Compensatory Left Ventricular Hypertrophy: Relation of Physiology to Management

Craig R. Malloy, M.D.

University of Texas Southwestern Medical Center

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Dr. Malloy is a professor in the Department of Radiology and the Department of Internal Medicine. His clinical interests are in CCU medicine. Research interests include myocardial metabolism and energetics, the physiology of gluconeogenesis, and development of innovative methods for analysis of metabolism in patients. Email: craig.malloy@utsouthwestern.edu or craig.malloy@med.va.gov .

Although left ventricular hypertrophy (LVH) may occur as a consequence of inherited or congenital disorders, the overwhelming majority of an internist's patients with LVH develop it as a compensatory response to a hemodynamic load. LVH is most frequently caused by hypertension which is a well-established risk factor for multiple adverse cardiac events. LVH, separate from hypertension, is itself a strong and independent risk factor for myocardial infarction, systolic heart failure, diastolic heart failure, and sudden death. The mechanism of this association of LVH with adverse outcomes has been the subject of speculation for some time. Some areas of interest seem to have fallen out of favor. For example, ventricular ectopy was associated initially with both LVH and with sudden death, but this explanation by current standards is incomplete. The early suggestion that myosin enzyme expression patterns would provide insight into adverse events has not been fulfilled.

The past decade has seen steady progress in our understanding of LVH on multiple fronts. The molecular biology of cardiomyocyte differentiation and hypertrophy is progressing rapidly with exciting reports appearing monthly. Recent experiments in the pathophysiology of LVH provide insight into clinical observations. However, it is ironic that in this era of multi-center trials focused on management of common disorders, our knowledge of the proper therapy for LVH and related syndromes is limited in important areas. For example, it is not known whether reversal of LVH with current drug therapy reverses the biological abnormalities and decreases the risk of cardiac complications independent of the effect on blood pressure. Management of diastolic heart failure, particularly in the elderly with LVH, and therapy to prevent progression to systolic failure are not sufficiently understood.

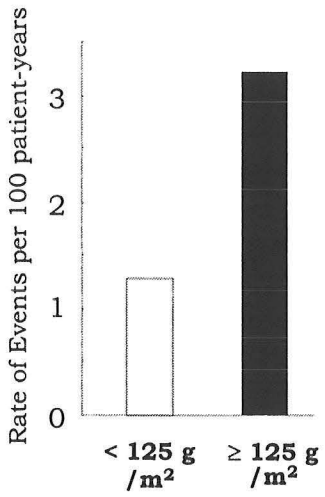

Figure 1. Influence of LVH (determined by 2D echo) on risk of cardiovascular morbidity. Redrawn from JACC 38: 1829, 2001.

The purpose of this short review is to summarize recent clinical observations on the cardiac risks of LVH, as well as current knowledge of the physiological basis of these risks.

1. Independent Risks of Left Ventricular Hypertrophy

LVH may occur simultaneously with many other independent risk factors for cardiovascular disease such as hypertension, diabetes, obesity and smoking. LVH is also an independent risk factor for adverse cardiac outcome, whether diagnosed by ECG or by 2D echo, but it is not usually considered a risk factor for cardiovascular disease because it is a target organ response, that is, LVH itself is considered evidence of injury due to hypertension. Nevertheless, identification of LVH provides important prognostic information (Figure 1). For example, among patients with LVH, all cause deaths are significantly more common: 16% in ten years among patients with LVH compared to 2% among patients without LVH. Interestingly, this effect is independent of coronary disease detected by catheterization. There are at least four known or commonly cited cardiac complications of LVH: sudden death, diastolic dysfunction, systolic heart failure, and poor outcome after MI.

Sudden Death

Several reports beginning about 20 years ago showed a positive correlation between ventricular arrhythmias and LVH. Since ventricular arrhythmias correlate with mortality among patients with structural heart disease, it is perhaps expected that LVH should be an independent risk factor for sudden death.

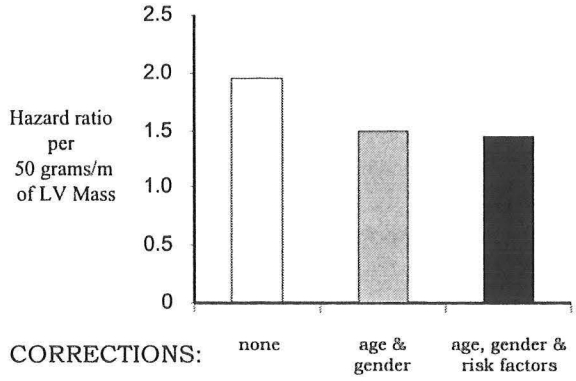

Figure 2. Risk of Sudden Death among patients with LVH. These hazard ratios were reported in JACC 32: 1454, 1998.

Solid evidence for this hypothesis based on echocardiography was not presented until relatively recently. In the Framingham Heart Study 3661 adults over 40 years of age had adequate - quality baseline echos. About another 1,200 patients were excluded because of inadequate echos which occurred most commonly among the obese and the elderly. Thus, although not an intentional feature of the design, some high - risk patients were not included in the study. Among these patients with an average age of 57 years and well-controlled blood pressures averaging 132/81 for men and 130/77 for women, there was an independent relation between the presence of LVH detected by echocardiography and the risk of sudden death (Figure 2). This relation was most evident in males, and persisted after adjusting for age, gender, anti-hypertensive therapy, smoking, and other risk factors for sudden death. As we shall see again, the exclusion of potentially high risk patients may indicate that the predictive value of LVH is most useful in otherwise low risk patients.

Diastolic Dysfunction and LVH

Heart failure is defined as a condition in which the heart is unable to maintain cardiac output at a level the match requirements of peripheral tissues, or can do so only with increased left ventricular diastolic pressure. This rather cumbersome definition is necessary because the clinical syndrome of heart failure covers, broadly, the following three circumstances. First, systolic heart failure means below-normal forward output and is associated a significantly depressed ejection fraction. Second, high-output failure refers to the appearance of systolic failure but occurs because the periphery demands a high cardiac output. Third, diastolic heart failure means that abnormally high filling pressures are required to maintain cardiac output in the setting of a normal or near-normal ejection fraction.

