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While the relationship between blood pressure (BP), hypertension and cardiovascular disease is unquestioned, recent epidemiologic evidence indicates that elevated BP is one of the major causes or contributing factors to the striking increase in prevalence of congestive heart failure. In this issue, 2 articles deal with this very important issue. Dr. Robert Phillips and Dr. Joseph Diamond have provided a succinct review of the role of BP elevation and left ventricular hypertrophy on the pathogenesis of primary systolic dysfunction. In addition, Dr. Howard Weinberger discusses the pathophysiology and treatment of isolated diastolic dysfunction, an entity being recognized with increased frequency. The third article, by Dr. Stevo Julius, continues the series by describing an ongoing clinical outcomes trial. The VALUE Study is designed to examine the comparative benefit of an angiotensin receptor blocker or a calcium channel entry blocker on cardiovascular morbidity and mortality (including congestive heart failure) in a large, world-wide population of high-risk hypertensive patients. While this trial is still in its early stages, it will contribute greatly to our understanding of how to best prevent cardiovascular events during the treatment of hypertensive patients.

Table 1 Association Between Left Ventricular Mass and Hemodynamic and Nonhemodynamic Factors: Strength of Evidence Supporting a Causal Role

Factor	Evidence	Reference
Blood pressure and wall stress	Very strong	Molkentin JD, et al. Cell 1998;93:215-228. Chantin A, et al. Arch Intern Med 1933;52:739. Rowlands DB, et al. Lancet 1982;1:467-470. Devereux RB, et al. Circulation 1983;68:470-476. Phillips RA, et al. J Am Coll Cardiol 1989;14:979-985. Lauer MS, et al. J Am Coll Cardiol 1991;18:1287-1294. Ganau A, et al. Circulation 1990;81:25-36. Guerrier M, et al. Circulation 1990;81:528-536.
Stroke volume	Very strong	Ganau A, et al. Circulation 1990;81:25-36. Jones EC, et al. J Am Coll Cardiol 1997;29:1303-1310.
Obesity	Very strong	MacMahon SW, et al. N Engl J Med 1986;314:334-339. Levy D, et al. Ann Intern Med 1989;110:101-107. Lauer MS, et al. J Am Coll Cardiol 1992;19:130-134. De Simone G, et al. Hypertension 1994;23:600-606. Marcus R, et al. Circulation 1994;90:928-936.
Growth hormone and IGF-1	Strong	Lim MJ, et al. Ann Intern Med 1992;117:719-726. Andronico G, et al. J Hypertens 1993;11:1097-1101.
Gender	Strong	Hinderliter AL, et al. Am J Hypertens 1992;5:33-36. Devereux RB, et al. J Am Coll Cardiol 1984;4:1222-1230. Cabral AM, et al. Hypertension 1988;11:93-97. Douglas PS, et al. J Am Coll Cardiol 1998;32:1118-1125.
Race	Strong	Beaglehole R, et al. J Chronic Dis 1974;28:549-559. Hammond IW, et al. Natl Med Assoc 1984;76:247-255. Liebson PR, et al. Circulation 1993;87:476-486. Mayet J, et al. BMJ 1994;308:1011-1014. Hinderliter AL, et al. Am J Cardiol 1992;69:1196-1199.
Age	Strong	Levy D, et al. Ann Intern Med 1989;110:101-107. Savage DD, et al. Circulation 1979;59:623-632. Gerstenblith G, et al. Circulation 1977;56:273-278. Shub C, et al. Mayo Clin Proc 1994;69:205-211. De Simone G, et al. Am J Cardiol 1991;68:1704-1708.
Intracellular Ca ⁺⁺	Strong	Molkentin JD, et al. Cell 1998;93:215-228. Marban E, et al. Hypertension 1990;15:652-658.
Insulin resistance	Strong	Marcus R, et al. Circulation 1994;90:928-936. Phillips RA, et al. J Clin Endocrinol Metab 1998;83:4284-4288.
Angiotensin II	Strong	Sadoshima J, et al. Cell 1993;75:977-984. Schmieder RE, et al. Circulation 1996;94:1304-1309.
Alcohol	Needs confirmation	Manolio TA, et al. J Am Coll Cardiol 1991;17:717-721.
Intrinsic myocardial contractility	Needs confirmation	Ganau A, et al. Circulation 1990;81:25-36.
Blood viscosity	Needs confirmation	Devereux RB, et al. Am J Cardiol 1986;54:592-595.
Parathyroid hormone	Needs confirmation	Bauwens FR, et al. Am J Cardiol 1991;68:925-929.
Aldosterone (collagen synthesis)	Needs confirmation	Schmieder RE, et al. Circulation 1996;94:1304-1309. Weber KT, et al. Circulation 1991;83:1849-1865. Rossi GP, et al. Hypertension 1996;27:1039-1045.
Sodium intake	Needs confirmation	Schmieder RE, et al. Circulation 1988;78:951-956.
Na ⁺ /H ⁺ exchanger and Na ⁺ -K ⁺ -Cl ⁻ cotransport system	Needs confirmation	De la Sierra A, et al. Circulation 1993;88:1628-1633.
Polymorphism of the ACE gene	Controversial	Schunkert H, et al. N Engl J Med 1994;330:1634-1638. Perticone F, et al. J Am Coll Cardiol 1997;29:365-369.
Plasma renin activity	Controversial	Bauwens FR, et al. Am J Cardiol 1991;68:925-929. Sen S, et al. Circ Res 1974;35:775-781. Devereux RB, et al. J Clin Hypertens 1987;3:87-103.
Norepinephrine	Controversial	Sen S, et al. Circ Res 1974;35:775-781. Adams TD, et al. Circulation 1985;71:39-44. Trimarco B, et al. Circulation 1985;72:38-46. Simpson P, et al. Am J Cardiol 1988;62:13G-19G. Shub C, et al. Am J Cardiol 1986;57:971-975.
Na ⁺ /Li ⁺ exchanger	Controversial	De la Sierra A, et al. Circulation 1993;88:1628-1633. Nosadini R, et al. Hypertension 1991;18:191-198.
βARK	Controversial	Choi DJ, et al. J Biol Chem 1997;272:17223-17229. Akhter SA, et al. J Biol Chem 1997;272:21253-21259.

