkopff et al reported that treatment with perindopril induced a significant decrease in periarteriolar fibrosis. Brilla et al showed that treatment with lisinopril, but not with hydrochlorothiazide, reduced myocardial fibrosis, independently from blood pressure control and left ventricular hypertrophy regression, and that this was associated with improved left ventricular diastolic function. We have shown that treatment with losartan for 1 year was associated with inhibition of collagen type I synthesis and regression of myocardial fibrosis in patients with essential hypertension (Figure 3). In contrast, hypertensive patients treated with amlodipine did not show any significant changes in collagen type I metabolism or myocardial fibrosis. Interestingly, the effect of the two compounds on blood pressure was similar during the entire treatment period. More recently, we reported that the ability of losartan to induce regression of severe myocardial fibrosis was independent of its capacity to reduce blood pressure or left ventricular mass, but was associated with a decrease in myocardial stiffness in hypertensive patients. These data confirm experimental studies in rats with genetic hypertension where pharmacological interference with the production and actions of angiotensin II has proved to be effective in reversing cardiac fibrosis, over and above the antihypertensive efficacy.

**CONCLUSIONS**

In hypertensive heart disease, it is not the quantity of myocardium, but rather its quality that accounts for the increased risk of adverse cardiovascular events. Thus, strategies directed toward the identification of the changes in myocardial structure (eg, fibrosis) involved in the transition from compensated left ventricular hypertrophy to heart failure are likely to offer the greatest promise of reducing the incidence of congestive heart failure and its associated mortality among hypertensive patients.

On the other hand, current management of hypertension should not simply focus on reduction in blood pressure.
pressure and left ventricular mass, it must also target the adverse structural myocardial remodeling that is present in hypertensive heart disease. Thus, as stated recently by the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC) in their guidelines for the management of arterial hypertension, “future studies should investigate treatment-induced effects on indices of collagen content or fibrosis of the left ventricular wall, rather than on its mass only.”

In this conceptual framework, the data reviewed here set the stage for large-scale and long-term clinical trials aimed at determining whether changes in the CV of ultrasonic backscatter signal and/or serum concentration of PICP are linked to changes in cardiac function and prognosis in patients with hypertension.

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Hypertension and left ventricular hypertrophy: how much attention should we pay to the renin-angiotensin-aldosterone system?

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Left ventricular hypertrophy (LVH) is an important independent cardiovascular risk factor. Angiotensin II and aldosterone, the effectors of the renin-angiotensin-aldosterone system (RAAS), have been found to increase LVH in a blood-pressure-independent fashion in several animal models of RAAS activation and in observational studies in humans. Pharmacological interventions interacting with the RAAS, namely, angiotensin-converting enzyme inhibition, blockade of the angiotensin II type 1 receptor, and antagonism at the mineralocorticoid receptor, have been shown to reduce LVH. These beneficial effects are in addition to, and independent from, their blood pressure-lowering properties and improve cardiovascular prognosis. The main question to be answered in the future is which combination of drugs interfering with the RAAS will prove to be most beneficial.

Keywords: hypertension; left ventricular hypertrophy; risk factor; RAAS; angiotensin II; ACE inhibition; prognosis

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SELECTED ABBREVIATIONS AND ACRONYMS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>4E-LVH</td>
<td>Eplerenone, Enalapril and Eplerenone/Enalapril–Left Ventricular Hypertrophy (study)</td>
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<tr>
<td>ARB</td>
<td>angiotensin receptor blocker</td>
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<tr>
<td>AT₁, AT₂</td>
<td>angiotensin II type 1 (2) (receptor)</td>
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<td>LIFE</td>
<td>Losartan Intervention For Endpoint reduction in hypertension</td>
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<tr>
<td>LVH</td>
<td>left ventricular hypertrophy</td>
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<tr>
<td>LVMI</td>
<td>left ventricular mass index</td>
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<td>MR</td>
<td>mineralocorticoid receptor</td>
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<td>PIC²EL</td>
<td>Preterax In a double-blind Controlled study Versus Enalapril in Left ventricular hypertrophy</td>
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<td>RAAS</td>
<td>renin-angiotensin-aldosterone system</td>
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<td>VALUE</td>
<td>Valsartan Antihypertensive Long-term Use Evaluation</td>
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PHYSIOLOGY AND PHARMACOLOGY OF THE RAAS

Figure 1 (page 34) shows the well-known cascade of the RAAS. The physiological function of the RAAS is to regulate blood pressure and to maintain salt and water homeostasis. The principal effectors of the system are angiotensin II and aldosterone. Angiotensin II is a potent vasoconstrictor and has profibrotic, hypertrophy-inducing, and growth-promoting effects on the heart as well as other organs. It exerts its effects through (at least) two receptors: the angiotensin II type 1 receptor (AT₁) and type 2 receptor (AT₂). The main effects of angiotensin II are mediated by the AT₁ receptor.
Activation of the AT\textsubscript{2} receptor has been shown to be at least in part, and in some tissues completely, antagonistic to activation of the AT\textsubscript{1} receptor. Aldosterone regulates renal sodium handling and also exerts profibrotic effects on the heart, kidney, and blood vessels. It acts mainly via the mineralocorticoid receptor (MR), although nongenomic effects of aldosterone are also well described.\textsuperscript{4}

Drugs blocking the RAAS include the angiotensin-converting enzyme (ACE) inhibitors, selective antagonists at the AT\textsubscript{1} receptor (ARBs, angiotensin receptor blockers), and antagonists at the MR (MR antagonists). The role of renin inhibitors is not further discussed, since at the moment orally active compounds are not available (though aliskiren may be, in the near future). The effects of these drug classes are similar, but clearly not identical. ACE inhibitors cause a decrease in angiotensin II levels and thereby decreased activity at the AT\textsubscript{1} and AT\textsubscript{2} receptors, but they increase bradykinin levels. ARBs cause an increase in angiotensin II levels via a negative feedback loop, and therefore increase the activity at the AT\textsubscript{2} receptor. Higher bradykinin levels and activation of the AT\textsubscript{2} receptor are specific effects of ACE inhibitors and ARBs, respectively, which might contribute to the effect of either class in addition to RAAS blockade. This also means that ACE inhibitors and ARBs do not have identical pharmacological profiles.

Blockade of the MR only affects the actions of aldosterone, and leaves angiotensin II concentrations unchanged or even increased, whereas plasma aldosterone levels are increased. This, in turn, could promote nonclassic effects of aldosterone.

The pharmacological differences between these drug classes are one reason why combination of different drug classes might be more effective than monotherapy. Another reason for combining various RAAS blocking drugs is that, over time, ACE-inhibitor blockade of the RAAS might become incomplete, leading to a loss of suppression of aldosterone plasma levels. This phenomenon is called aldosterone escape and occurs in about one third of patients treated with ACE inhibitors, and thus limits their effectiveness.

In the following sections, we discuss the evidence from experimental studies, observational human data, and clinical trials confirming the role of the RAAS in inducing LVH.