Identification of diastolic heart failure, according to the above, requires evidence of elevated pulmonary artery pressures (exertional dyspnea, rales, S3 gallop, pulmonary congestion on the chest x-ray) plus demonstration of left ventricular ejection fraction greater than 45%. The nearly normal ejection fraction must be measured during symptoms to exclude transient LV systolic dysfunction due to extensive ischemia. Of course, diastolic dysfunction due to pericardial constraint, right ventricular compression or intrapericardial masses must be excluded.

An association between LVH and diastolic failure is commonly mentioned in reviews of diastolic failure. In fact, we have little information about the interaction between compensatory

LVH and diastolic failure. LVH is more common among the elderly, and diastolic failure is also a geriatric disease. Of all patients with heart failure less than 60 years old, only 6% have diastolic failure, but figure is > 40% for those over 70 years old. Patients with LVH are susceptible to diastolic heart failure because of increased left ventricular stiffness and myocyte dysfunction. Diastolic function has been exhaustively studied among patients with hypertrophic cardiomyopathy. However, there is little information on the independent risk of diastolic dysfunction imposed by LVH separate from coincident risk factors such as age, coronary disease, renal insufficiency, aortic and mitral valve disease, diabetes and hypertension.

Progression to Systolic Heart Failure

One of the earliest findings of the Framingham study was that LVH due to long-standing arterial hypertension is associated with a high risk of progression to systolic dysfunction and congestive heart failure. Deterioration of cardiac structure and function may occur among patients with apparently compensated LVH and well-controlled blood pressure. The mechanism of this process is poorly understood but involves interactions among the various cell populations of the heart (myocardial, endocrine, endothelial, interstitial, or immune) with systemic activation of the renin-angiotensin-aldosterone system.

Outcome After Myocardial Infarction

In the past decade a series of reports have shown that patients presenting with an MI plus increased LV mass have a significantly worse outcome, whether diagnosed by ECG or by echocardiography. For example, a recent cohort study was designed to select low-risk patients after myocardial infaction. In this group of 111 patients with first MI, Killip class was 1 or 2, LVEF > 50%, and no recurrent angina had occurred at the time of enrollment. Of these low risk patients, 53 had LVH. Among these patients there were 46 adverse events, including cardiac death, nonfatal recurrent infarction or angina among 24 of the patients. By contrast, among the 58 patients without LVH, only 4 had adverse outcome. There were no deaths or reinfarction; the only event was angina.

It has been suggested that LVH provides the most useful diagnostic information among patients without other high-risk indicators such as depressed LV systolic function. Since LVH is associated with impaired coronary flow reserve, abnormal high energy phosphates, abnormal calcium handling and fibrosis, the mixture of LVH plus preserved LVSF in the setting of CAD may identify a population that will benefit from aggressive medical therapy includieng beta blockers and angiotensin-converting enzyme inhibitors, and perhaps revascularization.

2. What is left ventricular hypertrophy?

LVH is defined as a larger LV mass than a threshold value, corrected for body size. This increase in LV mass certainly occurs in part in response to increased work. However, nonhemodynamic factors such as gender, activation of the rennin-angiotensin-aldosterone system, activation of the sympathetic nervous system, and poorly - understood genetic factors may play a significant role. It has been estimated that known effectors of LV mass only account for about 60% of the variability observed in humans.

The increase in LV mass is primarily due to an increase in myocyte size. This increase in mass is cellular hypertrophy which occurs through the addition of contractile elements, the sarcomeres. The diameter of the myocyte must increase from the normal 15 microns to 25 microns or more. The number of cardiomyocytes is not increased.

A distinction is often made between two patterns of hypertrophy which occur in response to two different stimuli. So-called concentric hypertrophy occurs in the setting of pressure overload such as hypertension or aortic stenosis with increased wall thickness relative to volume. Eccentric hypertrophy is attributed to volume overload such as occurs with mitral regurgitation and aortic insufficiency, and refers to an increase in both ventricular radius and wall thickness.

3. Diagnosis

The traditional electrocardiogram continues to provide an important method for cardiovascular risk stratification in the setting of possible LVH. In spite of the availability of methods to directly image the left ventricle, the ECG remains important because it is standardized, inexpensive and widely available. Automated ECG reading systems are quite good, but it is important to be aware of ECG standards for LVH and their limitations in order to confirm the diagnosis as well as to avoid serious diagnostic errors.

The three general abnormalities on the ECG associated with LVH are: abnormal voltage in limb leads, abnormal voltage in the precordial leads, and abnormal morphology of the P wave, QRS complex or ST/T wave. Many cardiac and systemic illnesses influence the electrocardiogram, as does age, gender, electrolyte status, body habitus, associated drug therapy and many other factors. Because of these recognized factors, considerable effort has gone into developing innumerable scoring systems. One of these scoring systems, proposed by Romhilt and Estes, is summarized in the Table.

Table. Romhilt-Estes Criteria for LVH. A threshold of 4 or 5 points has been suggested as diagnositic of LVH.

	Criterion	**points**
Amplitude	Any one of the following: Largest R or S in limb leads ≥ 20 mm, S wave in V1 or V2 > 30 mm R wave in V5 or V6 > 30 mm	3
Strain	ST and T changes shifted in the direction opposite to the mean QRS vector; not on digoxin	3
Atrial	Terminal negativity of the P wave is 1 mm or more in depth with a duration of 0.04 sec or more	3
Axis	Left axis deviation -30 degrees or more	2
Duration	QRS duration ≥ 0.09 secs	1
Intrinsicoid	Intrinsicoid deflection in V5 and V6 ≥ 0.05 secs	1

The earliest studies emphasized the correlation between the ECG score and the gold standard of LV mass determined at post-mortem. Even the optimal scoring system failed to detect a significant fraction of LVH determined at post mortem. Modification of the criteria to improve sensitivity were met with unacceptably poor specificity. Because the ECG is particularly influenced by age, application of these criteria is less specific among patients less than 40 years old, even in combination with the nonvoltage criteria. Other heart disease, such as right ventricular hypertrophy or conduction disturbances may also mask the diagnosis.

Probably it is only important to be aware that currently-used scoring systems are oriented towards good specificity (>85%) but relatively poor sensitivity. Stated another way, the ECG misses a significant fraction of patients with anatomical LVH, but a positive ECG diagnosis is likely reliable.