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In addition to diastolic dysfunction (see Weinberger), hypertensive heart disease is characterized by increased left ventricular mass, systolic dysfunction, and coronary flow abnormalities. Left ventricular hypertrophy (LVH) increases the risk of coronary heart disease, stroke, ventricular arrhythmias, and sudden death.¹ Most antihypertensive treatments promote regression of LVH which is associated with improved survival.^{2,3}

Two large community based studies indicate that elevated blood pressure (BP) is the most common risk factor for congestive heart failure (CHF), both with and without systolic dysfunction.^{4,5} In the Framingham Study, after adjusting for usual risk factors for systolic heart failure in proportional hazards regression models, the risk for developing heart failure in hypertensive compared with normotensive subjects was nearly 2-fold in men and 3-fold in women. In multivariate analysis, hypertension was the greatest risk factor for CHF, accounting for 39% of cases in men and 59% in women.⁴ Another population-based study of CHF in Olmsted County, Minnesota showed similar findings. Of 216 patients studied, 52% presented with hypertension. Out of these patients, 137 underwent evaluation of LV systolic function. Hypertension was the underlying risk factor in 53% of subjects with left ventricular ejection factor (LVEF) <50% and was present in 58% of subjects with LVEF ≥50%. Of note, long-term survival was not significantly different between subjects with normal or low LVEF.⁵ The prognosis for hypertensive patients with newly diagnosed CHF-S was poor in both studies (≤35% by 5 years).

