

*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 than 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

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**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 <sub>1</sub> 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 $\beta$ 3 subunit gene (96, 97)	Single base substitution at position 825 of exon 9 in the short arm of chromosome 12	Enhanced Na <sup>+</sup> -H <sup>+</sup> 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
$\beta$ -Adrenergic receptor kinase ( $\beta$ ARK) regulator gene (6, 100)	Chromosome 22	Elevated gene expression, attenuates $\beta$ -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
$\alpha$ -1B adrenergic receptor (ADRA1B) gene (101)	Chromosome 5	Indirectly stimulate intracellular calcium release and protein kinase C activation

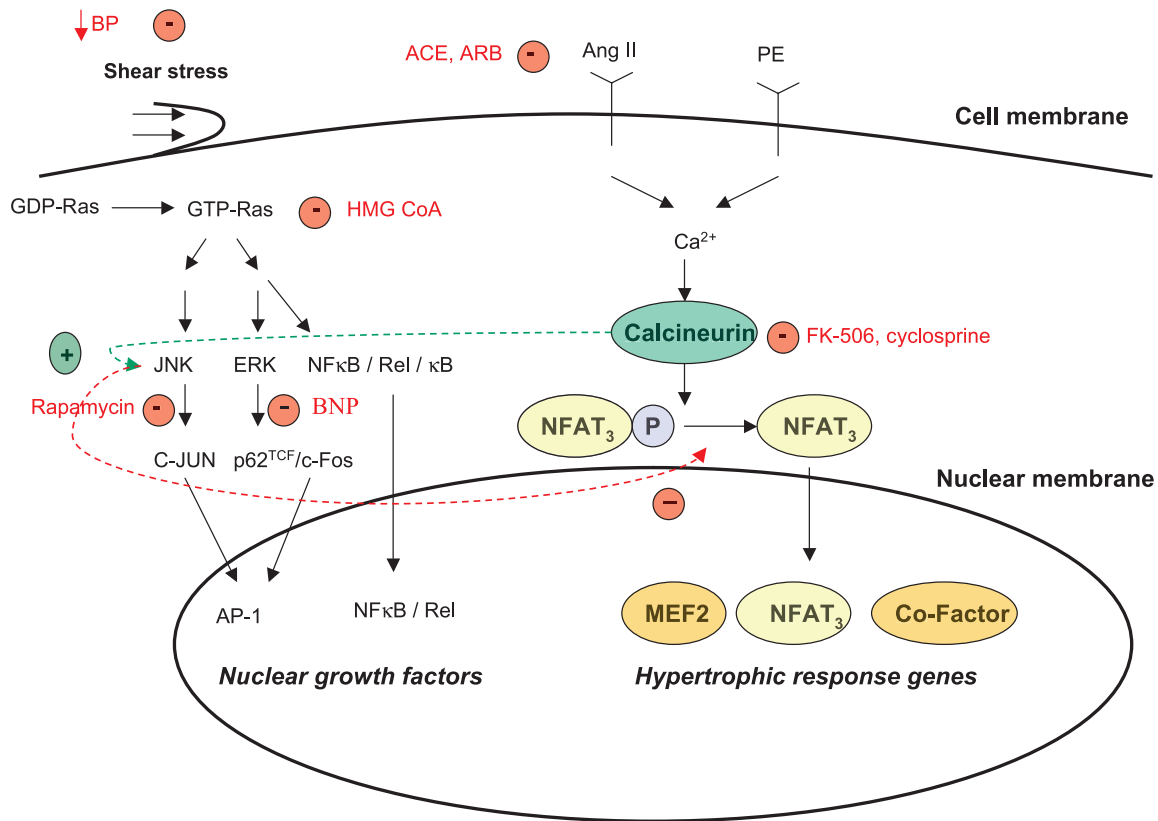
ACE, angiotensin converting enzyme; AT<sub>1</sub>, angiotensin II type 1; BNP, brain natriuretic peptide.

peptide receptor gene, and the G-protein  $\beta$  3-subunit gene affecting Na<sup>+</sup>-H<sup>+</sup> 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  $\beta$ -adrenergic receptor kinase ( $\beta$ ARK) 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<sub>3</sub>, resulting in its translocation to the

nucleus. In the nucleus, AT<sub>3</sub> interacts with another transcription factor, GATA<sub>4</sub>, to initiate transcription of genes that lead to myocyte hypertrophy (11), such as  $\beta$ -myosin heavy chain and  $\beta$ -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

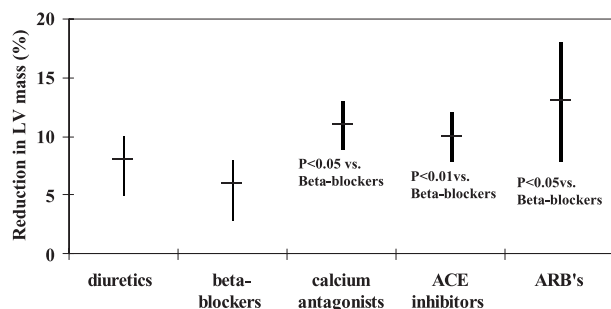


**Fig. 1.** A model for the calcineurin-dependent transcriptional pathway in cardiac hypertrophy and for the sequential events of signaling and gene expression via the MAPK pathways in response to shear stress or mechanical strain. There is a complex feed-back among these pathways. Calcineurin promotes 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  $\beta$  (TGF- $\beta$ ), 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 Regression: 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 ( $\beta$ -blocker,  $\alpha$ -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,  $\beta$ -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  $\beta$ -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  $\beta$ -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  $\beta$ -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  $\beta$ -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 Anti-hypertensive 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<sub>1</sub> 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<sub>1</sub> receptor blocker, candesartan, suppress calcineurin production and subsequent LVH and fibrosis in salt-sensitive hypertensive Dahl (DS) rats (46). Chronic AT<sub>1</sub> receptor blockade also appears to improve the balance between MMPs and TIMPs, in part by preventing angiotensin II from stimulating the production of TGF- $\beta$ , 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<sub>2</sub>) receptor activity results in antiproliferative remodeling *via* increased apoptosis. This appears to involve feedback inhibition of the AT<sub>1a</sub> receptor and upgraded expression of a family of proteins in the bcl-2 family (49). Experimental blockade of the AT<sub>2</sub> 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, hydroxymethylglutaryl 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<sub>1</sub> receptor antisense gene (64) and AT<sub>1</sub> 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<sub>1</sub> 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<sub>1</sub> 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<sub>1</sub> 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  $\beta$ -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,  $\beta$ -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- $\beta$  is another integrin promoting fibroblast activation. Direct inhibition of TGF- $\beta$  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- $\beta$  and thus promotes interstitial cardiac fibrosis. A recently developed chymase inhibitor, SUNC8257, has been shown to decrease LV end-diastolic pressure and  $\tau$  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  $\alpha$  (PPAR- $\alpha$ ), that inhibits cardiac fibrosis. PPAR- $\alpha$  interferes with a transcription factor, NF $\kappa$ B, 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  $\beta$ -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.

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