Voltage may be assessed in the limb or precordial leads. In the limb leads, three highly specific criteria are: R(I) + S(III) > 25 mm, R in aVL > 11 mm, or R in aVF > 20 mm. Numerous criteria have also been suggested in the precordial leads, including the following: R wave in leads V4, V5, or V6 >26 mm, R wave in leads V5 or V6 plus S wave in lead V1 > 35 mm, or the largest R wave plus largest S wave in precordial leads > 45 mm.

The P wave in lead V1 is often biphasic with a late negative depolarization that covers less than one "little box". This phenomenon occurs because the right atrium depolarizes first and the

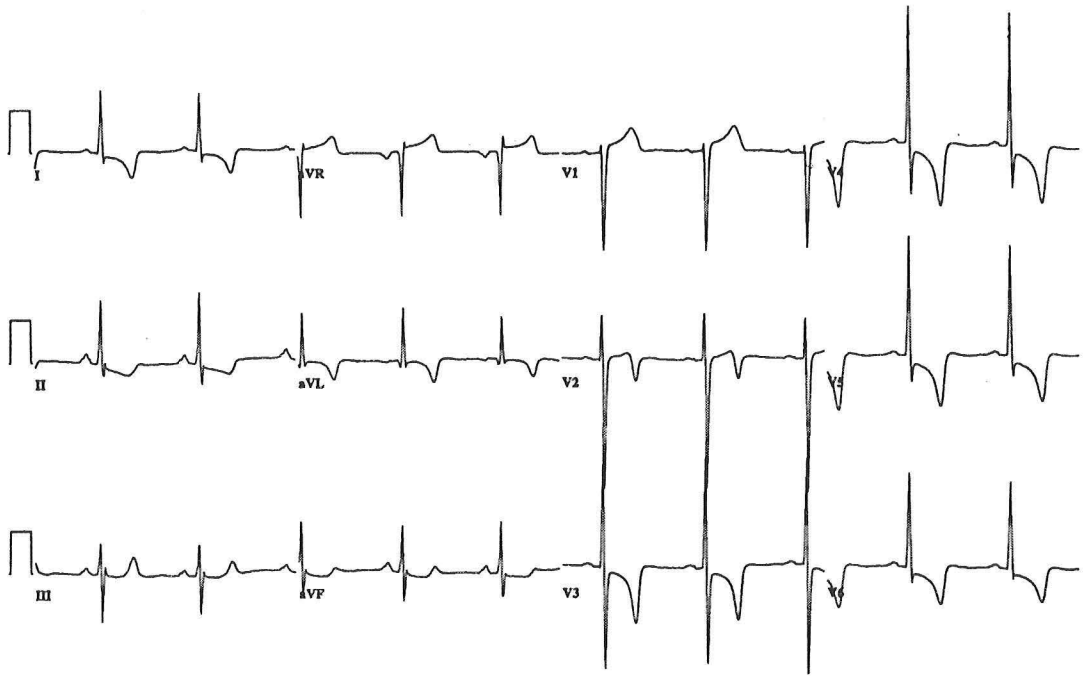

Figure 3. Typical ECG from a patient with LVH.

forces are largely anterior; hence the positive initial P in V1. The left atrium depolarizes later and the forces are directed posteriorly. Usually the magnitude of the negative forces are minor, perhaps because of the distance of the left atrium from V1. Left ventricular hypertrophy is often associated with a larger late negative force, or with any late negative forces in V2. P wave duration may also be prolonged to greater than 0.11 seconds.

The typical changes in the ST segment and T waves in LVH are ST segment depression and T wave inversion. This pattern is termed "strain" although it looks suspiciously like ischemia. It is very important to recognize that the electrocardiographic inverse of significant strain in the left precordial leads is ST elevation in the right precordium, especially lead 2. There are reported instances of patients being given fibrinolytic therapy with this type of electrocardiogram. On occasion this pattern presents real diagnostic difficulty in a patient with dyspnea or ischemic chest discomfort. Conversely, among patients with known LVH, the diagnosis of ischemic heart disease could be obscured by lateral ST depression with T inversion indicative of subtotal coronary occlusion. One solution is comparison with an old electrocardiogram.

Regardless of the scoring system, sensitivity is at best modest. By contrast, echo measurements of LV mass correlate strongly with mass at autopsy, and the echocardiogram also determines the geometric pattern of LVH. Nevertheless, ECG offers prognostic information, and it is concievable that the information is different than that provided by echocardiography. Recently, investigators have skipped the stage of asking if the mass of the ventricle is abnormal, but instead whether the ECG is predictive of adverse cardiovascular outcome. In a recent study of hypertensive men and women, the prevalence of LVH was scored according to six criteria: Cornell, Framingham, Romhilt-Estes, LV strain, Sokolow-Lyon, or Perugia. Depending on the criteria, on entry to the study the prevalence of LVH ranged from 3.9% according to the Framingham criteria to 17.8% according to the Perugia score. After only 3.3 years of followup, of the six methods, five predicted an excess cardiovascular event rate; the one exception was the Sokolow-Lyon method. The Perugia score was the best of the six methods for predicting cardiovascular morbidity and mortality compared with classic methods for detection of LVH.

4. The Neurohumoral Environment

LVH: An Adaptive Responses to Pressure Overload

Left ventricular hypertrophy is thought to be a short-term compensatory and adaptive response that allows the myocardium to maintain for ward cardiac output in response to increased afterload. As pressure overload gradually develops, myocytes hypertrophy in order to maintain a fixed systolic wall tension. A useful approximation of the Laplace relationship is:

$$\text{Systolic wall tension} \propto [\text{systolic pressure} \cdot \text{LV radius}]/[2 \cdot \text{LV wall thickness}]$$

If the "goal" of the left ventricle is to maintain systolic wall tension within a normal range, then it is easy to appreciate the consequences of increased systolic pressure: radius must shrink, or wall thickness must increase. A reduced radius would decrease cardiac output, so a proportionate increase in wall thickness will maintain systolic wall tension. This hypertrophy must involve not only the cardiomyocytes but the interstitial matrix and vasculature as well. As we shall see, clinically recognized LVH actually means a complex mixture of abnormalities in coronary hemodynamics, the interstitium, and in the myocytes themselves.