The effect of BP, as well as virtually every factor known to influence BP, has been investigated for its independent effect on LV mass (Table 1 on page 2). The underlying molecular mechanisms that couple hypertrophic signals at the cell membrane to the reprogramming of cardiomyocyte gene expression is beginning to be elucidated. Intracellular calcium release may be an early response to myocyte stretch induced by wall stress and by humoral stimuli, including angiotensin II (AT II), phenylephrine, and endothelin. The increase in intracellular calcium results in activation of the phosphatase calcineurin, which then dephosphorylates transcription factor NF-AT3, resulting in its translocation to the nucleus. In the nucleus, AT3 interacts with another transcription factor, GATA4, to initiate transcription of genes that lead to myocyte hypertrophy⁶ such as in the β-myosin heavy chain.

The factors that cause the transition from “compensated” LVH to systolic dysfunction are also beginning to be elucidated. As part of the hypertrophic response, cardiac fibroblasts undergo a phenotypic change, assuming a myofibroblast configuration. The stimulated myofibroblast proliferates and increases its 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 cells’ ability to interact with their environment.⁷ Progressive fibrosis of the heart is a major component of the remodeling process in hypertensive heart disease and leads to LV systolic dysfunction through impaired myocyte contractility, oxygenation, and metabolism. Several experimental studies suggest this process

may be reversible, including a study of hypertensive patients which showed that AT I receptor blockade with losartan results in decreased plasma levels of growth factors including endothelin-1, basic fibroblast growth factor, and platelet-derived growth factor.⁸ This may help to explain the positive survival impact of angiotension-converting enzyme inhibitors (ACEIs) and may suggest positive benefits of angiotensin receptor blockers in patients with CHF.^{9,10}

Myocyte hypertrophy may alter excitation-contraction coupling, leading to decreased efficiency of contraction and development of systolic dysfunction.¹¹ Normally, depolarization triggers influx of calcium through dihydropyridine receptors (L-type Ca⁺⁺ channels), leading to local cytoplasmic increases in Ca⁺⁺ concentration. This local increase “sparks” the release of Ca⁺⁺ from the sarcoplasmic reticulum (SR) through activation of ryanodine receptors (RyRs). The efflux of Ca⁺⁺ from the SR leads to activation of the troponin-actin-myosin complex and myocyte contraction. Physical alteration of the hypertrophied myocyte in LVH increases the distance between the voltage-dependent calcium channels and the ryanodine receptors on the SR, resulting in failure of local Ca⁺⁺ to trigger sarcoplasmic Ca⁺⁺ release.

Fortunately, BP control significantly prevents the development of CHF. In the Systolic Hypertension in the Elderly Program (SHEP), patients with isolated systolic hypertension and a prior history of myocardial infarction (MI) (by electrocardiogram [ECG]) who were treated with diuretic-based therapy with BP lowering to a systolic of <150 mm Hg had only a 2% to 3% chance of developing heart failure over a 4 year period. By contrast, patients treated with placebo had an 810% chance of developing CHF.¹² Meta-analysis of randomized placebo-controlled antihypertensive therapy trials demonstrated that adequate BP control decreases the incidence of CHF by half.¹³

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Heart failure is the leading cause of hospitalization in those older than 65 and is the single largest healthcare cost item in the United States. Traditionally, heart failure has been attributed to left ventricular systolic or pump failure. Abnormalities of diastolic function in the absence of systolic dysfunction (isolated diastolic dysfunction) can also lead to the syndrome of CHF and account for up to 40% of CHF cases. The most common cause of diastolic dysfunction is systolic dysfunction, while the most common causes of isolated diastolic dysfunction are myocardial ischemia, hypertension, aging, diabetes, obesity, and aortic stenosis. Isolated diastolic heart failure has a better prognosis than systolic failure with the annual mortality rate for isolated diastolic heart failure, on average, one fourth to one third that of systolic failure.