**RAAS AND LVH: EXPERIMENTAL EVIDENCE**

There is strong evidence from cell culture and animal experiments that angiotensin II exerts profibrotic, hypertrophy-inducing, and growth-inducing effects, which cause hypertrophy of the left and right ventricles. The mechanisms by which angiotensin II causes these effects are complex and still the subject of intensive research. These effects appear to mainly result from, among others, an increase in transforming growth factor \( \beta \) (TGF\( \beta \)) production,\textsuperscript{5} the activation of myocardial calcineurin,\textsuperscript{6} and an increase in intracellular calcium.\textsuperscript{7} Although these effects seem to be mediated by the AT\textsubscript{1} receptor,\textsuperscript{8} conflicting findings have also been reported.\textsuperscript{9}

With regard to aldosterone, chronic elevation of aldosterone levels combined with sodium intake induces myocardial fibrosis in rat left and right ventricles. The observation that fibrosis takes place even in the right ventricle argues for the concept that the fibrotic processes are blood pressure–independent.\textsuperscript{10,11} Furthermore, it has been proposed that aldosterone causes fibrosis and hypertrophy by interaction with angiotensin II. It has been shown in aldosterone-salt–treated rats that
aldosterone increases AT1 receptor mRNA and the ventricular density of the AT1 receptor. Robert et al showed that myocardial fibrosis was almost blunted to the same extent by ARBs as by spironolactone.12

**RAAS AND LVH: OBSERVATIONAL HUMAN DATA**

**Renal artery stenosis**

Renal artery stenosis causes excessive renin release from the macula densa, which causes activation of the RAAS, leading to an increase in circulating angiotensin II and aldosterone. Accordingly, patients with renovascular hypertension have pronounced hypertensive end-organ damage when compared with patients with essential hypertension. In one study, 32.6% of patients with renovascular hypertension exhibited LVH, in contrast to only 10.8% of patients with essential hypertension.13

**Primary hyperaldosteronism**

Primary hyperaldosteronism is characterized by elevated aldosterone levels accompanied by suppressed renin and angiotensin II, thus excluding significant concurrent effects of angiotensin II. In a cross-sectional study, LVH was shown to be more pronounced and to precede other organ damage, eg, of eyes or kidneys, in patients with primary hyperaldosteronism, compared with patients with essential hypertension.14

Patients with Conn’s adenoma exhibited a greater left ventricular mass and relative wall thickness than patients with essential hypertension matched for other confounding determinants of left ventricular mass.15 In parallel with the exaggerated concentric left ventricular remodeling and mass, these patients were characterized by an impaired diastolic filling of the left ventricle. These studies therefore suggest a blood pressure-independent effect of aldosterone on left ventricular structure and function.

**Essential hypertension**

In essential hypertension, a connection between angiotensin II as well as aldosterone and LVH has been repeatedly documented. In 68 otherwise healthy untreated mildly hypertensive men, we showed that patients with angiotensin II levels high with respect to the corresponding urinary salt excretion had greater left ventricular mass than patients with relatively low angiotensin II levels (Figure 2).16 Since high sodium intake suppresses the activity of the RAAS, our results suggest a blood pressure–independent effect of aldosterone on left ventricular mass after correction for the effects of blood pressure.17 In a cohort of hypertensive patients of young age and with only mild hypertension, a close relationship between urinary aldosterone excretion during high salt intake and left ventricular mass was consistently demonstrated.18

**Genetic polymorphisms of the RAAS**

Several linkage studies have been performed trying to link polymorphisms of genes of the RAAS to hypertension and hypertensive end-organ damage, especially LVH. In a study in 120 normotensive and mildly hypertensive young men, it was shown that hypertensive subjects with the –344 CC genotype of the aldosterone synthase promoter had a greater left ventricular end-diastolic diameter and smaller relative wall thickness than those with the TT genotype. The latter showed a greater increase in urinary sodium excretion after oral sodium loading. Accordingly, suppression of aldosterone levels was found in hypertensive

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**Figure 2.** Left ventricular mass in mildly essential hypertensive patients with relatively high angiotensin II levels for their salt intake was significantly higher than in patients with relatively low angiotensin II levels for their salt intake.

subjects with the –344 TT and –TC genotype, but not in patients with the CC genotype. This suggests that decreased ability to suppress aldosterone levels on salt loading is linked with early eccentric left ventricular remodeling in hypertensives with the –344 CC genotype of the aldosterone synthase promoter.19

In a similar study, it could be shown that the +1675 G/A-polymorphism of the AT2 receptor is linked to LVH in young mildly hypertensive males.20 Blood pressure levels as potential confounding factors were ruled out by including 24-hour ambulatory blood pressure into the analysis. The WHO-MONICA (World Health Organization–MONItoring trends and determinants in CArdiovascular diseases) study, a large epidemiological study in Augsburg, confirmed the link between AT2-receptor polymorphism and the degree of LVH. Interestingly, this AT2-receptor polymorphism has also been found to be a powerful prognostic marker for coronary heart disease.21

These and other studies suggest that polymorphisms modulating the activity of the RAAS influence left ventricular structure. Thus, these data support the view that activity of the RAAS is linked to LVH.

**RAAS AND LVH: THERAPEUTIC CLINICAL TRIALS**

**Meta-analyses**

Several meta-analyses have been performed, all of which consistently showed that drugs blocking the RAAS are superior to conventional antihypertensives with regard to reduction of LVH. The most recent meta-analysis, by Klingbeil et al,22 included for the first time a larger amount of data from ARB trials. In this meta-analysis, 3767 patients from 146 active treatment arms and 346 patients from 17 placebo arms were included. All studies were randomized, double-blinded, controlled, parallel group studies, using echocardiography for the diagnosis. Results were adjusted for blood pressure and treatment duration. Left ventricular mass index (LVMI) decreased by 13% with ARBs, by 11% with calcium antagonists, by 10% with ACEIs, by 8% with diuretics, and by 6% with β-blockers (Figure 3). The difference in reduction of left hypertensives, the main inclusion criterion. During a mean follow-up of 4.8 years, 11% of losartan-treated and 13% of atenolol-treated hypertensive patients reached the composite primary end point (death, myocardial infarction, stroke), which reflects a 13% reduction in relative risk with losartan treatment.23 Further analyses revealed that about one third of the benefit of losartan, compared with atenolol, was attributable to the greater reduction in LVH.

**Figure 3.** Meta-analysis of the efficacy of different antihypertensive drug classes in decreasing left ventricular mass. *P<0.05 vs β-blockers; †P<0.01 vs β-blockers. Modified from reference 22: Klingbeil AU, Schneider M, Martus P, Messerli FH, Schmieder RE. A meta-analysis of the effects of treatment on left ventricular mass in essential hypertension. Am J Med. 2003;115:41-46. Copyright © 2003, Elsevier, Inc.
comparing changes in LVH clearly show the pressure independence of these effects (Figure 4b). Therefore, the results of this study reflect a blood pressure–independent effect of RAAS blockade on LVH compared with β-blockade.

**The 4E-LVH Study**

In this small study (4E-LVH, Eplerenone, Enalapril and Eplerenone/Enalapril–Left Ventricular Hypertrophy study), monotherapy with enalapril 40 mg (n=54) or the new MR antagonist eplerenone 200 mg (n=50) was compared with the combination of both (enalapril 10 mg, eplerenone 200 mg). Left ventricular mass was assessed by magnetic resonance imaging (MRI), which is able to assess changes in LVH with very high sensitivity. Eplerenone and enalapril reduced left ventricular mass similarly, by 14.5±3.4 g and 19.7±3.2 g, respectively. The combination therapy reduced left ventricular mass by 27.2±3.4 g. This decrease was significantly greater than with eplerenone alone (P<0.007), whereas this difference was not significant (P=0.107) compared with enalapril. These data suggest that combination therapy to block the RAAS might be more effective than just blocking single steps of the cascade (Figure 5, page 38).

