Review

Hypertensive Heart Disease

Joseph A. DIAMOND*,** and Robert A. PHILLIPS***

Left ventricular hypertrophy (LVH) and diastolic dysfunction (CHF-D) are the early manifestations of cardiovascular target organ damage in patients with arterial hypertension and signify hypertensive heart disease. Identification of hypertensive heart disease is critical, as these individuals are more prone to congestive heart failure, arrhythmias, myocardial infarction and sudden cardiac death. Regression of left ventricular (LV) mass with antihypertensive therapy decreases the risk of future cardiovascular events. The goal of antihypertensive therapy is to both lower blood pressure (BP) and interrupt BP-independent pathophysiologic processes that promote LVH and CHF-D. The purpose of this review is to summarize current and emerging approaches to the pathophysiology and treatment of hypertensive heart disease. (*Hypertens Res* 2005; 28: 191–202)

***Key Words*: left ventricular hypertrophy, left ventricular diastolic function, left ventricular mass, techniques, treatment**

Introduction

Interactions between genetic and hemodynamic factors cause hypertensive heart disease in patients with arterial hypertension. The resulting structural and functional adaptations lead to increased left ventricular (LV) mass, diastolic dysfunction, congestive heart failure (CHF), arrhythmias and abnormalities of myocardial perfusion due to microvascular endothelial dysfunction. Consequently, hypertensive individuals with hypertensive heart disease are more prone to myocardial infarction, congestive heart failure, stroke, and sudden death then persons with hypertension alone. As our understanding of the pathophysiology leading to hypertensive heart disease becomes more clear, antihypertensive treatments may be better targeted to lowering the risk of these complications.

Epidemiology of Hypertensive Heart Disease

Left ventricular hypertrophy (LVH), as determined by echocardiography, is defined as LV mass in the upper 2.5 to 5% of the adult population. It occurs in 15–20% of hypertensive patients (*1*). Considered as a discrete, categorical variable, LVH significantly increases the risk of coronary artery disease, CHF, decreased LV ejection fraction, cerebrovascular accidents, ventricular arrhythmia, and sudden death (*2*–*7*). LVH increases the relative risk of mortality twofold in subjects with coronary artery disease and fourfold in those with normal epicardial coronary arteries (*8*, *9*). In addition, when LV mass is considered as a continuous variable, a direct and progressive relationship exists between cardiovascular risk and the absolute amount of LV mass (*3*).

Pathophysiology of Hypertensive Heart Disease

Up to 60% of the variance of LV mass may be due to genetic factors independent of blood pressure (*10*). An increasing number of genes are being identified that contribute to the development of hypertensive heart disease (Table 1). Most appear to target the renin-angiotensin-aldosterone system, although some newly identified genetic variations appear to affect other pathways, including the human type A natriuretic

From the *Division of Cardiology, Long Island Jewish Hospital, New York, USA; **Albert Einstein College of Medicine, New York, USA; and ***Department of Medicine, Lenox Hill Hospital, and NYU School of Medicine, New York, USA.

Address for Reprints: Joseph A. Diamond, M.D., Division of Cardiology, Long Island Jewish Medical Center, 270–05 76th Ave, New Hyde Park, New York 10040, USA. E-mail: jdiamond@lij.edu

Received November 22, 2004; Accepted in revised form December 14, 2004.

Table 1. Genes Implicated in the Development of Left Ventricular Hypertrophy and Diastolic Dysfunction in Essential Hypertension

Gene	Location	Physiological role
ACE gene (*91–93*)	Insertion/deletion polymorphism of 287 base pair marker intron 16 on chromosome 17	Production of angiotensin II
X-linked angiotensin II type-2 receptor gene (*94*)	Intronic polymorphism (−1332G/A) on the X-chromosome	Oppose the effects of AT_1 receptor
Angiotensinogen gene (*95*)	−6G/A polymorphism in exon 2 on chromosome 1	Production of angiotensinogen
Aldosterone synthase gene (*39*)	−344C/T polymorphism in the promoter region of the aldosterone synthase gene on chromosome 8	Production of intracardiac aldosterone
G protein β 3 subunit gene (*96*, *97*)	Single base substitution at position 825 of exon 9 in the short arm of chromosome 12	Enhanced Na^+-H^+ exchange due to enhanced G-protein activation
Type A human natriuretic peptide receptor gene (*98*)	Deletion mutation of the 5′ flanking region in chromosome 1	Elevated BNP due to decrease natriuretic peptide receptors
Myosin binding protein C (MyBP-C) gene (*99*)	Short arm of chromosome 11	Production MyBP-C, which has several structural and regulatory functions in the contractility of myocytes
β-Adrenergic receptor kinase (βARK) regulator gene (*6*, *100*)	Chromosome 22	Elevated gene expression, attenuates β-adrenergic signaling and contributes to contractile dysfunction
Calcium-modulating cyclophilin ligand (CAMLG) gene (*101*)	Chromosome 5	The regulation of calcium ion signaling, may play role in calcium transport during myocardial contraction/relaxation
α-1B adrenergic receptor (ADRA1B) gene (*101*)	Chromosome 5	Indirectly stimulate intracellular calcium release and protein kinase C activation

ACE, angiotensin converting enzyme; AT_1, angiotensin II type 1; BNP, brain natriuretic peptide.

peptide receptor gene, and the G-protein β 3-subunit gene affecting Na^+-H^+ exchanger activity. Certain variants of these genes promote LVH in hypertensive individuals. Other genes have been identified that affect myocardial contractility, *e.g.*, the myosin-binding protein C (MyBP-C) gene, and the β-adrenergic receptor kinase (βARK) gene. There are other identified genes that appear to modulate diastolic dysfunction. These are summarized in Table 1.

The sequence of events that leads from increased wall stress to cellular hypertrophy is due to interaction among several systems that translate wall stress into cardiac myocyte hypertrophy. The coupling of hypertrophic signals at the cell membrane with the reprogramming of cardiomyocyte gene expression involves intracellular calcium release, which is an early response to myocyte stretch and other humoral stimuli, including angiotensin II, phenylephrine and endothelin. The increase in intracellular calcium results in activation of the phosphatase calcineurin, which then dephosphorylates transcription factor $NFAT_3$, resulting in its translocation to the nucleus. In the nucleus, AT_3 interacts with another transcription factor, $GATA_4$, to initiate transcription of genes that lead to myocyte hypertrophy (*11*), such as β-myosin heavy chain and β-skeletal actin (Fig. 1). In the hypertrophic response, other genes are also upregulated, such as those for atrial natriuretic peptide and phospholamban (*12*). There are other pathways that interact with the calcineurin–NFAT pathway to regulate cardiac myocyte growth. The mitogen-activated protein kinase (MAPK) pathway appears to regulate calcineurin *via* the c-*jun* N-terminal kinases (JNKs) and extracellular signal-regulated kinases (ERKs) (*13*, *14*). As noted in the following sections, new therapeutic targets for promoting LV mass regression target these pathways (Fig. 1).