Renin-Angiotensin-Aldosterone System

The physiology of the rennin-angiotensin-aldosterone system has been exhaustively studied from the perspective of blood pressure maintenance. Briefly, renin is a protease secreted into blood by juxtaglomerular cells of the kidney. Secretion is stimulated by decreased blood pressure and potentiated by sympathetic stimulation. Renin converts the glycoprotein from the liver, angiotensinogen, into angiotensin I which is undergoes further proteolysis by the angiotensin-converting enzyme into angiotensin II, a potent vasoconstrictor which also potentiates the vasoconstricting effects of the sympathetic nervous system. Angiotensin II also stimulates the release of arginine vasopressin (antidiuretic hormone) from the posterior lobe of the pituitary. Finally, angiotensin II binds to receptors in zona glomerulosa of the adrenal cortex to stimulate production and secretion of the mineralocorticoid, aldosterone. Aldosterone facilitates Na+ reabsorption from distal collecting tubules and secretion of K+. In summary, angiotensin II elevates blood pressure by 1) direct vasoconstriction, 2) potentiation of sympathetic nervous system activity, 3) stimulation of aldosterone synthesis and release, and 4) stimulation of arginine vasopressin release.

Angiotensin II has direct trophic effects on the myocardium. There is a positive correlation between angiotensin II levels in the circulation and LV mass independent of blood pressure and body size which implies that a component of LVH is not due exclusively to the hemodynamic load but also to the neurohumoral environment.

Sympathetic Nervous System

Norepinephrine directly stimulates myocyte hypertrophy as well as growth of cardiac fibroblasts. The hypothesis that the sympathetic nervous system may drive the hypertrophic process has attracted extensive study. Peripheral sympathetic hyperactivity is well - known to occur among patients with mild hypertension. However, the role of sympathetic activity in established LVH is difficult to determine since the presence of LVH itself (arising due to hypertension) may cause abnormalities of intracardiac sympathetic efferents, abnormal atrial stretch, and intermittently reduced forward output, all of which could stimulate sympathetic hyperactivity. Recently, patients with LVH and hypertension were compared to patients with hypertension but no LVH. The two groups were very well-matched for medical therapy, age, gender, body mass and hemodynamic variables. Peripheral sympathetic nerve activity was determined in both groups, and found to be greater among patients with LVH compared to those without.

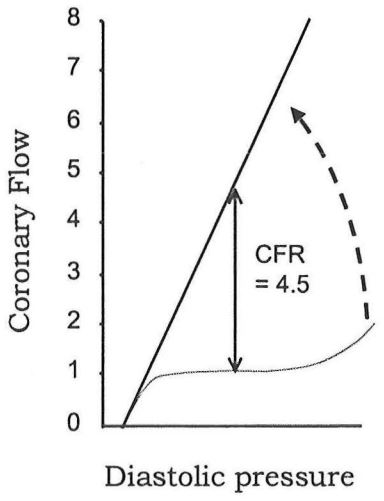

Figure 4. Schematic of Coronary Flow Reserve (the "coronary conductogram").

5. Underlying Biological Features

Coronary Physiology in LVH and Coronary Flow Reserve

An important underlying mechanism of risk is disruption of coronary hemodynamics even in the absence of epicardial coronary artery disease. One group of studies have relied on the measurement of coronary flow reserve (see Figure 4). This concept is simple: coronary blood flow is measured both before and after a coronary vasodilating intervention. That intervention may be physiological such as exercise or a pharmacological coronary vasodilator such as papaverine or adenosine. The ratio of flow (after/before) is the coronary flow reserve, that is, an index of the ability of the coronary circulation to increase flow in the setting of demand. In healthy humans, CFR is about 4 to 5. Coronary flow reserve is consistently abnormal in patients with LVH or prolonged hypertension in the absence of detectable epicardial coronary disease. Other studies have demonstrated that minimal coronary resistance is elevated among patients with LVH which correlates with the volume of myocardial fibrosis.

Although these observations are consistent among several studies, the physiological mechanism is not known. Coronary flow reserve, since it is a ratio, can appear to be abnormal because of increased baseline flow even if maximal vasodilatory response is preserved. High baseline flow because of increased metabolic demand, for example, might be expected to decrease CFR even if the vasculature is completely normal. Conversely, baseline flow may be normal but the vasodilatory response may be impaired because of mechanical properties of the microvaculature or inadequate sizing of the epicardial vessels. The complexity of this problem is multiplied by the recent insights into endothelial dysfunction which may be dynamic an sensitive to diverse factors. In general, there is agreement that LVH is associated with primary alterations in coronary physiology, perhaps on the level of the microcirculation, and that these abnormalities may play an important role in development of angina, MI and sudden death.

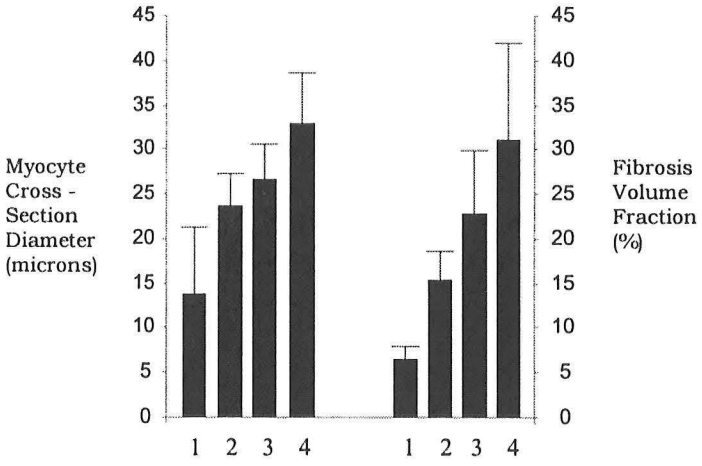

Figure 5. Myocyte diameter and fibrosis volume fraction among patients with LVH. From J. Hypertension 16: 1031, 1998.

Reduced Capillary Number Relative to Myocyte Volume

Later hypertrophy (at least several months after the inciting stimulus) is characterized by reduced mitochondrial volume relative to the myofibrillar volume and reduced capillary density. This anatomical imbalance indicates that capillary growth does not occur proportionate to myocyte growth. The reduced capillary density combined with excess myofibrillar volume relative to mitochondria may make the hypertrophied myocardium susceptible to ischemia.