Physiology of Diastole

Myocardial contraction is dependent on the release of stored calcium while myocardial relaxation is dependent on the rapid reduction of activator calcium. Calcium resequestration occurs against a 10,000-fold concentration gradient and is highly energy dependent. The SR calcium-ATPase pump is responsible for removing 80% to 90% of cytosolic calcium, while additional calcium is removed from the cytosol via sodium-calcium exchange. Abnormal calcium resequestration leads to impairment of left ventricular isovolumic relaxation and a decrease in rapid filling.¹

Etiology of Isolated Diastolic Dysfunction

The two major components of isolated diastolic heart failure, ventricular relaxation and compliance, are affected by the deleterious neurohormonal activation and ventricular remodeling following an initial insult to the myocardium characteristic of the syndrome of CHF. Impaired ventricular relaxation occurs in early diastole and decreased ventricular compliance occurs throughout diastole. Several factors that increase left ventricular diastolic pressure by impairing relaxation or decreasing compliance are listed in Table 2.

Isolated diastolic dysfunction has been reported in up to 90% of patients with coronary artery disease.² Myocardial ischemia leads to impaired relaxation due to a reduction of high-energy phosphates needed for the rapid reuptake of activator calcium by the SR.³

Table 2 Factors That Increase Diastolic Pressure⁴

Impairing Ventricular Relaxation	Decreasing Ventricular Compliance
Hypertrophy	Hypertrophy
Myocardial ischemia	Fibrosis
Aging	Aging
Regional asynchrony	Cellular disarray
Increased preload, afterload	Infiltrative conditions
Abnormal calcium flux	Pericardial disease
Tachycardia	Right ventricular with left ventricle interactions

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Approximately 60% of patients with CHF and normal left ventricular systolic function have hypertension.⁵ LVH impairs left ventricular relaxation by altering the energy dependent dissociation of myocardial contractile proteins and decreases compliance by increasing interstitial collagen and fibrosis. Obese subjects without hypertension demonstrate abnormal left ventricular compliance and left ventricular filling.^{2,6}

Aging impairs relaxation by prolonging contraction duration and reducing calcium sequestration by the SR as well as decreasing compliance by increasing the interstitial collagen matrix. Myocardial ischemia and LVH are more common with increasing age and contribute to the association of diastolic dysfunction with increasing age.

Diagnosis of Diastolic Heart Failure

It is imperative to identify systolic versus isolated diastolic dysfunction when a patient presents with signs and symptoms of CHF, since the treatment for one may aggravate or worsen the other. Unfortunately, the classic signs and symptoms of CHF are not reliable for distinguishing systolic from diastolic heart failure.⁷ After confirming the presence of CHF and identifying possible causative or contributing factors with a thorough history and physical examination, noninvasive evaluations are needed to distinguish systolic from isolated diastolic heart failure.

Echocardiography is an ideal noninvasive modality to distinguish systolic from isolated diastolic dysfunction and to exclude other conditions such as valvular and pericardial abnormalities that lead to secondary diastolic dysfunction. Two-dimensional echocardiography provides information on chamber size, wall thickness, systolic function, and regional wall motion, as well as the appearance and function of the intracardiac valves and the pericardium. Doppler echocardiography provides information about blood flow, valvular stenosis or regurgitation, intracardiac pressures, and diastolic filling characteristics including left ventricular relaxation and compliance. Because echocardiography provides information about the structure and function of the intracardiac valves and pericardium, in addition to information about hemodynamics, chamber size, structure, and function, it is the noninvasive diagnostic test of choice.