While the transition from LVH to heart failure involves many factors, increased fibrosis plays a central role. Oxidative stress, a common feature of arterial hypertension, most likely plays some role in this process by promoting cardiomyocyte apoptosis and fibrosis. This is demonstrated in the aortic-banded experimental rat model of concentric LVH

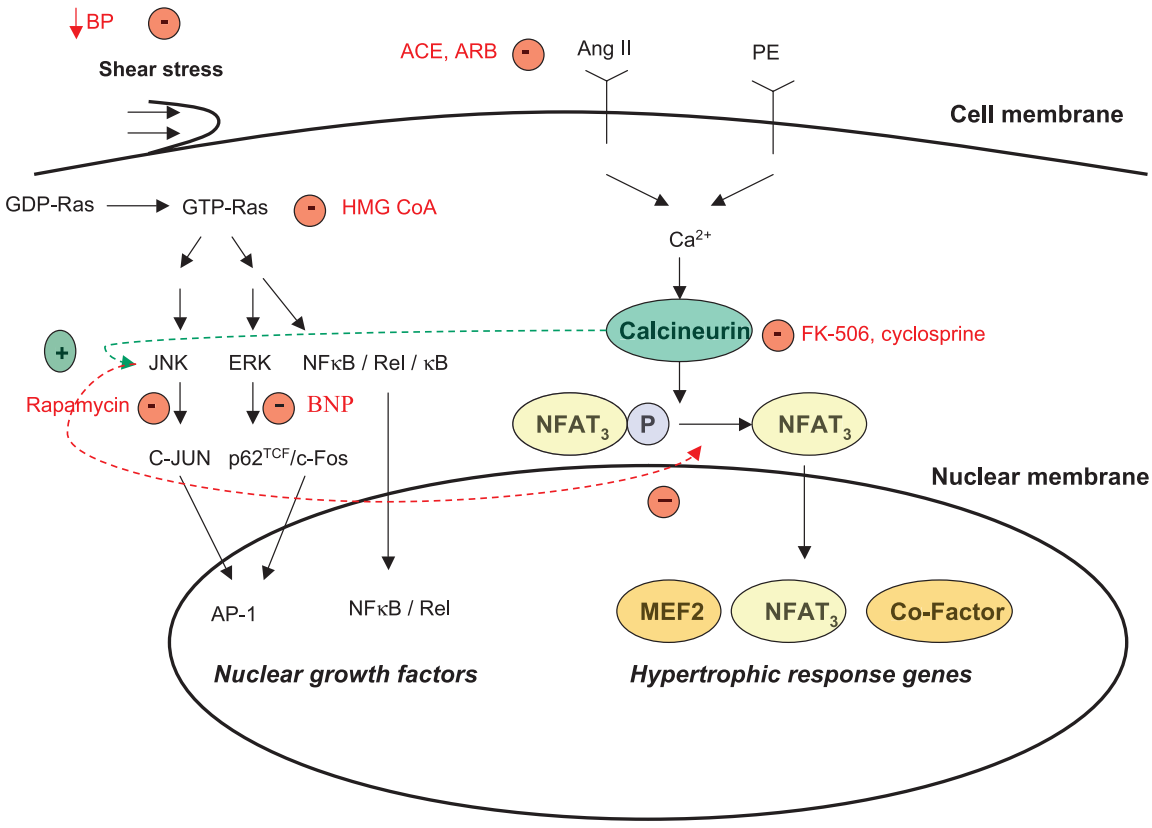

Fig. 1. *A model for the calcineurin-dependent transcriptional pathway in cardiac hypertrophy and for the sequential events of signaling and gene expression* via *the MAPK pathways in response to shear stress or mechanical strain. There is a complex feedback among these pathways. Calcineurin promotes production of active JNK and ERK. JNK, on the other hand, appears to inhibit the effects of calcineurin on NFAT by promoting phosphorylation of NFAT. The effects of medications are also noted in the figure.*

(*15*). As part of the hypertrophic response, cardiac fibroblasts undergo a phenotypic change, assuming a myofibroblast configuration. Stimulated myofibroblasts proliferate and increase production of extracellular matrix proteins, including fibronectin, laminin, and collagen I and III. This results in progressive fibrosis. Many of these processes are controlled by integrins, which are cell surface receptors that mediate the cell's ability to interact with its environment (*12*). One such integrin, called osteopontin, has been targeted for treatment to improve diastolic function (see below).

Another factor that influences fibrosis is the dysregulation of the interaction between matrix metalloproteinases (MMPs) and their inhibitors, the tissue inhibitors of metalloproteinases (TIMPS). MMPs are enzymes locally produced in the extracellular matrix. MMPs are inhibited by another family of enzymes, TIMPs. MMPs increase the degradation of fibrillar collagen and extracellular matrix. In the failing heart, they augment the degradation of normal type collagens, which are then replaced by fibrous intestinal deposits of poorly cross-linked collagens. This promotes dilatation of the ventricle. In addition, the digestion of matrix components by MMPs causes a reactive increase in the production of other factors, including transforming growth factor β (TGF-β), insulin-like growth factor and fibroblast growth factor. Among other functions, TIMPs inhibit MMPs by preventing their activation in the presence of soluble collagen (*16*). There is a delicate balance between MMPs and TIMPs regulating both the production and degradation of collagen in extracellular matrix. This balance is disrupted in hypertensive heart disease. Of these enzymes, one called TIMP-1 appears to play a more significant role in this regulation in the human heart. During the transition from compensated hypertrophy to decompensated CHF, there appears to be upregulation of MMPs with inadequate feedback inhibition by TIMP-1, resulting in proliferation of fibroblasts and progression of myocardial fibrosis (*17*). Data from the Framingham study and other echocardiographic studies show a correlation between circulating TIMP-1 and echocardiographic measures of LVH and diastolic function (*18–20*). These studies suggest that inadequate TIMP-1 inhibition of MMPs (TIMP-resistance) results in the production of more TIMPs. Thus they may be used as a surrogate marker of progressive fibrosis in hypertensive heart

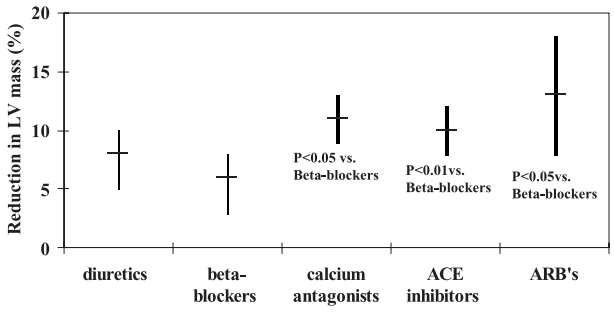

Fig. 2. *Change in left ventricular (LV) mass index (as a percentage of the baseline value) with antihypertensive treatment by drug class in a meta-analysis of 80 double-blind prospective randomized trials. Mean values with 95% confidence intervals are shown, adjusted for change in diastolic BP and duration of treatment (*5*).*

disease.

LV Mass Regresion: Current Approaches

Effective control of blood pressure (BP) promotes regression of LV mass. This has been shown in over 400 clinical studies (*21*). Furthermore, improved survival has been demonstrated with LV mass regression (*22–24*). This is in part due to early improvement in LV function. Midwall fractional shortening, a sensitive echocardiographic measure of intrinsic myocardial systolic performance, shows early significant improvement with LV mass regression in hypertensive individuals (*25*).

BP reduction results in LV mass regression with most classes of antihypertensive medication. However, pure vasodilators such as minoxidil and hydralazine lower BP without promoting LV mass regression (*26*). A meta-analysis of more than 100 studies yielded a moderately strong relationship between BP reduction and LV mass regression (*27*). Thus, lowering BP helps to promote LV mass regression, but is not the only driving force.