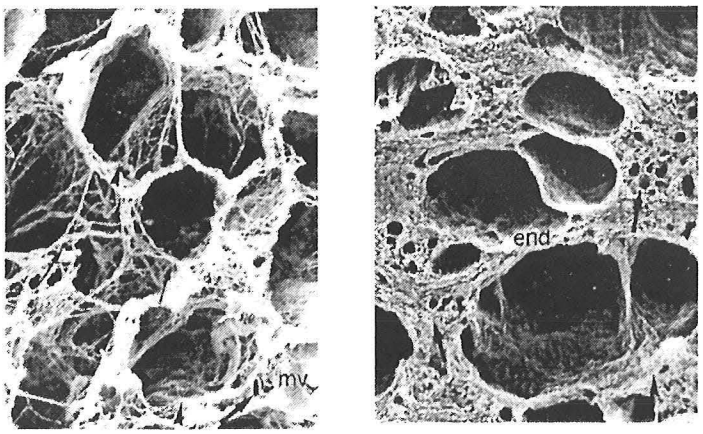

Figure 6. Comparison of normal (left) and hypertrophied (right) human myocardium. From J. Hypertension 16: 1031, 1998.

Myocardial Fibrosis and Mechanical Properties

The cardiac extracellular matrix surrounds and supports myocytes, fibroblasts and vessels. There are four components: the structural proteins, the adhesive proteins, the nonadhesive proteins and the proteoglycans. The structural proteins are the most abundant proteins and include collagen and elastin. Of the five types of collagen, types I and III together represent more than 90% of collagen, and are synthesized by smooth muscle cells and fibroblasts. The adhesive proteins such as laminin and fibronectin bind to the myocyte membrane via the integrins which are a group of transmembrane receptors. The impact of LVH on the organization of the extracellular cardiac skeleton is beyond this review, but it is important to appreciate that hypertrophy does involve substantial reorganization of the matrix, and that this reorganization likely has adverse effects.

The mechanical properties of the hypertrophied myocardium contribute to abnormal diastolic function and perhaps to abnormal metabolism and a propensity for arrhythmias. For example, a distinctive feature of pathological LVH is the presence of excess fibrosis (see figures 5 and 6). The presence of myocyte hypertrophy in humans correlates directly with collagen deposition as illustrated in Figure 5. It is reasonable to speculate that oxygen diffusion into the cardiomyocyte and flow of cellular waste back into the circulation is impaired by proliferation of the extracellular matrix.

In animal models and probably among many patients with LVH, the rate of left ventricular relaxation during diastole is reduced and the isovolumetric relaxation time is increased. The separate roles of extracellular fibrosis and abnormal cellular metabolism and calcium handling are difficult to separate, but both are likely clinically important. There may be an important correlation from the work by Morgan, Gwathmey and colleagues who examined isolated muscle strips from patients with hypertrophic cardiomyopathy (see Figure 7). At very slow pacing rates, the patterns

of contraction and relaxation were no different from normal human myocardium. However, at pacing rates over 60/min they observed decreased developed tension and increased resting tension. This may be relevant to the use of beta blockers for patients with LVH. Although beta stimulation improves relaxation of the left ventricle (positive lusitropic effects), beta adrenergic stimulation also increases heart rate. These observation of the rate dependent mechanical properties of hypertrophied myocardium may indicate that, on the balance, patients derive more benefit from control of HR. Further, these observations suggest that atrial fibrillation will be very poorly tolerated.

Abnormal Substrate Oxidation: the "Fetal Phenotype"

The heart is equipped to completely oxidize ketones, fatty acids of various chain lengths and saturation, glucose, pyruvate, lactate and other energy - providing substrates. The final steps in the stoichiometric oxidation of all of these compounds to CO_2 and water requires the citric acid cycle. Since the concentration of these substrates may vary by a factor of 10 or more under physiological and disease conditions, the myocardium is exposed to a very complex mixture of substrates and metabolic conditions. It has a remarkable capacity to switch among these substrates as needed depending on availability.

The normal, aerobic heart in vivo derives about 50-60% of its energy from oxidation of long chain fatty acids, virtually nothing from glucose, and the balance from ketones, lactate and pyruvate. This profile of substrate preferences is altered in animal models of pressure-overload LVH, but the results vary somewhat depending on the experimental design. Hearts that are supplied only with a nonphysiological mixture of fatty acids and glucose generally demonstrate increased glucose oxidation and inhibition of fatty acid oxidation. If hypertrophied hearts are exposed to a physiological mixture of substrates, then fatty acid oxidation is inhibited, but the balance of energy is not derived from glucose, but other substrates.

The physiological benefit of this shift may be improved myocardial efficiency. It is known that efficiency of energy production by the heart, defined as ATP yield per mole of oxygen, is better for carbohydrates compared to long chain fatty acids. It has been suggested that the cardiomyocyte in the hypertrophied heart is chronically hypoxic and that a shift in substrate oxidation away from fatty acids to glucose improves ATP yield per mole of oxygen consumed. Regardless of the mechanism, the substrate oxidation profile is similar to the newborn heart where carbohydrate oxidation is a dominant source of energy. This profile has been referred to as the fetal phenotype for substrate utilization.

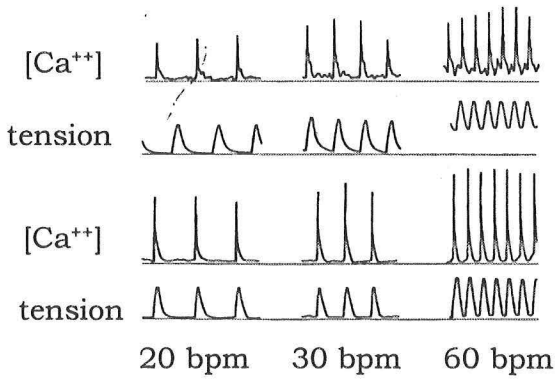

Figure 7. Effect of pacing rate on tension development and aequorin-detected calcium in human myocardial strips from control (bottom tracings) and hypertrophied (top tracing) myocardium. The hypertrophied tissue was obtained from a patient with asymmetric septal hypertrophy. Redrawn from J. Clin. Invest. 87: 1023, 1991.