Treatment

Despite numerous clinical trials demonstrating benefit of a variety of agents for the treatment of systolic heart failure, there are relatively few studies directly investigating the efficacy of specific agents for treating isolated diastolic dysfunction. The general goals of treatment include treating any underlying or aggravating causes; enhancing left ventricular relaxation if abnormal; decreasing left ventricular filling pressure without decreasing cardiac output; controlling heart rate if increased or if in atrial fibrillation; maintaining atrioventricular synchrony and sinus rhythm; and avoiding positive inotropic, positive chronotropic, and arterial vasodilating agents in the absence of

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Table 3 Summary of Medical Therapy for Isolated Diastolic Dysfunction⁴

	Calcium Channel Antagonist	β-adrenergic Receptor Blocker	ACEI	Diuretic	Nitrate
Direct beneficial effect on myocardial relaxation	+	–	?	–	–
Reduce blood pressure	+	+	+	+	–
Reduce and/or prevent ischemia	+	+	–	–	+
Promote LVH regression	++	+	++	+	–
Slow heart rate	+	+	–	–	–
Reduce collagen, fibrosis	–	–	+	–	–
Improve noninvasive filling parameters	+	?	+	?	?
Improve symptoms	+	?	+	+ ^a	?

?—no studies evaluating these agents and parameters

^a if pulmonary congestion

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decreased left ventricular systolic function. Medical therapy for isolated diastolic heart failure includes the use of calcium channel antagonists (verapamil, diltiazem), β-adrenergic receptor blockers, (ACEIs), and cautious use of diuretics for pulmonary congestion and nitrates for myocardial ischemia (Table 3). The lack of firm data regarding the optimal treatment of isolated diastolic dysfunction suggests a need for a randomized therapeutic trial of a disorder that affects over 2 million Americans.

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The long-term use of antihypertensive medication decreases cardiovascular events but most of the benefit stems from the reduction in stroke and prevention of CHF. The reduction of coronary events is less than one would have expected from the magnitude of in-trial BP reduction.¹⁻³ Pathophysiologically, BP elevation is only one symptom of the complex abnormalities in essential hypertension. These abnormalities differ from patient to patient and, importantly, are differentially affected by specific antihypertensive medication. Thus, the VALUE Study was designed to explore this issue further, using newer agents.

Rationale and Hypothesis

The major hypothesis of the VALUE Study is that, for the same level of BP control in a group of high-risk patients, the angiotensin receptor blocking agent valsartan will be more efficacious in reducing cardiovascular morbidity and mortality than the calcium channel entry blocking agent amlodipine. The hypothesis is rooted in the clinical and epidemiologic evidence that the renin-angiotensin-aldosterone system (RAAS) is a predictor of negative outcomes in hypertension⁴⁻⁶ and in the understanding of mechanisms by which angiotensin can cause cardiovascular damage. Cardiac hypertrophy enhances coronary risk whereas vascular hypertrophy accelerates hypertension and decreases coronary reserve.

Angiotensin has a pressure-independent role in the development of vascular⁷ and cardiac^{8,9} hypertrophy. Hypertension is associated with abnormal endothelium-dependent vascular relaxation.¹⁰ Angiotensin aggravates endothelial dysfunction in hypertension and treatment with an ACEI reverses the preexisting coronary endothelial dysfunction.¹¹ Physiologically, the RAAS and sympathetic nervous system strongly reinforce each other's actions. Patients with high renin also have high norepinephrine levels.¹² These interactions between the 2 pressor systems, each of which is elevated in a large proportion of patients with hypertension, suggest that blocking the action of AT II may also have a sympatholytic effect. Sympathetic overactivity in hypertension enhances the coronary risk through multiple mechanisms.¹³⁻¹⁵