In addition to BP reduction, other mechanisms, such as inhibition of the renin-angiotensin aldosterone system, may also contribute to the reduction of LV mass. There is evidence both in favor and against this hypothesis. Two large echocardiographic-based randomized trials suggest that diuretics are as effective, if not more effective than other drug classes for reducing LV mass. In the Treatment of Mild Hypertension Study (TOMHS), BP was reduced by a combination of weight loss plus either placebo, or one of five antihypertensive drug classes (β-blocker, α-blocker, calcium-channel blocker, angiotensin converting enzyme [ACE] inhibitor and diuretic) (*28*). At 1 and 4 years, all groups showed LV mass regression, confirming that weight loss in conjunction with BP reduction reduces LV mass. Surprisingly, only subjects receiving chlorthalidone had greater LV mass regression than those undergoing weight loss and receiving placebo. Reduced internal dimension as well as reduced wall thickness accounted for this finding. In a human study using endomyocardial biopsy to compare the effects of lisinopril with hydrochlorothiazide, there was more regression of myocardial fibrosis with the ACE inhibitor. However, only the diuretic was associated with regression of LV mass (with significant reduction of myocyte diameter) (*29*). The Veterans Administration (VA) Cooperative Study Group also reported similar results: for equal levels of BP reduction, hydrochlorothiazide had a greater effect on LV mass regression than other antihypertensive agents (*30*). In this trial of 493 patients completing 1 year of maintenance antihypertensive therapy, LV mass was not reduced despite hemodynamic improvement in patients taking prazosin, clonidine or diltiazem. In the VA trial, ACE inhibition was nearly as beneficial as diuretic-based therapy. In the Heart Outcomes Prevention Evaluation (HOPE) trial, treatment of individuals with cardiovascular risk factors with angiotensin converting enzyme inhibitor therapy (ramapril, 10 mg daily) appeared to slow the progression of LV mass in comparison to individuals not on ramapril despite controlled and equivalent BP in both groups (*31*). Approximately 10% of patients were on diuretics in all treatment groups.

Despite the randomized trials, one meta-analysis of human studies suggested that for equal levels of BP reduction, β-blockers, ACE inhibitors, and calcium-channel blockers cause the same degree of LVH regression, whereas diuretics reduce chamber dimension but do not lead to regression of hypertrophied muscle (*21*). This initial meta-analysis was redone 6 years later, adding several more trials to the analysis for a total of 80 studies including 4,000 patients. The overall reduction in LV mass index differed significantly among different antihypertensive classes of medication after adjusting for decrease in BP and duration of treatment (Fig. 2). Overall LV mass index decreased the most (13%) with angiotensin receptor blockers, followed by calcium channel blockers (11%), ACE inhibitors (10%), diuretics (8%) and β-blockers (6%) (*5*). Pairwise comparisons among the drug classes suggest that, on the whole, angiotensin II type 1 (AT_1) receptor antagonists, calcium channel blockers and ACE inhibitors are more effective than β-blockers in regression of LVH. Indeed, in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE), which randomized 9,193 hypertensive patients with ECG LVH to either β-blocker (atenolol) or AT_1 receptor antagonist (losartan). Losartan was significantly more effective in regressing ECG evidence of LVH than atenolol. Furthermore, there were significantly fewer composite cardiovascular end point events in the losartan-treated group (r=0.87). However, the most prominent difference in outcomes was in stroke reduction, not myocardial infarction (*32*). This may reflect the beneficial effects of β-blockers in reducing myocardial oxygen demand in ischemic heart disease. A substudy of 960 patients undergoing echocardiographic assessment of LV mass confirmed the above findings, showing that after 2 years of treatment, there was greater reduction of indexed LV mass in patients on losartan (*33*). In

a subsequent analysis of serial ECG assessment of LVH, and serial echocardiographic measurements of LV mass during antihypertensive treatment, patients with more pronounced regression of LV mass (by either measurement) had significantly less cardiac morbidity and mortality. Regression of LV mass appears to have prognostic significance independent from baseline mass and amount of BP reduction (*34*, *35*). These studies shed new light on the role of LV mass assessment in predicting future cardiac events and suggest that LV mass may be another important cardiac risk factor requiring monitoring.

An important but potentially underrecognized feature of the LIFE study is that a significant proportion of patients in both treatment groups received the diuretic hydrochlorothiazide (HCTZ). Taken together with the results from the VA and TOHMS trial noted above, as well as the results of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), this suggests that it may be prudent to add a diuretic when using a drug that blocks the renin-angiotensin aldosterone system (*36*). Renin-angiotensin-aldosterone inhibition in combination with diuretic therapy may be the treatment of choice for hypertensive heart disease, since it combines both the maximal BP lowering with physiologic inhibition of the processes leading to LVH.

Calcium channel blockers are known to promote LV mass regression and, as noted above, are almost as potent as drugs that inhibit the renin-angiotensin-aldosterone system. The regression of LV mass by calcium channel blockers may be accomplished by inhibiting the activation of calcineurin. Influx of calcium ions through L-type calcium channels is one of the stimuli of calcineurin activation. Nifedipine inhibits this influx of calcium and has been experimentally shown to reduce calcineurin activation (*37*).

More recently, direct aldosterone inhibitors have been introduced into the armamentarium of antihypertensive medication. Theoretically, these agents may also be useful for regression of LVH. Recent evidence suggests that a polymorphism (–344C/T) in the promoter region of the aldosterone synthase gene on chromosome 8, resulting in increased intracardiac aldosterone production (independent of adrenal activity), leads to increased LV mass and diastolic dysfunction in hypertensive individuals with similar mild to moderate hypertension (*38*, *39*). Aldosterone, the synthesis of which is partially controlled by angiotensin II levels, appears to regulate cardiac fibroblast metabolism and growth (*40*). A large clinical trial was recently conducted using cardiac MRI to study the effect of the aldosterone antagonist eplerenone on LV mass. There were similar reductions of both BP and LV mass after 9 months of therapy in comparison to the ACE inhibitor, enalapril. Even more interesting, the combination of ACE-inhibitor and aldosterone inhibitor therapy had additive effects with significantly greater reduction of systolic BP and LV mass in comparison to single therapy (*e.g.*, in comparison to single drug therapy with eplerenone) (*41*). This effect was observed earlier using the combination of spironolactone with either trandolapril or enalapril (*42*).

LV Mass Regression: Future Approaches

As described above, calcineurin is a key protein phosphatase in the molecular pathway that promotes pathological cardiac hypertrophy (*43*). Pharmacologic inhibition of calcineurin activity (Fig. 1) with cyclosporine has been shown to block the development of hypertrophy under several circumstances—*i.e.*, in mice prone to LVH, because they are genetically engineered to produce high levels of calcineurin (*11*); in mice genetically predisposed to develop hypertrophic cardiomyopathy (*44*); and in rats whose aortae were banded so as to produce a pressure stimulus for hypertrophy (*44*, *45*). Cyclosporine may also promote regression of LV mass in a negative fashion by promoting fibrosis and cardiomyocyte death *via* increased apoptosis (*45*). While cyclosporine will not be clinically useful in the non-transplant population, it is likely that new classes of calcineurin inhibitors (*e.g.*, FK 506) that regulate transcription will become available to modulate responses such as hypertrophy (*46*). It is likely that ACE inhibitors and AT_1 receptor blockers also attenuate the development of cardiac hypertrophy by inhibiting angiotensin from upregulating the production of factors that stimulate fetal-type genes, particularly calcineurin. Non-antihypertensive doses of the AT_1 receptor blocker, candesartan, suppress calcineurin production and subsequent LVH and fibrosis in salt-sensitive hypertensive Dahl (DS) rats (*46*). Chronic AT_1 receptor blockade also appears to improve the balance between MMPs and TIMPs, in part by preventing angiotensin II from stimulating the production of TGF-β, a regulator of TIMP-1 gene expression (*47*). TIMPs may not be used clinically, because they are very short acting. However, experimental synthetic inhibitors of MMP are under development. In a spontaneous hypertensive rat (SHR) model, one MMP-inhibitor reduced myocardial fibrosis and restored the proper balance of MMP/TIMP expression to an extent similar to that seen with ACE inhibition (*48*). Development of these agents may provide another avenue of treatment for preventing heart failure in hypertensive heart disease and may be complementary with angiotensin II blockade.