Myocardial Energetics

The cardiomyocyte require continuous generation of ATP to support its essential functions: the contraction-relaxation cycle and maintenance of cation gradients. When oxygen delivery is not limiting, this need for ATP is met almost completely by oxidative phosphorylation. The overall reaction (combining mitochondrial ATP synthesis plus the adenine nucleotide translocase and phosphate transporters) is: ADP (out) + Pi (out) + $4H^+$ (out) → ATP (out) + $4H^+$ (in) where "out" and "in" refer to the cytosol and mitochondrial matrix, respectively. The heart is capable of dramatic changes in work output over a few seconds, so it must be able to step up the rate of this reaction over the same time frame. This capability must involve the interaction of multiple complex processes: glycolysis, beta-oxidation, tricarboxylic acid cycle flux, electron transport, oxidative phosphorylation and ion and metabolite transport steps. In spite of the complexity of the overall system, most discussions of myocardial energetics in LVH focus only on the effects of high

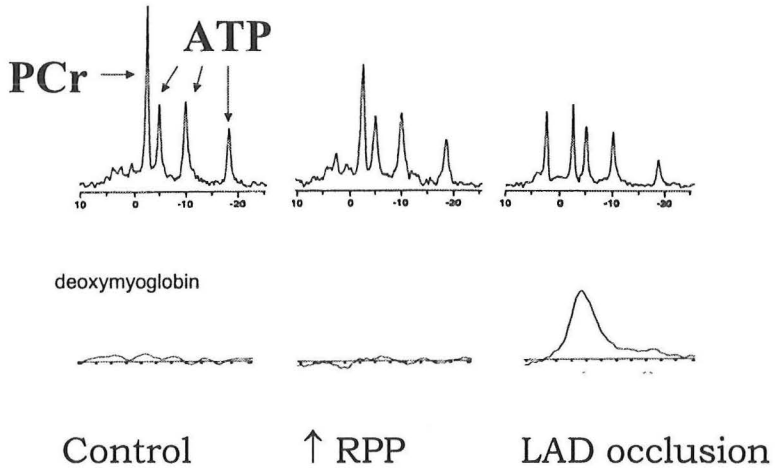

Figure 8. Effect of increased rate-pressure product on the ^{31}P NMR spectrum of a dog heart with LVH. Redrawn from Bache et al., Cardiovascular Research 42: 616, 1999.

energy phosphates. These studies are dominated specifically by measurement of ATP, ADP and inorganic phosphate (Pi) because under ordinary intracellular conditions, the relative concentration is a measure of the energy available from ATP hydrolysis, the so-called phosphorylation potential: [ATP]/([ADP][Pi]).

The role of phosphocreatine and the creatine kinase system may also be important in LVH. Phosphocreatine is present in high concentration in the cardiomyocyte, roughly twice [ATP]. The enzyme that transfers high energy phosphates between ATP and creatine, creatine kinase, is familiar to all clinicians since its detection in plasma is an index of myocardial injury. Creatine kinase catalyzes a single reaction: phosphocreatine^{2-} + $MgADP^-$ + H^+ ↔ creatine + $MgATP^{2-}$. The equilibrium constant for this reaction is Keq = ([Cr][ATP]) / ([H+][PCr][ADP]) which on rearrangement and assuming pH near 7 yields: [ADP] ∝ [Cr][ATP]/[PCr].

The "need" of the myocardium for an apparent dead-end reaction involving ATP has generated interest for many years. One role is now generally-accepted: phosphocreatine serves as an energy reservoir. During fluctuations in ATP synthesis rates or changes in ATP hydrolysis rates such as might occur with brief ischemia or rapid changes in loading conditions, the CK reaction allows rapid regeneration of ATP from ADP. Notice that the consumption of phosphocreatine to generate ATP from ADP also consumes a proton. Thus, during brief ischemia where creatine phosphate serves as an energy reserve, the CK reaction also protects against intracellular acidification. This function is strongly supported by experimental observations.

In contrast to the more-or-less passive role of the CK system to replenish ATP, an additional function of the CK system has been postulated. According to this picture, CK flux is directly coupled to oxidative phosphorylation. A key feature of this hypothesis is the spatial distribution of CK isoforms. About 70% of CK activity is localized in the cytosol with a significant fraction associate with the myofibrillar M band, the sarcoplasmic reticulum, and glycolytic enzymes. The reminder, about 30% of activity, resides on the outer leaflet of the inner mitochodrial membrane. Since the enzyme is physically adjacent to the site of ATP synthesis, it may have preferential access to mitochondrially-generated ATP and therefore rapidly consume ATP to generate phosphocreatine essentially at the surface of the mitochondria. PCr may then diffuse through the cytosol to myofibrils where the high energy phosphate group is transferred to ADP to generate ATP for consumption. According to this picture, phosphocreatine shuttles energy from site of ATP generation (mitochondria) to sites of utilization (myofibrils). Experimental evidence for the energy shuttle is conflicting and the overall significance of the CK system in energy transfer is not resolved.

Myocardial energetics and the creatine kinase system have been extensively studied in animal models of LVH. There is general agreement that the PCr/ATP ratio is reduced in the myocardium of animals with LVH. Since $[ADP] \propto [Cr][ATP]/[PCr]$, this observation implies that [ADP] is elevated even in the absence of hemodynamic or metabolic stress. Perhaps more important is the response of the hypertrophied myocardium to acute changes in rate pressure product. Multiple studies using ^{31}P NMR spectroscopy to continuously monitor the [ATP] and the PCr/ATP ratio under these circumstances. There is general agreement that hypertrophied myocardium demonstrates reduced PCr/ATP and accumulation of inorganic phosphate during increased oxygen demand.

However, two major problems restrict the interpretation of these studies. *First*, since there is evidence that coronary flow reserve is impaired, any changes in high energy phosphates could be attributed to demand ischemia secondary to disordered microvasculature rather than any abnormality in cell metabolism. *Second*, because of the interstitial fibrosis, oxygen diffusion distances are increased. Furthermore, because of increased myocyte diameter relative to capillary density, intracellular oxygen diffusion may also be impaired. Recently, Bache and colleagues examined the effects of increased rate pressure product on myocardial energetics in dogs with aortic stenosis with an experiment designed to control both variables. Across the subendocardium, midwall and subepicardium perfusion was measured under baseline and increased RPP conditions with standard microsphere methods. ^{1}H NMR spectroscopy was simultaneously used to monitor deoxymyoglobin which by definition is an indicator of intramyocellular oxygenation state. Myocardial perfusion measured per gram of myocardium was not different in the hypertrophied heart compared to control at any level of work, and deoxymyoglobin could not be detected even at the highest work state. In spite of demonstrated normal perfusion and apparently adequate oxy-

gen delivery, the PCr/ATP was consistently lower in hypertrophied hearts at rest and with hemodynamic stress. Thus, although the hypertrophied myocardium was able to support very high work loads, it did so in the setting of altered regulation of oxidative phosphorylation.