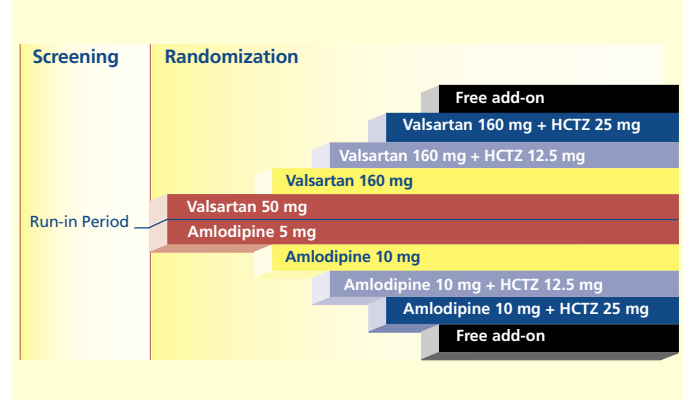
Design

This is a prospective, multinational, randomized, active-controlled trial in high-risk patients with essential hypertension to compare the effect of valsartan (80 and 160 mg daily) with or without addition of hydrochlorothiazide (HCTZ) to that of amlodipine (5 and 10 mg daily) with or without addition of HCTZ on cardiovascular morbidity and mortality. The drug dosage will be titrated in order to achieve the BP goal in both groups (<140 and/or <90 mm Hg). The response-dependent titration scheme is given in Figure 1.

The study is designed to detect a 15% difference in endpoints between the 2 treatment groups with 90% power. A total of 14,400

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Figure 1 Schedule of Procedures


patients equally allocated to each of the 2 treatment groups will be followed until 1,450 patients have reached a primary endpoint. The follow-up period is expected to last 4 to 6 years.

In addition to hypertension, the patient must have a cardiovascular disease factor and/or associated risk factors. Disease factors are past MI, proven coronary heart disease, coronary revascularization, documented peripheral vascular disease, and proven stroke or LVH with strain pattern on ECG. Risk factors are age, male gender, diabetes, smoking, high cholesterol, family history of early cardiac death, LVH on the ECG (without strain), proteinuria, and creatinine between 1.7 and 3.0 mg/dL.

The primary endpoints are cardiovascular mortality and cardiovascular morbidity. Strokes are considered secondary endpoints since we assume that the 2 drugs will have an equally beneficial effect in that regard.

The study, funded by the Novartis Pharmaceutical Company, is being conducted in 31 countries representing all 5 continents. At the end of August 1998 over 2000 patients have been randomized. The enrollment of patients is planned to be completed by September 1999. An Executive Committee (S. Julius, Chair; H. Brunner, L.

Hansson, S.E. Kjeldsen, J.H. Laragh, G.T. McInnes, M.A. Weber, and A. Zanchetti) is responsible for the conduct of the study. The assessment of endpoints will be conducted by an Endpoint Committee (L. Ruilope, Chair). A Data Monitoring and Safety Board (S. MacMahon, Chair) will oversee the study.

Significance

The VALUE Study is the first to compare a new AT II antagonist with a modern calcium channel antagonist. We are aware of the calcium antagonist controversy and have purposely chosen to compare valsartan with the safe, very effective, and most widely used calcium antagonist amlodipine.

Coronary heart disease is the leading cause of cardiovascular mortality in the world. Improving coronary outcomes in hypertension is an urgent priority. Theoretical considerations suggest that angiotensin receptor blocking agents may be particularly effective in reducing coronary morbidity in hypertension. We believe the VALUE Study is an important step in the right direction and that it stands a good chance to further advance the therapeutics of hypertension.

Dr. Stevo Julius is a consultant for Novartis Pharmaceuticals Corporation, CibaGeneva Pharmaceuticals, and Pfizer, Inc.

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The American Society of Hypertension would like to thank our readers for their tremendous response to the recent survey in *Current Concepts in Hypertension*. Your input is a valuable resource to help us develop future issues that are clinically relevant to our readership. In response to your suggestions, *Current Concepts in Hypertension* will begin publishing six times per year beginning with this issue. We hope the new four-color design will make it easier to read the figures and tables while increasing the overall aesthetics of the publication.

ASH hopes many of you will be able to join us at its Fourteenth Scientific Meeting which will be held in New York City from May 19-22, 1999. For program and registration information, please contact the ASH office at 212-644-0650 phone or 212-644-0658 fax; or visit our web site at www.ash-us.org.