Angiotensin II also plays a role in stimulating cardiomyocyte apoptosis. In vascular smooth muscle, angiotensin II type 2 (AT_2) receptor activity results in antiproliferative remodeling *via* increased apoptosis. This appears to involve feedback inhibition of the AT_{1a} receptor and upgraded expression of a family of proteins in the bcl-2 family (*49*). Experimental blockade of the AT_2 receptor appears to decrease the amount of LV mass regression normally seen with angiotensin receptor blockers (*50*). The implications with respect to overall vascular and myocardial remodeling are unclear. Apoptosis may decrease overall muscle mass. In the heart, however, apoptosis usually results in increased fibrosis and decreased LV function. More recent data suggests that angiotensin II promotes the development of cardiac fibrosis and hypertro-

phy by the upregulation of osteopontin (*51*). Osteopontin is a large-acid phosphoprotein adhesion molecule that is secreted by cardiac interstitial fibroblasts and myocytes and acts like an integrin. It appears to act through a paracrine mechanism by promoting fibroblast growth and function. Thus blockade of the renin-angiotensin-aldosterone system may promote LV mass regression by down-regulating osteopontin production. Future studies may lead to the development of therapies that directly target the modulation of osteopontin. The aldosterone antagonist eplerenone may be one such agent (*52*).

Brain natriuretic peptide (BNP) is an autocrine–paracrine factor that regulates myocyte growth. It blocks the development of LVH due to angiotensin II or mechanical stress by inhibiting activation of ERK (Fig. 1). This was demonstrated in a transgenic model of mice that overexpress BNP. Acute infusion of angiotensin II resulted in significantly less cardiac fibrosis and hypertrophy than in mice producing normal amounts of BNP (*53*). BNP is known to be elevated in patients with congestive heart failure, and a recombinant form of human B-type natriuretic peptide (hBNP) has been approved for the intravenous treatment of patients with acutely decompensated congestive heart failure. BNP also appears to be a marker of increased cardiac morbidity in patients with hypertrophied hearts, and may also predict early changes of diastolic dysfunction (though it does not clearly correspond to LV mass) (*54–57*). Agents that increase systemic BNP levels may promote LV mass regression. The vasopeptidase inhibitor omapatrilat is an example of such an agent. It inhibits neutral endopeptidase, an enzyme that deactivates BNP. In experimental animal models, omapatrilat promotes regression of myocardial fibrosis and LV mass (*58*, *59*).

Other classes of "non-antihypertensive" medications may also interfere with the pathways that lead to cellular hypertrophy. In addition to providing cardiovascular benefit by their cholesterol-lowering actions, hydroxymethlylglutaryl coenzyme A (HMG-CoA) reductase inhibitors may also reduce cardiac morbidity and mortality by preventing cardiac hypertrophy. The activation of fetal cardiac and growth genes, such as c-*myc* and c-*jun*, to upregulate myocardial cell protein synthesis is accomplished by stimulating the production of several mitogen-activated protein kinases, *e.g.*, the *Ras-Raf1-ERK1* kinase cascade. The proper plasma membrane localization of GTP-binding proteins such as *Ras* is inhibited by HMG-CoA reductase inhibitors (Fig. 1). Thus in animal experimental models of LVH (aortic-banded Wistar rats), simvastatin has been shown to limit the development of cardiac hypertrophy by inhibiting *Ras* signaling (*60*). In addition, simvastatin appears to inhibit the process of oxidative stress that promotes apoptosis in hypertrophied hearts (*15*). In another experiment of aortic banding in order to produce cardiac hypertrophy in mice, rapamycin attenuated the development of hypertrophy (*61*). Rapamycin inhibits the mammalian target of rapamycin (mTOR), a component of the insulin–phosphoinositide 3-kinase pathway, which is also thought to play an important role in the determination of cell size. In addition, rapamycin also appears to affect the MAPK pathways by inhibiting JNK1.

Studies applying the principles of physiological genomics are assessing the effect of the ACE and angiotensinogen genes on hypertensive heart disease. This is accomplished by altering expression levels *via* transgenics, knockouts and gene targeting in animal models (*62*). In spontaneously hypertensive rats, an antisense probe targeting angiotensinogen mRNA delivered by an adeno-associated virus produced sustained reduction in BP and reduction in LVH (*63*). This suggests a potential future gene therapy approach for the treatment of hypertension and regression of LVH. Other targets for gene therapy to promote regression of LVH (that do not necessarily depend on BP reduction) include AT_1 receptor antisense gene (*64*) and AT_1 receptor gene transfer (*65*).

Treatment Aimed at Reversing Diastolic Dysfunction

In addition to LVH, diastolic dysfunction is a major factor contributing to hypertensive heart disease and the progression to symptomatic congestive heart failure. Furthermore, diastolic dysfunction is associated with a high mortality rate. Up to 23% of patients died within 3.1 years of follow up in the Digitalis Investigation Group (DIG) trial, with the highest mortality associated with advanced age, male gender and evidence of impaired renal function (*66*). Although heart failure due to diastolic dysfunction (CHF-D) has been recognized for over two decades, treatment strategies for symptomatic patients are guided by relatively few studies.

ACE Inhibitors and AT_1 Receptor Blockers

Three studies have evaluated the efficacy of ACE inhibitors in CHF-D. In one nonrandomized, uncontrolled study, 10 subjects with hypertension, LVH and CHF-D were treated with the ACE inhibitor enalapril and a low-sodium diet (*67*). After an average of 9 months of treatment, heart failure symptoms were resolved in all subjects without the use of diuretics. Diastolic function as measured by Doppler echocardiography did not change after the initial decrease in BP, but significantly improved (decreased A/E ratio and deceleration time) after LV mass regression. Another study compared treatment with enalapril to standard therapy without enalapril in 21 elderly patients with CHF-D, prior non-Q-wave myocardial infarction, and normal ejection fraction (*68*). In the enalapril group, BP and LV mass were significantly reduced with treatment, and this was accompanied by a significant improvement in New York Heart Association functional score (decrease from 3.0 to 2.4, $p<0.01$), increased exercise time on a treadmill, and an improvement in diastolic function as measured by Doppler echocardiography. In the third study, 35 patients with hypertension and LVH underwent endocardial biopsy after 6 months of treatment with lisinopril (*69*). There

was evidence of significant regression of myocardial fibrosis as evidenced by collagen volume fraction and myocardial hydroxyproline concentration, irrespective of the degree of LVH regression. This was accompanied by echocardiographic signs of improved LV diastolic function, including increased E/A and decreased isovolumic relaxation time. In the Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM)-Preserved study, an AT_1 receptor antagonist was assessed in comparison to placebo in 3,023 patients with a history of class II–IV CHF, but LV ejection fraction (EF) > 40%. Though not purely a population of cases of isolated CHF-D, given this EF cutoff value, there was a significant benefit over placebo in terms of preventing further hospitalizations for CHF (*70*).

Direct Aldosterone Inhibitors

The above-described studies employing ACE inhibitors and AT_1 receptor antagonists suggest that inhibition of the renin-angiotensin system reverses the pathophysiologic processes leading to diastolic dysfunction. Since aldosterone appears to regulate cardiac fibroblast metabolism and growth (*40*), direct aldosterone inhibition may also be of benefit. Grandi *et al*. showed improved M-mode echocardiographic parameters of diastolic dysfunction using the aldosterone antagonist canrenone on 34 untreated and asymptomatic hypertensive patients with evidence of diastolic dysfunction (*71*). More recently, Mottram *et al*. showed benefits of aldosterone antagonism in 30 treated hypertensive patients with symptomatic diastolic dysfunction. In this study, sensitive echocardiographic techniques measuring subtle myocardial dysfunction in early hypertensive heart disease (strain rate and cyclic variation of integrated backscatter) showed improvement after 6 months of treatment with spironolactone (*72*).