**The PICχEL study**

Low-dose combination therapy is a new therapeutic option for the first-line therapy of hypertension. The Preterax In a double-blind Controlled study Versus Enalapril in Left ventricular hypertrophy (PICχEL) study compared the effect on LVH regression of a low-dose combination of perindopril 2 mg and indapamide 0.625 mg with enalapril 10 mg monotherapy in a parallel group, double-blinded, randomized trial with 556 patients with LVH at baseline. To achieve blood pressure control, doses could be increased up to perindopril 8 mg and indapamide 0.625 mg with enalapril 10 mg monotherapy in a parallel group, double-blinded, randomized trial with 556 patients with LVH at baseline. After an observation period of 52 weeks, perindopril/indapamide therapy had lowered LVMI by 13.6%, whereas enalapril alone had lowered LVMI by 3.9% only (P<0.001). This greater LVMI reduction remained significant, even after adjustment for the greater blood pressure reduction obtained with the perindopril/indapamide combination versus enalapril.
Hypertension and LVH: how much attention should we pay to the RAAS? - Schmidt and Schmieder

The VALUE trial

Valsartan Antihypertensive Long-term Use Evaluation (VALUE) was a large-scale trial comparing the effects of valsartan and amlodipine on cardiovascular outcome in 15,245 hypertensive patients at high cardiovascular risk. This study failed to show a superiority of the ARB with regard to the combined cardiac end point and confirmed the beneficial effects on development of congestive heart failure, although the valsartan-treated group had a worse blood pressure control. To date, no data about the effects of these two drugs on LVH are yet available. Furthermore, inadequate blood pressure control has been identified as a determinant of LVH in the VALUE trial.

CONCLUSION

There is now strong evidence for specific blood pressure–independent effects of angiotensin II and aldosterone on the myocardium. Thus, in patients with LVH, we should pay much attention to achieving adequate blockade of the RAAS.

The main question to be answered in the future is which combination of drugs interfering with the RAAS will achieve the most beneficial effects. Finally, the VALUE trial reminds us that, alongside the favorable effects of RAAS blockade, which exceed the effect of blood pressure lowering alone, strict blood pressure control is the most important issue of antihypertensive therapy.

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Figure 5. Change in left ventricular mass in the Eplerenone, Enalapril and Eplerenone/Enalapril– Left Ventricular Hypertrophy (4E-LVH) study.
EPL = eplerenone, ENAL = enalapril; *P<0.007 vs eplerenone; †P=0.107 vs enalapril; ‡P=0.258 vs enalapril.


Heart and Literature

Another kind of heart

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As day after day flies by, in these increasingly hectic times, we are busily occupied in the office, in the ward, or in the lab, treating patients or carrying out research, wielding stethoscopes, pills, test tubes, electrocardiographs, and the other paraphernalia of our trade, reassuring an anxious parent, or breathlessly dashed off to apply the paddles to resuscitate a patient who’s turned blue—in short, up to our ears in cardiological pursuits. So, we may well ask, what room or time is left for the ordinary, everyday, romantic vision of the heart—ultimately, the only one that really counts—the antithesis of the charts in Gray’s anatomy, of the abstract shapes revealed by x rays or scans, or of the garish mass pulsating during open-chest surgery: I am talking about the classic, card-deck, valentine, Cupid’s arrow heart—in short. Of course such considerations hold true not only for the cardiologist, but likewise for the gynecologist, the pediatrician, the psychiatrist: through the veil of disease, are we still able to marvel about the beauty of love, of a woman, of a child, or of the mind?

PHRASES, IDIOMS, SAYINGS, PROVERBS

Let us, then, stray a bit from our narrow field of interest, and look at the heart from a linguistic perspective: no organ has inspired so many phrases, idioms, sayings, and proverbs, a sure sign of its importance in our collective wisdom. Take your pick from the following.

“To love with all one’s heart”; “She is so kind at heart”; “I have your best interests at heart”; “You broke my heart”; “Sick at heart”; “She knew him by heart”; “Why did he have a change of heart?”; “He wears his heart on his sleeve”. He is so close to my heart”; “Take heart!”. “I drank to my heart’s content”; “Cross my heart and hope to die”; I love you from the very bottom of my heart”; “I love you from the very bottom of my heart”; “I love you from the very bottom of my heart”; “I love you from the very bottom of my heart”; “This gives me much heart”; “What a heartthrob he is!” “How very heart-warming!” “Let’s have a heart-to-heart discussion”. “Absence makes the heart grow fonder”; “Cold hands, warm heart”; “The way to a man’s heart is through his stomach”; “Faint heart never won fair lady; “A heart of gold”; “In one’s heart of hearts”; “This warms the cockles of my heart”; “What the eye doesn’t see, the heart doesn’t see”.

“I didn’t have the heart to tell her”; “His heart is in this project” “Take care you don’t lose heart”; “She poured out her heart to her mother”; “His heart was in his mouth as he pushed the door open”. “My heart sinks”. “This person surely has his heart in the right place”. “He had his heart set on doing things right”; “Father took heart from the good news”. “You really shouldn’t take this so much to heart”. “This story tugs at my heartstrings”;

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grieve over”; “To win somebody’s heart”; “To harden one’s heart”; “a heavy/light heart”; “My heart bleeds for you”; “His heart missed a beat”; “Her head should rule her heart”;

You can surely think of plenty more…

POETRY

Poetry is the true haven of the heart; the following quotations are merely intended to whet your appetite and start you off on your own “auscultation” of the bards of the heart.

And what shoulder, and what art,
Could twist the sinews of thy heart?
And when thy heart began to beat,
What dread hand? and what dread feet?

William Blake (1757-1827)
Songs of Experience: The Tiger

Be near me when my light is low,
When the blood creeps, and the nerves prick
And tingle; and the heart is sick,
And all the wheels of Being slow.

Alfred Tennyson (1809-1892)
In Memoriam A. H. H. Canto 50

I pray thee leave, love me no more,
Call home the heart you gave me,
I but in vain the saint adore,
That can, but will not, save me.

Michael Drayton (1563-1631)
To His Coy Love

The heart has its reasons which reason knows nothing of. (Le cœur a ses raisons que la raison ne connaît pas).

Blaise Pascal (1623-1662)
Pensées, sect. 4, No. 211

The desires of the heart are as crooked as corkscrews
Not to be born is the best for man
The second best is a formal order
The dance’s pattern, dance while you can.

Dance, dance, for the figure is easy
The tune is catching and will not stop

Dance till the stars come down with the rafters
Dance, dance, dance till you drop.

W. H. Auden (1907-1973)
Death’s Echo

In the deserts of the heart
Let the healing fountain start,
In the prison of his days
Teach the free man how to praise.