Myocardial metabolism has also been evaluated among patients with hypertension using ^{31}P NMR. In an important study, Lamb found that the PCr/ATP was reduced among patients with hypertension even in the absence of pharmacological stress compared to controls (1.20 ± 0.18 vs. 1.39 ± 0.17). This is a significant report since it demonstrates reduced PCr/ATP ratio among patients without obvious ischemia. Among patients with valvular heart disease associated with LVH (aortic stenosis, aortic insufficiency and mitral regurgitation), patients with NYHA functional class I or II status did not have significant abnormalities of PCr/ATP, but clinically severe heart failure was associated with reduced PCR/ATP.

In summary, there is abundant evidence from animal models that LVH reduces PCr/ATP under baseline and hemodynamic stress conditions compared to control. Under physiological conditions, numerous mechanisms assure that ADP is maintained at a low level. Because of the creatine kinase reaction, even small changes in the PCr/ATP translates to a marked increases in [ADP]. ADP is a substrate for all the critical ATPases of the myocyte including the Na-K ATPase, the calcium ATPases and the actomyosin ATPase, which might imply that abnormal control of energetics plays a primary role in the risks of LVH. However, these studies also demonstrate that hypertrophied ventricles can support very high afterload, at least briefly. Thus, it appears unlikely that abnormal energetics play a primary role in the observed hemodynamic abnormalities of LVH.

Intracellular Cations and Abnormal Calcium Handling

Steep concentration gradients of metal cations exist between the extracellular and intracellular compartments of cells. For example, Na_i is roughly 10 mM and Na_e is about 140 mM. The calculated electrical potential (from the Nernst equation) is + 70.5 mV. Since the measured potential is about - 80 mV, both the concentration gradient and the electrical gradient strongly favor the movement of extracellular sodium into the cell. These gradients which are critical for normal function are maintained by a network of energy - requiring reactions.

Calcium, of course, is the activator of the myofilaments and contraction; the rate and magnitude of calcium delivery into the cytosol and its later removal during diastole plays the central role in contraction and relaxation. Therefore, calcium may be considered the single most important ion in cardiac physiology. As expected, an elaborate set of energy-requiring ion pumps, exchange mechanisms, and intracellular compartments controls calcium transients. During diastole, cytosolic calcium is low. During the cardiac action potential the concentration of cytocolic calcium rises through direct calcium delivery via the depolarization activated calcium channels, plus the release of calcium from the sarcoplasmic reticulum. At the conclusion of the action potential, calcium is removed from the cytosol by multiple processes. Two mechanisms transfer calcium from the cytosol to the extracellular space, the sodium-calcium exchange and a calcium ATPase. Calcium is also taken up into the sarcoplasmic reticulum by a different calcium ATPase. Finally, mitochondria are also capable of sequestering calcium although this is thought to be a relatively minor component. Normal relaxation, therefore, may be sensitive to both [ATP] and [Na]. Preservation of [Na], in turn, is dependent on regulation of both intracellular [H] and [K]

Maintenance of the calcium, sodium and potassium gradients depends critically on the Na-K ATPase. The concentration gradient of sodium and potassium is sustained by the action of the Na-K ATPase which of course requires high free energy of ATP hydrolysis (Figure 9).

Energy in the form of ATP is required to maintain a gradient of numerous cations across the cellular membrane. The consistent abnormalities observed in the free energy of ATP hydrolysis in the hypertrophied heart suggest that cation gradients may be abnormal in the hypertrophied ventricle. In fact, it is very difficult to study intracellular cations in functioning ventricular myocytes. Intracellular sodium has been examined by both ion-sensitive electrodes and by ^{23}Na NMR. Most but not all studies indicate that [Na+]i under baseline conditions is increased from 1.5 to 2.0 times control. No information is available regarding response to ischemia or catecholamines.

Even at baseline, this increase could have significant effects on cell viability and sensitivity to ischemia. Intracellular sodium is involved in multiple cation exchange processes that are not directly energy-dependent. For example, the sodium – calcium exchanger is very active in mammalian heart and continues to function in the presence of cyanide which would be expected to block energy-dependent processes. A simple model of the energetics of the exchange (assuming that 2 Na ions enter the cell as one calcium is extruded) indicates the following ratios: $[Ca]o / [Ca]i = ([Na]o/[Na]i)^2$. Thus, a 50% increase in intracellular sodium would more than double intracellular calcium. Since excess free calcium is thought to cause impaired relaxation and (in higher concentrations) irreversible injury, even a modest increase in baseline sodium may predispose the myocyte to adverse outcomes.

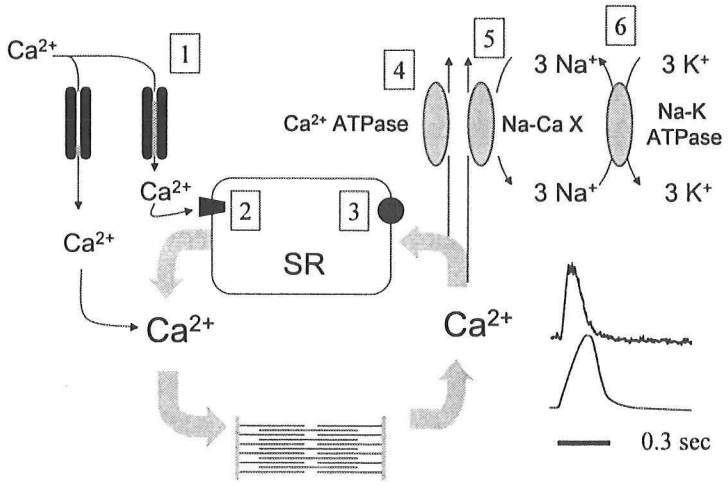

Figure 9. Pathways of normal calcium flux in the myocardium. Legend: 1) L type calcium channel; 2) ryanodine receptor; 3) sarcoplasmic reticulum calcium ATPase; 4) sarcolemmal calcium ATPase; 5) sodium calcium exchanger; 6) Na-K ATPase. The inset shows the cytosolic calcium transient and the simultaneously recorded tension development.