Calcium-Channel Blockers

Three small, short-term studies have been reported in which calcium-channel blockers were the mainstays of therapy in CHF. In a prospective study of 20 patients (15 of whom had hypertension), verapamil and placebo were compared in a 5-week crossover design. Compared to the baseline values, verapamil significantly improved LV filling, decreased symptoms and improved exercise time (*73*), whereas placebo had no significant effect. However, possibly because of a "carry-over" effect of verapamil-induced improvement into the placebo phase of the cross-over design, there was no difference between verapamil and placebo in LV filling. In 6 severely hypertensive patients followed for 4 months, of whom 4 received a concomitant diuretic, treatment with nifedipine was associated with symptomatic improvement (*74*). In 15 elderly patients with normal EF and New York Heart Association (NYHA) functional class II–III, 3 months of placebo or verapamil (120 mg once daily) was administered in a cross-over placebo controlled design for 3 months. Verapamil improved the CHF score, exercise time and Doppler indices of diastolic function (*75*).

β-Blockade

There is very limited data regarding the role of β-blockade in isolated CHF-D. A study in patients with idiopathic dilated cardiomyopathy (EF < 25%) evaluated the effect of metoprolol, up to 50 mg tid, on diastolic dysfunction (*76*). Not only did diastolic function improve within 3 months of treatment, but also the investigators suggested that the better diastolic performance might have allowed for the subsequent observed boost in systolic function. Another study compared atenolol *vs.* nebivolol in hypertensive patients with a history of CHF-D. After 6 months of treatment, there was a significant improvement in the E/A ratio of all patients, though the effect was somewhat more pronounced in the latter treatment group (*77*).

Diuretics

Although no clinical trial data are available, several investigators recommend cautious use of diuretics to reduce the congested state in CHF-D (*78*, *79*). Diuretics reduce congestion by lowering LV preload and by reducing right ventricular filling pressure, and thereby relieve pericardial restraint on the LV (*80*). However, the use of diuretics remains controversial because of the lack of clinical trials evaluating this strategy and the concern that preload may be inappropriately reduced with "overdiuresis." In fact, the Fifth Report of the Joint National Committee on the Detection and Treatment of Hypertension (JNC-V) considers diuretic therapy as "relatively or absolutely contraindicated" in patients with hypertensive hypertrophic cardiomyopathy with diastolic dysfunction (*81*). Nevertheless, diuretic-based therapy very effectively prevents development of CHF in patients with hypertension.

Digoxin and Inotropes

Although digoxin may improve LV filling by decreasing heart rate, its ability to increase intracellular calcium may increase LV stiffness (*82*). In the National Institutes of Health-sponsored Digitalis Investigation Group trial, which included nearly 8,000 patients (*83*), digoxin did not appear to be deleterious in those with abnormal systolic function (CHF-S) and might have improved functional status.

CHF-D: Summary of Current Treatment

The first line of treatment for CHF-D is to keep the BP down. This is clear from studies which demonstrate that when patients with CHF-D present with pulmonary edema they are almost always in a hypertensive crisis with normal systolic function (*84*). Some authorities recommend that the first line

of treatment include β-blockers or calcium antagonists (*79*, *81*). Others agree that management of symptoms in these patients often requires use of diuretics (*78*). Some investigators advocate improvement of diastolic dysfunction by inhibition of the renin-angiotensin system with ACE inhibitors, angiotensin receptor blockers and/or aldosterone antagonists, with an aim to reversing the interstitial cardiac fibrosis (*85*). The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-VII) recommends ACE inhibitors, β-blockers, angiotensin receptor blockers and aldosterone blockers along with loop diuretics for patients with symptomatic heart failure with either systolic or diastolic ventricular dysfunction. Evaluation for ischemic heart disease is also recommended (*86*).

LV Diastolic Dysfunction: Future Approaches

The mechanisms by which diastolic dysfunction develops in arterial hypertension are complex. However, as we learn more about these mechanisms, new treatment approaches may develop. Traditional approaches such as angiotensin II inhibition appear to affect pathways promoting myocardial fibrosis, a major factor in the development of diastolic dysfunction and eventually LVH. New approaches to treatment may target more specific molecular and inflammatory processes along this pathway. As part of the hypertrophic response, cardiac fibroblasts undergo a phenotypic change, assuming a myofibroblast configuration. As noted in the previous section, osteopontin is an integrin involved in this process. Secreted by cardiac fibroblasts, it behaves like a paracrine factor, promoting cardiac fibroblast growth, adhesion to extracellular matrix and collagen contraction (*51*). Thus, in addition to promoting LV mass regression (see above), inhibiting osteopontin may specifically prevent diastolic dysfunction without necessarily lowering BP. TGF-β is another integrin promoting fibroblast activation. Direct inhibition of TGF-β was shown to prevent diastolic dysfunction in a pressure overload rat model of hypertension by inhibiting myocardial fibrosis (*87*). In addition to activating ACE, human cardiac chymase activates TGF-β and thus promotes interstitial cardiac fibrosis. A recently developed chymase inhibitor, SUNC8257, has been shown to decrease LV end-diastolic pressure and τ in a tachycardia-induced model of heart failure in dogs, suggesting a potential role of direct chymase inhibition in preventing diastolic dysfunction (*88*).

The lipid-lowering HMG-CoA reductase inhibitors were noted above to potentially promote LV mass regression through mechanisms independent of their lipid-lowering effects. Another class of lipid-lowering agents, the fibrate inhibitors, may prevent diastolic dysfunction by mechanisms other than lipid lowering. They promote a factor, peroxisome proliferator-activated receptor α (PPAR-α), that inhibits cardiac fibrosis. PPAR-α interferes with a transcription factor, NFκB, needed to modulate gene expression in situations requiring rapid inflammatory response, including the development of myocardial fibrosis. The fibrate inhibitor fenofibrate has been shown to improve diastolic dysfunction in a deoxycorticosterone acetate (DOCA)-salt hypertensive rat model (*89*).

Conclusion

The goals of chronic antihypertensive therapy for individuals with early manifestations of hypertensive heart disease (*e.g.*, LVH or diastolic dysfunction) are different from the goals for other hypertensive individuals. First, sufficient BP lowering must be achieved in order to relieve the mechanical stress initiating pathophysiological processes in susceptible individuals. The current JNC-VII guidelines recommend lowering BP to $<$135/85 mmHg in patients with target organ damage. However, this specific number is not based on a wealth of data (*86*, *90*). The choice of antihypertensive agent may also depend on non-BP-lowering mechanisms. Large clinical trial and physiologic data suggest that blockade of the renin-angiotensin-aldosterone system is important. In order to achieve both BP-lowering and non-BP-lowering effects, a combination of low dose diuretic with either an ACE inhibitor or angiotensin receptor blocker, perhaps together with a direct aldosterone inhibitor may be the initial treatment of choice. Calcium channel blockers and β-blockers are good secondary choices for further reduction of BP. In addition, they provide beneficial hemodynamic effects by lowering heart rate and improving diastolic filling. In the future, more specific therapies targeting molecular and genetic pathways may be used in conjunction with more traditional BP-lowering treatments.