W. H. Auden (1907-1973)
In Memory of W. B. Yeats

To wake the soul by tender strokes of art
To raise the genius, and to mend the heart;
To make mankind, in conscious virtue bold,
Live o’er each scene, and be what they behold:
For this the Tragic Muse first trod the stage.

Alexander Pope (1688-1744)
Prologue to Addison’s Cato

The thing on the blind side of the heart,
On the wrong side of the door,
The green plant growth, menacing Almighty lovers in the Spring,
There is always a forgotten thing,
And love is not secure.

G. K. Chesterton (1874-1936)
The Ballad of the White Horse

WILLIAM SHAKESPEARE (1564-1616)

The greatest bard of all is, of course, the one with the capital B, the Bard, aka, Shakespeare. He makes ample reference to our favorite organ in his works. To name a few, and for those among us who thrive on statistics, the word “heart” comes up 40 times in the Romeo and Juliet; 28 times in A Midsummer Night’s Dream; 39 times in Othello; 36 times in Hamlet; 16 times in The Tempest; and 59 times in King Lear, the all-time winner.

Excerpts:

The Sonnets

Mine eye and heart are at a mortal war,
How to divide the conquest of thy sight,
Mine eye my heart thy picture’s sight would bar,
My heart mine eye the freedom of that right.

A closet never pierc’d with crystal eyes—
But the defendant doth that play deny,
And says in him thy fair appearance lies.

As thus; mine eye’s due is thy outward part,
And my heart’s right, thy inward love of heart.

Sonnet 46

Much Ado About Nothing

He hath a heart as sound as a bell, and his tongue is the clapper: for what his heart thinks his tongue speaks.

Act III, scene 2

Beatrice
You have stayed me in a happy hour. I was about to protest that I loved you.

Benedick
And do it with all thy heart.
Beatrice
I love you with so much of my heart
that none is left to protest.
Act IV, scene 1

Othello
Were I the Moor, I would not be Iago:
In following him, I follow but myself;
Heaven is my judge, not I for love
or duty,
But seeming so, for my peculiar end:
For when my outward action doth
demonstrate
The native act and figure of my heart
In compliment extern, 'tis not long
after
But will I wear my heart upon my sleeve
For daws to peck at: I am not what I am.
Act I, scene I

Julius Caesar
By heaven, I had rather coin my heart,
And drop my blood for drachmas,
than to wring
From the hard hands of peasants
their vile trash
By any indirection.
Act IV, scene 3

King Lear
A servingman, proud in heart and
mind, that curled my hair, wore gloves
in my cap, serv'd the lust of my
mistriss' heart and did the act of darkness
with her, swore as many oaths as I
spake words, and broke them in the
sweet face of heaven, one that slept
in the contriving of lust, and wak'd to
do it. Wine lov'd I deeply, dice dearly;
and in woman out-paramour'd the Turk. False of
heart, light of ear, bloody
of hand, hog in sloth, fox in stealth,
wolf in greediness, dog in madness,
lion in prey. Let not the creaking of
shoes nor the rustling of silks betray
thy poor heart to woman. Keep thy
foot out of brothel, thy hand out of
placket, thy pen from the lender's book,
and defy the foul fiend. Still through
the hawthorn blows the cold wind; says
suum, mun, hey, no, nonny. Dolphin
my boy, my boy, sessa! let him trot by.
Act III, scene 4

Macbeth
I would not have such a heart in my
bosom for the dignity of the whole body.
Act V, scene 1

Romeo and Juliet
Romeo
O, she doth teach the torches to burn
bright!
It seems she hangs upon the cheek
of night
Like a rich jewel in an Ethiop's ear;
Beauty too rich for use, for earth
too dear!
So shows a snowy dove trooping
with crows,
As yonder lady o'ver her fellow shows.
The measure done, I'll watch her
place of stand,
And touching hers, make blessed
my rude hand.
Did my heart love till now? forswear
it, sight!
For I ne'er saw true beauty till this night.
Act II, scene 1
Romeo
If my heart's dear love...

Juliet
Well, do not swear: although I joy in thee,
I have no joy of this contract to-night:
It is too rash, too unadvised, too sudden;
Too like the lightning, which doth cease to be
Ere one can say "It lightens." Sweet, good night!
This bud of love, by summer's ripening breath,
May prove a beauteous flower when next we meet.
Good night, good night! as sweet repose and rest
Come to thy heart as that within my breast!

Act II, scene 2

Hamlet
Queen: O Hamlet! thou hast cleft my heart in twain.
Hamlet: O! Throw away the worser part of it,
And live the purer with the other half.

Act III, scene 4

Love's Labour Lost
Had she been light like you,
Of such a merry, nimble, stirring spirit,
She might ha' been a grandma ere she died;
And so may you, for a light heart lives long.

Act V, scene 2

And this last quote from Love's Labour Lost brings us back to our usual concerns: counseling patients on how to change their lifestyle to avoid stress, a risk factor for heart disease... Well, I guess it's high time to get back to work.

Heart: A hollow muscular organ that receives the blood from the veins and propels it to the arteries. In mammals it is divided by a musculomembranous septum into two halves...

Stedman's Medical Dictionary
27th Edition

\n\n\n
Another kind of heart - Scheffler
Perhaps the most remarkable and certainly one of the best known epidemiological studies in the history of medicine is the Framingham Heart Study. For 50 years, the residents of Framingham, Massachusetts, USA, have been synonymous with the remarkable advances made in the prevention of heart disease. Data collected from these residents have resulted in over 1000 scientific papers, identified major risk factors associated with cardiovascular diseases, created new opportunities and avenues for interventional clinical trials based on the study’s findings, and produced a revolution in preventative medicine.

One such example of a revolution in thinking generated by the Framingham Study is represented by this paper. For many years before, it was recognized that certain electrocardiographic criteria, characterized by large voltage QRS complexes, which may or may not be accompanied by ST-segment and T-wave abnormalities (so-called “strain pattern”), were associated with left ventricular hypertrophy (LVH), as confirmed on autopsy and other evidence. However, the prognostic implications, if any, of finding such changes on the electrocardiogram (ECG) were entirely unclear. This paper demonstrated clearly for the first time that the presence of LVH on the ECG was associated with a significant and important increase in the development of clinically apparent coronary heart disease, over the 14 years follow-up of the study. Subjects with “definite” LVH (defined by a combination of several of the following ECG findings: increased R-wave amplitude in the left precordial leads associated with ST-segment depression and T-wave flattening or inversion; deep S waves over the right precordial leads; left axis deviation; and slight prolongation of the ventricular activation time) had a threefold increase in coronary heart disease risk, even after adjustment for coexisting hypertension. Those with “possible” LVH (ECG characteristics similar to, but less striking than, those in subjects with “definite” LVH—predominantly consisting of tall R waves with no ST-segment or T-wave changes) had a twofold increase in risk, which was virtually abolished after adjustment for hypertension.

These findings have been corroborated in numerous large studies since. The precise meaning and significance of strain pattern in the presence of LVH by QRS voltage criteria may not always be entirely clear. In some cases, these changes may merely reflect the altered electrical properties of a hypertrophied myocardium. But in many cases, they may truly signify the presence of underlying, perhaps clinically silent, ischemic heart disease, or even myocardial ischemia with a relatively normal coronary arterial system. The most common cause of LVH is hypertension. We now know that hypertension is itself associated with the development of atherosclerotic disease, including coronary heart disease. Independently of this, as LVH (whatever the etiology) progresses, portions of the myocardium may not receive adequate blood flow even if the arterial supply is relatively undiseased.