References

1. Levy D, Anderson KM, Savage D, Kannel WB, Christiansen JC, Castelli WP: Echocardiographically detected left ventricular hypertrophy: prevalence and risk factors. The Framingham heart study. *Ann Int Med* 1988; **108**: 7–13.
2. Casale PN, Devereux RB, Milner M, *et al*: Value of echocardiographic measurement of left ventricular mass in predicting cardiovascular morbid events in hypertensive men. *Ann Intern Med* 1986; **105**: 173–178.
3. Levy D, Garrison RJ, Savage DD, Kannel WB, Castelli WP: Prognostic implications of echocardiographically determined left ventricular mass in the Framingham Heart Study. *N Engl J Med* 1990; **322**: 1561–1566.
4. Bikkina M, Larson MG, Levy D: Asymptomatic ventricular arrhythmias and mortality risk in subjects with left ventricular hypertrophy. *J Am Coll Cardiol* 1993; **22**: 1111–1116.
5. 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.
6. Choi DJ, Koch WJ, Hunter JJ, Rockman HA: Mechanism of beta-adrenergic receptor desensitization in cardiac hypertrophy is increased beta-adrenergic receptor kinase. *J Biol Chem* 1997; **272**: 17223–17229.

7. Drazner MH, Rame JE, Marino EK, *et al*: Increased left ventricular mass is a risk factor for the development of a depressed left ventricular ejection fraction within five years: the Cardiovascular Health Study. *J Am Coll Cardiol* 2004; **43**: 2207–2215.
8. Cooper RS, Simmons BE, Castaner A, Santhanam V, Ghali J, Mar M: Left ventricular hypertrophy is associated with worse survival independent of ventricular function and number of coronary arteries severely narrowed. *Am J Cardiol* 1990; **65**: 441–445.
9. Ghali JK, Liao Y, Simmons B, Castaner A, Cao G, Cooper RS: The prognostic role of left ventricular hypertrophy in patients with or without coronary artery disease. *Ann Intern Med* 1992; **117**: 831–836.
10. Deschepper CF, Boutin-Ganache I, Zahabi A, Jiang Z: In search of cardiovascular candidate genes: interactions between phenotypes and genotypes. *Hypertension* 2002; **39**: 332–336.
11. Molkentin JD, Lu JR, Antos CL, *et al*: A calcineurin-dependent transcriptional pathway for cardiac hypertrophy. *Cell* 1998; **93**: 215–228.
12. Hsueh WA, Law RE, Do YS: Integrins, adhesion, and cardiac remodeling. *Hypertension* 1998; **31**: 176–180.
13. Schunkert H, Jahn L, Izumo S, Apstein CS, Lorell BH: Localization and regulation of c-*fos* and c-*jun* protooncogene induction by systolic wall stress in normal and hypertrophied rat hearts. *Proc Natl Acad Sci USA* 1991; **88**: 11480–11484.
14. Molkentin JD: Calcineurin-NFAT signaling regulates the cardiac hypertrophic response in coordination with the MAPKs. *Cardiovasc Res* 2004; **63**: 467–475.
15. Chen MS, Xu FP, Wang YZ, *et al*: Statins initiated after hypertrophy inhibit oxidative stress and prevent heart failure in rats with aortic stenosis. *J Mol Cell Cardiol* 2004; **37**: 889–896.
16. Li YY, McTiernan CF, Feldman AM: Interplay of matrix metalloproteinases, tissue inhibitors of metalloproteinases and their regulators in cardiac matrix remodeling. *Cardiovasc Res* 2000; **46**: 214–224.
17. Polyakova V, Hein S, Kostin S, Ziegelhoeffer T, Schaper J: Matrix metalloproteinases and their tissue inhibitors in pressure-overloaded human myocardium during heart failure progression. *J Am Coll* Cardiol 2004; **44**: 1609–1618.
18. Sundstrom J, Evans JC, Benjamin EJ, *et al*: Relations of plasma total TIMP-1 levels to cardiovascular risk factors and echocardiographic measures: the Framingham heart study. *Eur Heart J* 2004; **25**: 1509–1516.
19. Lindsay MM, Maxwell P, Dunn FG: TIMP-1: a marker of left ventricular diastolic dysfunction and fibrosis in hypertension. *Hypertension* 2002; **40**: 136–141.
20. Tayebjee MH, Nadar SK, MacFadyen RJ, Lip GY: Tissue inhibitor of metalloproteinase-1 and matrix metalloproteinase-9 levels in patients with hypertension. Relationship to tissue Doppler indices of diastolic relaxation. *Am J Hypertens* 2004; **17**: 770–774.
21. Schmieder RE, Martus P, Klingbeil A: Reversal of left ventricular hypertrophy in essential hypertension. A meta-analysis of randomized double-blind studies. *JAMA* 1996; **275**: 1507–1513.
22. Muiesan ML, Salvetti M, Rizzoni D, *et al*: Association of change in left ventricular mass with prognosis during long-term antihypertensive treatment. *J Hypertens* 1995; **13**: 1091–1095.
23. Bromberg JE, Rinkel GJ, Algra A, Limburg M, van Gijn J: Outcome in familial subarachnoid hemorrhage. *Stroke* 1995; **26**: 961–963.
24. Koren MJ, Ulin RJ, Koren AT, Laragh JH, Devereux RB: Left ventricular mass change during treatment and outcome in patients with essential hypertension. *Am J Hypertens* 2002; **15**: 1021–1028.
25. Schussheim AE, Diamond JA, Phillips RA: Left ventricular midwall function improves with antihypertensive therapy and regression of left ventricular hypertrophy in patients with asymptomatic hypertension. *Am J Cardiol* 2001; **87**: 61–65.
26. Sen S, Tarazi RC, Khairallah PA, Bumpus FM: Cardiac hypertrophy in spontaneously hypertensive rats. *Circ Res* 1974; **35**: 775–781.
27. Dahlof B, Pennert K, Hansson L: Reversal of left ventricular hypertrophy in hypertensive patients. A metaanalysis of 109 treatment studies. *Am J Hypertens* 1992; **5**: 95–110.
28. Neaton JD, Grimm RH Jr, Prineas RJ, *et al*: Treatment of mild hypertension study: final results. *JAMA* 1993; **270**: 713–724.
29. Brilla CG, Funck RC, Rupp H: Lisinopril-mediated regression of myocardial fibrosis in patients with hypertensive heart disease. *Circulation* 2000; **102**: 1388–1393.
30. Gottdiener JS, Reda DJ, Massie BM, Materson BJ, Williams DW, Anderson RJ: Effect of single-drug therapy on reduction of left ventricular mass in mild to moderate hypertension: comparison of six antihypertensive agents. The Department of Veterans Affairs Cooperative Study Group on Antihypertensive Agents. *Circulation* 1997; **95**: 2007–2014.
31. Lonn E, Shaikholeslami R, Yi Q, *et al*: Effects of ramipril on left ventricular mass and function in cardiovascular patients with controlled blood pressure and with preserved left ventricular ejection fraction: a substudy of the Heart Outcomes Prevention Evaluation (HOPE) Trial. *J Am Coll Cardiol* 2004; **43**: 2200–2206.
32. Dahlof B, Devereux RB, Kjeldsen SE, *et al*: 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.
33. Devereux RB, Dahlof B, Gerdts E, *et al*: Regression of hypertensive left ventricular hypertrophy by losartan compared with atenolol: the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) trial. *Circulation* 2004; **110**: 1456–1462.
34. Okin PM, Devereux RB, Jern S, *et al*: Regression of electrocardiographic left ventricular hypertrophy during antihypertensive treatment and the prediction of major cardiovascular events. *JAMA* 2004; **292**: 2343–2349.
35. Devereux RB, Wachtell K, Gerdts E, *et al*: Prognostic significance of left ventricular mass change during treatment of hypertension. *JAMA* 2004; **292**: 2350–2356.
36. ALLHAT Officers and Coordinators for ALLHAT Collaborative Research Group: Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker *vs* diuretic: the Antihypertensive and Lipid-Lowering Treatment to Prevent

Heart Attack Trial (ALLHAT). *JAMA* 2002; **288**: 2981–2997.
37. Zou Y, Yamazaki T, Nakagawa K, *et al*: Continuous blockade of L-type Ca^{2+} channels suppresses activation of calcineurin and development of cardiac hypertrophy in spontaneously hypertensive rats. *Hypertens Res* 2002; **25**: 117–124.
38. Kupari M, Hautanen A, Lankinen L, *et al*: Associations between human aldosterone synthase (CYP11B2) gene polymorphisms and left ventricular size, mass, and function. *Circulation* 1998; **97**: 569–575.
39. Stella P, Bigatti G, Tizzoni L, *et al*: Association between aldosterone synthase (CYP11B2) polymorphism and left ventricular mass in human essential hypertension. *J Am Coll Cardiol* 2004; **43**: 265–270.
40. Weber KT, Brilla CG: Pathological hypertrophy and cardiac interstitium. Fibrosis and renin-angiotensin-aldosterone system pathological hypertrophy and cardiac interstitium. Fibrosis and renin-angiotensin-aldosterone system. *Circulation* 1991; **83**: 1849–1865.
41. Pitt B, Reichek N, Willenbrock R, *et al*: Effects of eplerenone, enalapril, and eplerenone/enalapril in patients with essential hypertension and left ventricular hypertrophy: the 4E-left ventricular hypertrophy study. *Circulation* 2003; **108**: 1831–1838.
42. Sato A, Hayashi M, Saruta T: Relative long-term effects of spironolactone in conjunction with an angiotensin-converting enzyme inhibitor on left ventricular mass and diastolic function in patients with essential hypertension. *Hypertens Res* 2002; **25**: 837–842.
43. Wilkins BJ, Dai YS, Bueno OF, *et al*: Calcineurin/NFAT coupling participates in pathological, but not physiological, cardiac hypertrophy. *Circ Res* 2004; **94**: 110–118.
44. Sussman MA, Lim HW, Gude N, *et al*: Prevention of cardiac hypertrophy in mice by calcineurin inhibition. *Science* 1998; **281**: 1690–1693.
45. Yang G, Meguro T, Hong C, *et al*: Cyclosporine reduces left ventricular mass with chronic aortic banding in mice, which could be due to apoptosis and fibrosis. *J Mol Cell Cardiol* 2001; **33**: 1505–1514.
46. Nagata K, Somura F, Obata K, *et al*: AT1 receptor blockade reduces cardiac calcineurin activity in hypertensive rats. *Hypertension* 2002; **40**: 168–174.
47. Varo N, Iraburu MJ, Varela M, López B, Etayo JC, Díez J: Chronic AT_1 blockade stimulates extracellular collagen type I degradation and reverses myocardial fibrosis in spontaneously hypertensive rats. *Hypertension* 2000; **35**: 1197–1202.
48. Li H, Simon H, Bocan TM, Peterson JT: MMP/TIMP expression in spontaneously hypertensive heart failure rats: the effect of ACE- and MMP-inhibition. *Cardiovasc Res* 2000; **46**: 298–306.
49. Suzuki J, Iwai M, Nakagami H, *et al*: Role of angiotensin II-regulated apoptosis through distinct AT1 and AT2 receptors in neointimal formation. *Circulation* 2002; **106**: 847–853.
50. Mukawa H, Toki Y, Miyazaki Y, Matsui H, Okumura K, Ito T: Angiotensin II type 2 receptor blockade partially negates antihypertrophic effects of type 1 receptor blockade on pressure-overload rat cardiac hypertrophy. *Hypertens Res* 2003; **26**: 89–95.
51. Collins AR, Schnee J, Wang W, *et al*: Osteopontin modulates angiotensin II-induced fibrosis in the intact murine heart. *J Am Coll Cardiol* 2004; **43**: 1698–1705.
52. Matsui Y, Jia N, Okamoto H, *et al*: Role of osteopontin in cardiac fibrosis and remodeling in angiotensin II-induced cardiac hypertrophy. *Hypertension* 2004; **43**: 1195–1201.
53. Takahashi N, Saito Y, Kuwahara K, *et al*: Angiotensin II-induced ventricular hypertrophy and extracellular signal-regulated kinase activation are suppressed in mice overexpressing brain natriuretic peptide in circulation. *Hypertens Res* 2003; **26**: 847–853.
54. Suzuki M, Hamada M, Yamamoto K, Kazatani Y, Hiwada K: Brain natriuretic peptide as a risk marker for incident hypertensive cardiovascular events. *Hypertens Res* 2002; **25**: 669–676.
55. Vanderheyden M, Goethals M, Verstreken S, *et al*: Wall stress modulates brain natriuretic peptide production in pressure overload cardiomyopathy. *J Am Coll Cardiol* 2004; **44**: 2349–2354.
56. Uusimaa P, Tokola H, Ylitalo A, *et al*: Plasma B-type natriuretic peptide reflects left ventricular hypertrophy and diastolic function in hypertension. *Int J Cardiol* 2004; **97**: 251–256.
57. Nakamura M, Tanaka F, Yonezawa S, Satou K, Nagano M, Hiramori K: The limited value of plasma B-type natriuretic peptide for screening for left ventricular hypertrophy among hypertensive patients. *Am J Hypertens* 2003; **16**: 1025–1029.
58. Maki T, Nasa Y, Tanonaka K, Takahashi M, Takeo S: Direct inhibition of neutral endopeptidase in vasopeptidase inhibitor-mediated amelioration of cardiac remodeling in rats with chronic heart failure. *Mol Cell Biochem* 2003; **254**: 265–273.
59. Graham D, Hamilton C, Beattie E, Spiers A, Dominiczak AF: Comparison of the effects of omapatrilat and irbesartan/hydrochlorothiazide on endothelial function and cardiac hypertrophy in the stroke-prone spontaneously hypertensive rat: sex differences. *J Hypertens* 2004; **22**: 329–337.
60. Indolfi C, Di Lorenzo E, Perrino C, *et al*: Hydroxymethylglutaryl coenzyme A reductase inhibitor simvastatin prevents cardiac hypertrophy induced by pressure overload and inhibits p21ras activation. *Circulation* 2002; **106**: 2118–2124.
61. Shioi T, McMullen JR, Tarnavski O, *et al*: Rapamycin attenuates load-induced cardiac hypertrophy in mice. *Circulation* 2003; **107**: 1664–1670.
62. Glueck SB, Dzau VJ: Physiological genomics: implications in hypertension research. *Hypertension* 2002; **39**: 310–315.
63. Kimura B, Mohuczy D, Tang X, Phillips MI: Attenuation of hypertension and heart hypertrophy by adeno-associated virus delivering angiotensinogen antisense. *Hypertension* 2001; **37**: 376–380.
64. Pachori AS, Numan MT, Ferrario CM, Diz DM, Raizada MK, Katovich MJ: Blood pressure-independent attenuation of cardiac hypertrophy by AT_1R-AS gene therapy. *Hypertension* 2002; **39**: 969–975.
65. Metcalfe BL, Huentelman MJ, Parilak LD, *et al*: Prevention of cardiac hypertrophy by angiotensin II type-2 receptor gene transfer. *Hypertension* 2004; **43**: 1233–1238.
66. Jones RC, Francis GS, Lauer MS: Predictors of mortality in patients with heart failure and preserved systolic function in the Digitalis Investigation Group trial. *J Am Coll Cardiol* 2004; **44**: 1025–1029.
67. Gonzalez-Fernandez RB, Altieri PI, Diaz LM, *et al*: Effects