The findings of this study emphasize the need to take the presence of ECG evidence of LVH seriously, particularly in the presence of repolarization changes, and in such cases, it is reasonable to investigate in more detail for the possible presence of underlying coronary disease, even in the absence of clinical symptoms or signs.

1970

Muammar al-Qaddafi is proclaimed Premier of Libya; Japan becomes the fourth country to launch a satellite into orbit; and John Lennon pays £1344 in fines for 69 people who had protested against the South African rugby team playing in Scotland.
Echocardiographic determination of left ventricular mass in man. Anatomic validation of the method

R. B. Devereux, N. Reichek
Circulation. 1977;55:613-618

For many years, electrocardiography was used as the standard noninvasive method for detecting the presence of left ventricular hypertrophy (LVH). LVH detection assumed widespread importance with the realization that it provided an accurate and independent predictor of coronary heart disease and cardiac death. To this day, electrocardiography is used by many as an initial screening test for the presence of LVH in those at risk of developing it, especially patients with hypertension. However, the major drawback of ECG for LVH detection is its lack of sensitivity; although ECG criteria for the diagnosis of LVH have undergone a series of refinements over the years, it is estimated that ECG can detect the presence of LVH in only 10% to 15% of cases. Furthermore, the voltage criteria for LVH lack specificity, so that large-voltage QRS complexes can be seen in the presence of a structurally normal heart, especially in young patients with a thin chest wall. A clear need was perceived, therefore, for a more accurate, sensitive, and specific noninvasive measure of left ventricular mass (LVM).

With the increasingly widespread use of echocardiography in the 1970s, it was apparent that this technique had the potential to provide much more accurate estimates of LVM. Although the presence of LVH, especially if moderate to severe, was often obvious by eye, there was a need to develop a method allowing for the numerical determination of LVM, especially for the less obvious cases of LVH. This paper was the first to describe a method for doing so in an accurate, reproducible, and widely applicable manner; although some earlier papers, notably by Rackley over 10 years previously, had provided echocardiographic formulae for LVM calculation, they were extremely complex to apply and therefore of limited usefulness.

Devereux and Reichek examined the left ventricular echocardiograms of 34 subjects who had died and undergone autopsy within 4 months of echocardiography. All subjects studied had no evidence of significant myocardial infarction, ventricular aneurysm, severe right ventricular overload, or hypertrophic cardiomyopathy. They found that an accurate estimate of LVM, which corresponded closely to autopsy LVM, could be obtained by the application of a simple cube formula, across the range of LVMs studied (101-505 g):

\[
LVM = 1.04 \left( \frac{LVIDp \times PWTp \times IVSTp}{3} - \left( \frac{LVIDp}{3} \right)^3 \right) - 13.6 \text{ g}
\]

where LVIDp is left ventricular internal diameter, PWTp is posterior wall thickness, and IVST is interventricular septal thickness (all measured using the Penn Convention). This equation is still used in modified form for the echocardiographic calculation of LVM. Later analyses against autopsy specimens found that the original formula overestimated autopsy-determined LVM, and a mathematical modification is now in widespread use:

\[
LVM = 0.832 \left( \frac{LVIDp \times PWTp \times IVSTp}{3} - \left( \frac{LVIDp}{3} \right)^3 \right) + 0.6 \text{ g}
\]

In clinical practice, echocardiography remains the standard and most widely applicable method for the determination of LVM. In recent years, magnetic resonance imaging (MRI) has provided an even more accurate and reproducible method to determine LVM, and is being used ever more widely in research studies involving the measurement of cardiac chamber volumes and structure. In time, it may well also supplant echocardiography for this purpose in clinical practice, but at the time of writing this is true in only a handful of centers.

President Jimmy Carter pardons Vietnam War draft evaders; Sarah Lowndes Dylan files for divorce from her husband of 11 years, Bob Dylan; and scientists report using bacteria in the laboratory to make insulin
his paper follows on very naturally from the two discussed above. To recap, the first by Kannel et al (the same group as that who conducted the present study) demonstrated that left ventricular hypertrophy (LVH) on the electrocardiogram predicted future risk of coronary heart disease. The second by Devereux and Reichek showed that left ventricular mass (LVM) could be accurately assessed by echocardiography. In the present study, Levy et al show that LVM as determined by echocardiography is predictive of clinical events, including death, attributable to cardiovascular disease.

Once again, in this study, the residents of Framingham were used. Over 3000 Framingham subjects aged 40 or older, who had no clinical evidence of cardiovascular disease, underwent echocardiography, with determination of LVM according to the Devereux and Reichek formula. LVM was divided by height for each subject, in order to correct for differences in heart size in subjects of different body size, and LVH was defined by an LVM >143 g/m in men and 102 g/m in women.

Subjects were followed up for 4 years, and it was found that LVM was directly related to clinical events, even after correction for all other known cardiovascular risk factors (including electrocardiographic evidence of LVH). For every increase of 50 g/m in height-corrected LVM, there was (after adjustment for other risk factors) approximately a 50% increase in relative risk of cardiovascular disease in both sexes. For the same increase in height-corrected LVM, the incidence of cardiovascular death was increased by almost 75% in men and by over 100% in women, and all-cause mortality was increased by approximately 50% in men and 100% in women.

These results once again underline the role of LVM as an important, and independent, predictor of cardiovascular morbidity and mortality. The question arises as to the mechanisms by which increased LVM may increase cardiovascular risk. Several possibilities suggest themselves. In the first place, LVH increases myocardial oxygen demand while decreasing coronary flow reserve, creating a supply-demand mismatch, which will predispose to cardiac ischemia and sudden death. Secondly, many factors that predispose to LVH (especially hypertension, but also aortic stenosis and obesity) are also associated with atherosclerotic disease, including coronary heart disease. Finally, LVH is known to predispose to ventricular dysrhythmias, and hence sudden death, even in the absence of overt coronary disease.

An alternative explanation is that increasing LVM is not causative, but rather is associated with factors predisposing to cardiac events. Thus, for example, in a group of hypertensive patients with similar blood pressure readings at a given time point, LVM may be related to the duration of the hypertension; a longer history of hypertension would be expected to be associated (independently) with both a greater LVM and a higher risk of cardiovascular disease.

The question of whether LVM is an independent cause of cardiovascular events, or is simply an epiphenomenon, remains unclear. Further large-scale trials are needed to show whether regression of LVH is independently associated with a reduction in cardiovascular risk. For the present, it seems prudent to consider LVH an important prognostic determinant, especially in patients with other cardiovascular risk factors or with established coronary disease.
Ambulatory blood pressure is superior to clinic blood pressure in predicting treatment-induced regression of left ventricular hypertrophy. SAMPLE Study Group.*


Circulation. 1997;95:1464-1470

Determination of office blood pressure (OBP) has, for many decades, been the standard method for detecting hypertension and its response to treatment. Indeed, to this day, physicians generally use office-based readings for this purpose, as well as for determining the need for antihypertensive therapy. It has been well recognized for many years, however, that OBP readings can be misleading. The well-known syndrome of “white-coat” hypertension will result in artificially high OBP, and many patients exhibit wide variability in their blood pressure throughout the day. The use of 24-hour ambulatory blood pressure (ABP) monitoring has greatly facilitated the detection of white-coat syndrome, and has allowed much more accurate assessment of what has been termed blood pressure “load” over the 24-hour period, which in turn is believed to correlate much more closely with the presence and severity of target-organ damage (such as left ventricular hypertrophy, LVH) and other hypertensive complications than office readings. What was not clear until recently was whether regression of LVH in response to antihypertensive treatment was predicted better by OBP or ABP, and this was the subject of this paper.

Mancia et al treated 206 essential hypertensive patients with LVH (as determined by echocardiography) with the angiotensin-converting enzyme inhibitor lisinopril, with or without addition of the thiazide diuretic hydrochlorothiazide, aiming for a target diastolic pressure below 90 mm Hg. As predicted, therapy decreased both systolic and diastolic blood pressure readings very effectively, as measured both by OBP and ABP, additionally, it reduced left ventricular mass index (LVMI). They found that the pretreatment LVMI correlated very well with both systolic and with diastolic average ABP but did not correlate with OBP. They also found that, in response to antihypertensive treatment, LVMI reduction correlated well with the reduction in average ABPs, and the correlation was just as strong if they studied LVMI reduction in relation to average daytime or nighttime ABPs, by contrast, there was no relationship between LVMI reduction and OBP decrease.

These findings were confirmatory of previous studies, which collectively suggest that target-organ damage in hypertension relates better to ABP than to OBP. The findings also demonstrated, for the first time, that LVH regression is much better predicted by reduction in ABP than in OBP. This paper added to the accumulating evidence that ABP is more meaningful, and more predictive of future disease (or its prevention by antihypertensive therapy), than is OBP.

The fact remains, however, that ABP measurement in the clinical situation is much more laborious, technically difficult, and logistically complex to organize than determination of OBP. It is also more expensive, and therefore largely as a result of this less widely available. For these reasons, most large trials of antihypertensive therapy have continued to use OBP rather than ABP, and practicing physicians have continued to use OBP, despite its relative drawbacks. Wider availability of ABP monitoring, and the establishment of firm evidence-based guidelines for blood pressure targets as determined by ABP rather than OBP, must be desirable objectives for improving treatment of hypertension and prevention of its complications.

* Study on Ambulatory Monitoring of Blood Pressure and Lisinopril Evaluation

Bill Clinton starts his second term as President of the United States; Madeleine Albright becomes the first female US Secretary of State; and it is revealed that French Museums have nearly 2000 pieces of art that were stolen by the Nazis.
Signaling pathways for cardiac hypertrophy and failure

J. J. Hunter, K. R. Chien


Hunter and Chien, in this paper, provide a very good overview of the cellular and molecular changes associated with cardiac hypertrophy and failure. Both may be primarily genetic in origin (for example, hypertrophic cardiomyopathy or idiopathic dilated cardiomyopathy), or may result from various mechanical, hemodynamic, hormonal, and pathological stimuli. Either way, characteristic changes are found in a variety of mediator molecules and signaling pathways in the heart, and these may explain many of the structural and functional changes seen.

The paper starts by defining the different morphological types of cardiac hypertrophy, as seen at the cellular level: physiological hypertrophy (as occurs in athletes, where the cardiac myocytes exhibit proportional increases in length and width), eccentric hypertrophy (as occurs in dilated cardiomyopathy, with a relatively greater increase in myocyte length than width), and concentric hypertrophy (found in pressure overload, where myocyte width is increased to a greater degree than length). It also describes the morphology of hypertrophic cardiomyopathy, where myofibrillar disarray is seen, with secondary myocyte hypertrophy.

The review then describes the different biological systems that have been used to study the genetic and molecular mechanisms of cardiac hypertrophy and failure, principally cultured cardiac myocytes and genetically altered animals (mainly knockout and transgenic mice). The data from such studies have allowed a much greater mechanistic insight into the processes of cardiac hypertrophy and failure at the cellular level.

Cardiac hypertrophy is associated with increased expression of embryonic genes, including those for natriuretic peptides and fetal contractile proteins. Pressure overload causes the local release of a variety of growth factors, including endothelin-1, angiotensin II, and insulin-like growth factor-I (IGF-I), and also certain interleukin-6-related cytokines, such as cardiотrophin-1. The former appear to act predominantly via Gp proteins and ras (retrovirus-associated DNA sequence), while the latter work through gp130.

p38 mitogen-activated protein kinases are also activated through the action of growth factors. Interestingly, ras, Gp, and the b isoform of p38 simulate the hypertrophic response, whereas Gp and the a isoform of p38 stimulate apoptosis. Thus, many of the same signals that trigger hypertrophy also mediate apoptosis, the latter favoring the development of chamber dilatation and heart failure, creating a type of “ying-yang” effect. On the other hand, gp130 pathway activation, while stimulating hypertrophy, blocks apoptosis. The resultant effect of pressure overload, therefore, depends on the balance between the prohypertrophic and proapoptotic pathways.

In the context of dilated cardiomyopathy, genetic defects in the structural components of the linkage between cytoskeleton and extracellular matrix result in chamber dilatation and heart failure, and mutations in one of several such proteins may give rise to the same clinical picture. In the case of myocyte loss in the context of myocardial infarction, biomechanical stress induces the growth factor and cytokine responses described above, but here apoptosis predominates, leading to progressive ventricular dilatation and failure.

Much research is currently ongoing in this area. The hope is that, if we can better understand the molecular pathogenesis of cardiac remodeling, this will in the future allow better therapeutic strategies to treat or even to prevent the development of heart failure.
Summaries of Ten Seminal Papers - Ferro

Association of change in left ventricular mass with prognosis during long-term antihypertensive treatment

M. L. Muiesan, M. Salvetti, D. Rizzoni, M. Castellano, F. Donato, E. Agabiti-Rosei


Muiesan et al. in this study, return to the theme of whether left ventricular hypertrophy (LVH) is an important and independent predictor of cardiovascular events. Some years before the publication of the Heart Outcomes Prevention Evaluation (HOPE) study, these investigators examined the prognostic value of changes in left ventricular mass index (LVMI) with time, in hypertensive patients.

A group of just over 200 hypertensive patients who had undergone echocardiography 7 to 13 years previously, considered to be of acceptable technical quality, were identified. Of these patients, 151 were available and underwent repeat echocardiography, which was considered technically optimal. LVMI was calculated on both the initial and follow-up echocardiogram, and changes in LVMI over follow-up were related to the occurrence of nonfatal cardiovascular events. Antihypertensive treatment was not standardized, so that diuretics, β-blockers, calcium antagonists, and angiotensin-converting enzyme inhibitors were used, either alone or in various combinations, in these patients; however, there was no difference in the class(es) of drugs used in patients with and without LVH, and none of the patients had received antihypertensive therapy at baseline. LVH was defined by an LVM >134 g/m$^2$ in men and >110 g/m$^2$ in women. By these criteria, approximately 50% of patients had normal LVMI at both examinations, around 20% showed regression of LVH, 25% showed LVH at both visits, and only a small minority (7 out of 151) developed LVH between the first and second visits.