of enalapril on heart failure in hypertensive patients with diastolic dysfunction. *Am J Hypertens* 1992; **5**: 480–483.
68. Aronow WS, Kronzon I: Effect of enalapril on congestive heart failure treated with diuretics in elderly patients with prior myocardial infarction and normal left ventricular ejection fraction. *Am J Cardiol* 1993; **71**: 602–604.
69. Brilla CG, Funck RC, Rupp H: Lisinopril-mediated regression of myocardial fibrosis in patients with hypertensive heart disease. *Circulation* 2000; **102**: 1388–1393.
70. Yusuf S, Pfeffer MA, Swedberg K, *et al*: Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. *Lancet* 2003; **362**: 777–781.
71. Grandi AM, Imperiale D, Santillo R, *et al*: Aldosterone antagonist improves diastolic function in essential hypertension. *Hypertension* 2002; **40**: 647–652.
72. Mottram PM, Haluska B, Leano R, Cowley D, Stowasser M, Marwick TH: Effect of aldosterone antagonism on myocardial dysfunction in hypertensive patients with diastolic heart failure. *Circulation* 2004; **110**: 558–565.
73. Setaro JF, Zaret BL, Schulman DS, Black HR, Soufer R: Usefulness of verapamil for congestive heart failure associated with abnormal left ventricular diastolic filling and normal left ventricular systolic performance. *Am J Cardiol* 1990; **66**: 981–986.
74. Given BD, Lee TH, Stone PH, Dzau VJ: Nifedipine in severely hypertensive patients with congestive heart failure and preserved ventricular systolic function. *Arch Intern Med* 1985; **145**: 281–285.
75. Hung MJ, Cherng WJ, Kuo LT, Wang CH: Effect of verapamil in elderly patients with left ventricular diastolic dysfunction as a cause of congestive heart failure. *Int J Clin Pract* 2002; **56**: 57–62.
76. Andersson B, Caidahl K, di Lenarda A, *et al*: Changes in early and late diastolic filling patterns induced by long-term adrenergic beta-blockade in patients with idiopathic dilated cardiomyopathy. *Circulation* 1996; **94**: 673–682.
77. Nodari S, Metra M, Dei CL: Beta-blocker treatment of patients with diastolic heart failure and arterial hypertension. A prospective, randomized, comparison of the long-term effects of atenolol *vs.* nebivolol. *Eur J Heart Fail* 2003; **5**: 621–627.
78. Bonow RO, Udelson JE: Left ventricular diastolic dysfunction as a cause of congestive heart failure: mechanisms and management. *Ann Intern Med* 1992; **117**: 502–510.
79. Gaasch WH: Diagnosis and treatment of heart failure based on left ventricular systolic or diastolic dysfunction. *JAMA* 1994; **271**: 1276–1280.
80. Packer M: Abnormalities of diastolic function as a potential cause of exercise intolerance in chronic heart failure. *Circulation* 1990; **81** (2 Suppl): III78–III86.
81. Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure: The fifth report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC V). *Arch Intern Med* 1993; **153**: 154–183.
82. Lorell BH, Isoyama S, Grice WN, Weinberg EO, Apstein CS: Effects of ouabain and isoproterenol on left ventricular diastolic function during low-flow ischemia in isolated, blood- perfused rabbit hearts. *Circ Res* 1988; **63**: 457–467.
83. The effect of digoxin on mortality and morbidity in patients with heart failure. The Digitalis Investigation Group. *N Engl J Med* 1997; **336**: 525–533.
84. Gandhi SK, Powers JC, Nomeir AM, *et al*: The pathogenesis of acute pulmonary edema associated with hypertension. *N Engl J Med* 2001; **344**: 17–22.
85. Brutsaert DL, Sys SU, Gillebert TC: Diastolic failure: pathophysiology and therapeutic implications. *J Am Coll Cardiol* 1993; **22**: 318–325 [published erratum appears in *J Am Coll Cardiol* 1993; **22**: 1272].
86. Chobanian AV, Bakris GL, Black HR, *et al*: The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA* 2003; **289**: 2560–2571.
87. Kuwahara F, Kai H, Tokuda K, *et al*: Hypertensive myocardial fibrosis and diastolic dysfunction: another model of inflammation? *Hypertension* 2004; **43**: 739–745.
88. Matsumoto T, Wada A, Tsutamoto T, Ohnishi M, Isono T, Kinoshita M: Chymase inhibition prevents cardiac fibrosis and improves diastolic dysfunction in the progression of heart failure. *Circulation* 2003; **107**: 2555–2558.
89. Ogata T, Miyauchi T, Sakai S, Takanashi M, Irukayama-Tomobe Y, Yamaguchi I: Myocardial fibrosis and diastolic dysfunction in deoxycorticosterone acetate-salt hypertensive rats is ameliorated by the peroxisome proliferator-activated receptor-alpha activator fenofibrate, partly by suppressing inflammatory responses associated with the nuclear factor-kappa-B pathway. *J Am Coll Cardiol* 2004; **43**: 1481–1488.
90. Lenfant C, Chobanian AV, Jones DW, Roccella EJ: Seventh report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7). Resetting the Hypertension Sails. *Hypertension* 2003; **41**: 1178–1179.
91. Schunkert H, Hense H-W, Holmer SR, *et al*: Association between a deletion polymorphism of the angiotensin converting-enzyme gene and left ventricular hypertrophy. *N Engl J Med* 1994; **330**: 1634–1638.
92. Perticone F, Ceravolo R, Cosco C, *et al*: Deletion polymorphism of angiotensin-converting enzyme gene and left ventricular hypertrophy in southern Italian patients. *J Am Coll Cardiol* 1997; **29**: 365–369.
93. Gharavi AG, Lipkowitz MS, Diamond JA, Jhang JS, Phillips RA: Deletion polymorphism of the angiotensin-converting enzyme gene is independently associated with left ventricular mass and geometric remodeling in systemic hypertension. *Am J Cardiol* 1996; **77**: 1315–1319.
94. Alfakih K, Maqbool A, Sivananthan M, *et al*: Left ventricle mass index and the common, functional, X-linked angiotensin II type-2 receptor gene polymorphism (–1332 G/A) in patients with systemic hypertension. *Hypertension* 2004; **43**: 1189–1194.
95. Tang W, Devereux RB, Rao DC, *et al*: Associations between angiotensinogen gene variants and left ventricular mass and function in the HyperGEN study. *Am Heart J* 2002; **143**: 854–860.
96. Poch E, Gonzalez D, Gomez-Angelats E, *et al*: G-protein beta(3) subunit gene variant and left ventricular hypertrophy in essential hypertension. *Hypertension* 2000; **35**: 214–218.
97. Obineche EN, Frossard PM, Bokhari AM: An association study of five genetic loci and left ventricular hypertrophy

amongst Gulf Arabs. *Hypertens Res* 2001; **24**: 635–639.
98. Nakayama T, Soma M, Takahashi Y, Rehemudula D, Kanmatsuse K, Furuya K: Functional deletion mutation of the 5′-flanking region of type A human natriuretic peptide receptor gene and its association with essential hypertension and left ventricular hypertrophy in the Japanese. *Circ Res* 2000; **86**: 841–845.
99. Arnett DK, Devereux RB, Kitzman D, *et al*: Linkage of left ventricular contractility to chromosome 11 in humans: the HyperGEN Study. *Hypertension* 2001; **38**: 767–772.
100. Akhter SA, Milano CA, Shotwell KF, *et al*: Transgenic mice with cardiac overexpression of alpha1-adrenergic receptors. *In vivo* alpha1-adrenergic receptor-mediated regulation of beta-adrenergic signaling. *J Biol Chem* 1997; **272**: 21253–21259.
101. Tang W, Arnett DK, Devereux RB, Atwood LD, Kitzman DW, Rao DC: Linkage of left ventricular early diastolic peak filling velocity to chromosome 5 in hypertensive African Americans: the HyperGEN echocardiography study. *Am J Hypertens* 2002; **15**: 621–627.