The investigators found that, after adjustment for traditional cardiovascular risk factors, the incidence of nonfatal cardiovascular events was higher in those patients who had LVH at both examinations than in those who either had normal LVMI at both visits or those who exhibited regression of LVH; the relative risk was approximately 3.5 in the former group. There was no significant difference in events in the latter two groups. So far as the group who showed development of LVH over the follow-up period was concerned, because of the very small numbers in this group, it was not possible to assign an accurate relative risk to them; however, since 2 out of these 7 patients suffered a nonfatal cardiovascular event (a proportion comparable to the group with LVH at both time points), it seems highly probable that their relative risk was also elevated.

When the relative importance of various prognostic factors at baseline or follow-up, or both, was evaluated, only age and LVH status associated significantly with the occurrence of events; male sex was of borderline significance, and clinic blood pressure (systolic or diastolic) was not significant. No significant interaction was seen between age, sex, and LVH status. Indeed, the presence of LVH at the end of follow-up was the most important factor related to the occurrence of nonfatal cardiovascular events.

These data indicated that LVH persistence or increase is associated with a higher risk for cardiovascular events, whereas risk is significantly reduced, and probably normalized, by complete regression of LVH. This paper added to the growing body of evidence that LVH is an independent and important predictor of future cardiovascular events, and that adequate regression of LVH will largely (or even perhaps completely) abrogate the increase in risk. Today, this is largely taken for granted, and one of the important goals of hypertension treatment, aside from lowering blood pressure, is to ensure that LVH, when present, is adequately treated.

1995

Austria, Finland, and Sweden enter the European Union; a magnitude 7.2 earthquake kills over 5000 in Kobe, Japan; and Bill Clinton authorizes a $20 billion loan to Mexico to stabilize its economy
Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol


Lancet. 2002;359:995-1003

Reporting on the Losartan Intervention For Endpoint reduction in hypertension (LIFE) study, the authors address the age-old question of whether any particular type of antihypertensive drug offers advantages over others. The groundbreaking nature of this study was that, for the first time, a clear advantage was found for one drug over another, in terms of reducing clinical cardiovascular events, for the same degree of blood pressure lowering.

Angiotensin II is a potent growth factor for cardiac myocytes. It has been widely assumed, therefore, that blockade either of the production or of the action of angiotensin II should be especially effective in preventing or in regressing left ventricular hypertrophy (LVH). In this study, over 9000 hypertensive patients with established LVH (as determined by electrocardiography) were randomized to receive treatment with either losartan (an angiotensin receptor blocker) or atenolol (a β-blocker), add-on antihypertensive therapy using other drug classes was then permitted if necessary, with the goal of reducing sitting blood pressure to <140/90 mm Hg.

The investigators found that both arms (losartan- and atenolol-based therapy) had very similar baseline blood pressures, and achieved near-enough identical blood pressure reductions throughout a minimum of 4 years’ follow-up. However, LVH regression, as judged electrocardiographically, was indeed superior in the losartan-treated group. The question was, did this correspond with a lower rate of cardiovascular events in this group?

The answer was unequivocally yes. The primary composite end point—death, myocardial infarction, or stroke—was significantly reduced, by 13%, in the losartan group as compared with the atenolol group. In secondary analyses, although no difference was seen in myocardial infarction between the groups, stroke was decreased by 25% in losartan-treated as compared with atenolol-treated patients, and this finding was highly significant.

Another interesting finding was that losartan therapy was associated with less new-onset diabetes than atenolol therapy. Indeed, a large number of trials using angiotensin receptor blockers (including the recently published Valsartan Antihypertensive Long-term Use Evaluation [VALUE] study) now suggest that these drugs do indeed decrease the likelihood of development of diabetes (and the same may be true of the angiotensin-converting enzyme inhibitors), but the mechanism for this effect remains entirely unclear. It appears, therefore, that angiotensin receptor blockade with losartan confers clinical benefits over β-blockade with atenolol, in hypertensive patients with LVH.

It is interesting to speculate whether the same result would have been found for a different (non-β-blocker) comparator drug. As discussed for the Klingbeil et al paper (see last summary), β-blockers may reduce central aortic pressure less than other antihypertensive drug classes, for the same degree of lowering of peripheral arterial pressure, and in some cases may actually increase central pressure. The more recent VALUE study showed that valsartan reduced blood pressure less than did amiodipine, a calcium channel blocker. However, the primary end point of cardiac morbidity and mortality was similar in the two groups. This again might suggest a benefit of angiotensin blockade independent of blood pressure lowering, although the interpretation of this study is complicated by the fact that blood pressure lowering was inferior in the valsartan group. Further trials are needed to determine whether the angiotensin receptor blockers do indeed offer benefits over other antihypertensive drug classes, beyond blood pressure reduction.

Launch of Operation Anaconda, the US invasion of Afghanistan; death of Niki de Saint Phalle, the French sculptor (known for her “Nanas”), painter, and film maker; and a new order of insects, resembling praying mantises, the Mantophasmatodea, common name “Gladiators,” is discovered in Namibia.
For many years, it was unclear whether myocardium that had undergone pressure-overload hypertrophy, for example, in response to hypertension, exhibited normal contractility during systole. Most in vitro studies on myocardium obtained from animal models of cardiac hypertrophy had suggested that such heart muscle was hypocontractile; by contrast, studies in humans with left ventricular hypertrophy (LVH) had suggested that contractility of hypertrophic myocardium was normal, or even perhaps increased. It had been suggested that this difference might be due to the fact that, in human studies, chamber volume changes had been studied rather than myocardial mechanics, and a direct extrapolation from chamber dynamics to myocardial function is only justified if it is assumed that the myocardium thickens to the same degree across the whole left ventricular wall during systole.

However, theoretical considerations, as well as a variety of experimental data in both animals and humans, had suggested that the inner part of the left ventricular wall thickens more than the outer part, during systole. Thus, for example, a circumferential mid-wall fiber would exhibit relative migration towards the epicardium during systole and, as a consequence of such differential movements, chamber volume changes would overestimate overall myocardial contractile function.

To study this, Shimizu et al developed an ellipsoidal model of the left ventricle, in which the left ventricular wall was divided into two shells (inner and outer) of equal thickness at end-diastole. It was assumed that the volume of each shell did not change during systole and diastole. Using this model, wall thickness and midwall fiber position were calculated during the cardiac cycle, in the left ventricular cineangiograms of 14 subjects with normal blood pressure and 15 subjects with hypertension. Using this model, these workers found that midwall fractional shortening was significantly lower in hypertensives with an increased left ventricular mass index than in hypertensives with normal left ventricular mass index or in normotensives. This was so despite no difference being seen in ejection fraction between these groups, as determined from chamber volume changes during the cardiac cycle using standard methods.

This paper demonstrates convincingly that simple analysis of chamber dynamics in the left ventricle does not easily translate to give accurate information on myocardial function, and that in the presence of left ventricular hypertrophy it overestimates myocardial contractility, due to a greater degree of thickening of the inner as compared with the outer left ventricular wall in this situation. Both chamber volume changes and midwall fractional shortening have important clinical correlates. Ejection fraction will be a more direct determinant of cardiac output (which also depends on left ventricular chamber volume and heart rate), and hence tissue perfusion and arterial systolic pressure. On the other hand, depressed myocardial function, even in the presence of an apparently normal ejection fraction, can presage the future development of cardiac failure, and be an indication of reduced preload, increased afterload, or myocardial ischemia. Furthermore, the demonstration that LVH is associated with myocardial contractile dysfunction is, in itself, another strong indicator that regression of the hypertrophy with appropriate therapies must be an important goal in such patients.

Left ventricular midwall mechanics in systemic arterial hypertension. Myocardial function is depressed in pressure-overload hypertrophy


Circulation. 1991;83:1676-1684
Reduction of cardiovascular risk by regression of electrocardiographic markers of left ventricular hypertrophy by the angiotensin-converting enzyme inhibitor ramipril


Circulation. 2001;104:1615-1621

This paper addresses the question of whether regression of left ventricular hypertrophy (LVH) gives rise to an improvement in cardiovascular morbidity and mortality, irrespective of effects on blood pressure. For the reasons described in the following summary, angiotensin-converting enzyme (ACE) inhibition was used to cause LVH regression.

Approximately 9000 patients were enrolled into the Heart Outcomes Prevention Evaluation (HOPE) study. These patients were judged to be at high risk of vascular disease, or had diabetes with at least one additional cardiovascular risk factor (hypertension, dyslipidemia, smoking, or microalbuminuria). The participants were randomized to receive either 10 mg ramipril daily or placebo; for treatment of hypertension, investigators were encouraged to use antihypertensive agents other than ACE inhibitors. The patients were followed up for 4 to 6 years. At baseline, it was found that 676 of the patients had LVH as determined electrocardiographically, and they were equally distributed in the ramipril and placebo arms. By the end of the study, fewer patients in the ramipril arm showed development or persistence of LVH as compared with the control arm; and more ramipril-treated patients exhibited regression or prevention of LVH than control patients. In terms of clinical events, the primary outcome measure (cardiovascular death, myocardial infarction, or stroke) was reduced by approximately 20% in those patients who showed LVH regression/prevention as compared with those who showed LVH development/persistence, of the constituents of this end point, cardiovascular death and myocardial infarction were each reduced in the LVH regression/prevention group, and there was a trend to a reduction in stroke although this did not reach significance. Highly significant reductions were also seen in heart failure, revascularizations, total mortality, and sudden death/cardiac arrest, in the LVH regression/prevention patients.

In this paper, it was claimed that the benefits of ramipril in terms of LVH were independent of blood pressure reduction, since the effect on LVH status remained significant after adjusting for drop in systolic blood pressure. Indeed, the effect of ramipril on blood pressure in this study was small (mean 3/2 mm Hg), and was judged by the investigators to be too small to account for the LVH regression and reduction in clinical events seen. However, because according to the HOPE protocol ramipril was given once daily at bedtime, and blood pressure was measured in the office during the day, the 24-hour reduction of blood pressure may have been underestimated. In a subsequently published substudy of HOPE, 38 of the patients underwent 24-hour ambulatory blood pressure (ABP) measurement before randomization and after 1 year. At 1 year, ramipril did not significantly reduce office blood pressure or daytime ABP in these subjects, however, 24-hour ABP was significantly reduced (10/4 mm Hg), mainly because of a more pronounced and significant blood pressure–lowering effect during the night (17/8 mm Hg). On the basis of this, it seems likely that the effects on cardiovascular morbidity and mortality seen with ramipril in the HOPE study may, to a larger extent than ascribed in the present paper, relate to effects on blood pressure patterns over the 24-hour period.

Regardless of the dependence or independence of the findings on blood pressure effects, HOPE was a landmark study, showing that ACE inhibition confers marked benefits in patients at high risk of cardiovascular disease, and, largely as a result of HOPE, as well as more recent studies, ACE inhibitors are now routinely used in clinical practice in such patients.

2001

Tom Cruise and Nicole Kidman announce that they have separated; the foot and mouth disease crisis begins in the UK; and Erik Weihenmayer (Boulder, Colorado) becomes the first blind person to reach the summit of Mount Everest
A meta-analysis of the effects of treatment on left ventricular mass in essential hypertension

A. U. Klingbeil, M. Schneider, P. Martus, F. H. Messerli, R. E. Schmieder


As mentioned in the preceding summary, one of the major questions that has plagued physicians involved in the treatment of hypertension over the last 40 years, with the development of various classes of antihypertensive drug with different mechanisms of action, is whether any drug class is superior to any other in terms of preventing cardiovascular morbidity and mortality. This remains to a large extent unanswered in terms of clinical events, but many workers have examined the differential effects of different drug classes on cardiovascular surrogate end points.

This study by Klingbeil et al was a meta-analysis of eighty trials of blood pressure reduction (146 active treatment arms with 3767 patients, 17 placebo arms with 346 patients). The constituent trials studied the effects of diuretics, β-blockers, calcium channel antagonists, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin receptor blockers, on left ventricular mass index (LVMI) as determined by echocardiography. These workers found that, after adjustment for treatment duration and change in diastolic blood pressure, there were indeed differences between the different drug classes in terms of effects on LVMI. Angiotensin receptor blockers, ACE inhibitors, and calcium antagonists reduced LVMI by 10% to 13%, whereas diuretics and β-blockers reduced LVMI by 6% to 8% only. When pairwise comparisons were performed to compare individual drug classes directly, β-blockers were significantly less effective than angiotensin receptor blockers, ACE inhibitors, or calcium antagonists in decreasing LVMI.

The reason for this lesser effect of β-blockers is not clear. However, there has long been a suspicion that β-blockers may not be as good as diuretics in preventing clinical events; for example, the Medical Research Council trial of mild hypertension treatment in the 1980s showed that bendrofluazide decreased stroke more than propranolol treatment, and this difference was highly significant. Moreover, the recently published Losartan Intervention For Endpoint reduction in hypertension (LIFE) study (see previous summary) showed that, in patients with hypertension and LVH, losartan reduced the primary end point and LVMI significantly more than did atenolol. Other work suggests that, although β-blockers reduce peripheral arterial pressure well, they may have a much lesser effect on central aortic pressure (and indeed in some cases may actually cause central pressure to rise) than other antihypertensive drug classes.

Angiotensin II is known to be a potent growth factor for cardiac myocytes, and it is logical that blockade of its production or action should prevent, or even regress, cardiac hypertrophy especially well. Intracellular calcium accumulation also stimulates cell growth, so again one might predict an antihypertrophic effect for calcium channel blockers. Whether these mechanisms underlie the differences seen in this study remains uncertain, however.

Nor is it entirely clear whether such differences in effects on LVMI are clinically meaningful. However, on the basis of this paper as well as other more recent evidence, for example, from the LIFE study, it seems logical to use drugs other than β-blockers in patients with hypertension and LVH. The most effective drugs for regressing left ventricular hypertrophy would appear to be ACE inhibitors, angiotensin receptor blockers, and calcium antagonists, and these should probably be the antihypertensive drugs of choice in such patients.

The US Supreme Court upholds California’s “Three strikes and you’re out” law, on the basis of which any person convicted of more than two felonies gets a life sentence, with no parole before 25 years; WHO issues a global alert on SARS; and Sweden rejects adopting the euro in a referendum.
Hypertension & Left Ventricular Hypertrophy

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