Intracellular sodium also participates in the Na – H exchanger. Under aerobic conditions, this exchange process is not highly active, but even mild intracellular acidification activates the exchanger. If intracellular sodium increases, then the electrochemical gradient for sodium is diminished and the ability of the exchange mechanism to extrude protons is impaired. During brief ischemia, it could be postulated that elevated intracellular sodium blunts the ability of the myocardium to eliminate protons, and even mild intracellular acidification dramatically impairs diastolic function.

The molecular basis of abnormalities of intracellular calcium and sodium handling has been examined by numerous investigators. An attempt to summarize a very large literature is

shown in Figure 10. It is evident that, unfortunately, the data are contradictory and in many instances it is possible to find an increase, no change, or decrease in a particular key protein depending on the reporting lab or the animal model. This summary is further flawed by combining data on mRNA expression, protein expression, and protein activity. Furthermore, some key elements in calcium handling are ignored, such as phospholamban. Nevertheless, it appears that the early phases of excitation-contraction coupling (the calcium channel and the ryanodine receptor) are not altered by LVH. Very early in the LVH process the ATP dependent calcium transporting proteins are either unchanged, or increased which may imply that increased capacity to handle calcium is a key feature of early LVH. Finally, in spite of the inconsistencies in the above table, it appears that severe LVH prior to CHF is always associated with depressed function and expression of SR calcium ATPase.

	Early LVH	Severe LVH	Early CHF
L-type Ca^{2+} channel density	↔	↔	↓
Ryanodine receptor	↔	↓ ↔	↓
SR Ca^{2+} ATPase	↑↔	↓	↓↓
SL Ca^{2+} ATPase	↑↔	↑	↓
Na^{+} - Ca^{2+} exchange	↑↓	↑↑↓	↑↑
Na^{+} - K^{+} ATPase	↔↓↑	↓↔	↓↓

Figure 10. Expression of critical proteins in calcium handling.

6. Implications for Management

Management of Ischemic Chest Discomfort and Acute Coronary Syndrome

The key concept in acute coronary syndrome pathophysiology is the concept of "vulnerable" plaque composition, disruption of the overlying fibrous cap due to an imbalance between collagen synthesis and degradation in the cap, and resulting partial or complete thrombosis of the coronary artery. It is far beyond the scope of these comments to review current concepts in acute coronary syndromes, but features of LVH, when associated with known or suspected epicardial coronary disease may be useful in guiding therapy. The evaluation will rely on the history, electrocardiogram and cardiac enzymes.

First, the initial evaluation of ischemic symptoms by electrocardiography may be difficult because some ECG features of LVH mimic acute ischemia. Usually comparison with prior electrocardiograms, serial electrocardiograms during initial therapy, and correlation with symptoms provides sufficient information. On occasion urgent 2D echo may be helpful to clarify wall motion and exclude acute LV dysfunction. However, in spite of careful bedside management, patients may have impressive symptoms and/or physical findings that require aggressive evaluation. Under these conditions urgent coronary angiography is uniformly helpful in planning management.

Second, cardiac enzymes are essential to evaluation. The use of CK-MB to evaluate acute ischemia is important particularly because of the rapid onset and disappearance, but there is little to add to current practice based on recent literature. There are three troponins, I, C and T, and they are intricate parts of the contractile apparatus. In contrast to studies on CK-MB, useful reports continue to appear which clarify and further reinforce the utility of troponins for evaluating

coronary syndromes. The following are noteworthy. One question that occasionally arises is whether reversible myocardial ischemia causes an elevation of serum troponins. A very recent study examined the effects of dobutamine - induced ischemia on peak troponins during stress echocardiography. Among patients with reversible wall motion abnormalities induced by dobutamin, troponins did not rise, indicating that ischemia does not cause a "troponin leak." Another recent report examined the prognostic implications of positive troponins. This meta-analysis of 26 studies included both cohort and clinical trials as well as troponins I and T. Depending on the study design, patients had excess risk with positive troponins. In cohort studies (consecutive patients) the odds ratio for mortality was 8.5. For clinical trials the odds ratio was 3. A final interesting report examined the relation between positive troponins and angiographic appearance of coronary arteries among patients with acute coronary syndromes. Patients with positive troponins were more likely to have plaque rupture, plaque dissection and thrombosis. Regardless of whether or not a patient has LVH, positive troponins in the setting of possible myocardial ischemia indicate high risk.

Third, aggressive control of hemodynamics is likely at least as important among patients with LVH compared to others. Specifically, since diastolic function and calcium handling are abnormal, it is likely that control of heart rate with beta blockers is particularly important.

Dyspnea and Diastolic Dysfunction

The clinical definition of diastolic dysfunction is the syndrome of congestive heart failure, both symptoms and signs, plus simultaneous or near-simultaneous documentation of LVEF > 45%. LVH is a risk factor for diastolic dysfunction, as are other factors mentioned above, especially age > 60 years. Patients with diastolic dysfunction often present with exertional dyspnea, so the combination of this complaint plus LVH should call attention to this diagnosis. Among patients with symptoms and signs of heart failure, diastolic dysfunction is always a consideration and LVH may be contributory. The eventual outcome is strongly related to the comorbid disorders such as coronary artery disease.

The diagnosis of congestive heart failure is made clinically based on the symptoms of pulmonary venous hypertension, plus appropriate physical findings and a consistent chest x-ray. Nevertheless, the clinical picture is often confused by intercurrent pulmonary or renal disease, and the overall evaluation of these clinical finding is subjective. Furthermore, even if the findings of congestive heart failure are clear, it may be impossible to distinguish from left heart failure based solely on the clinical exam. Therefore, objective assessments of heart failure are sought.

Elevated levels of B-type naturietic peptide do not distinguish between systolic and diastolic heart failure. Therefore, the proper diagnosis relies on demonstrating preserved LV systolic function during or as close as possible to the onset of symptoms. Timing may be important because transient myocardial ischemia due to coronary disease may cause transient but severe systolic dysfunction. Overwhelmingly the preferred method for evaluating symptoms of left heart failure is echocardiography. In addition to assessing LV function, it also excludes valvular heart disease, constrictive pericarditis, hypertrophic cardiomyopathy and infiltrative heart diseases.

Diastolic dysfunction may cause elevated left ventricular end diastolic pressure, passive increased pulmonary venous pressure, and therefore the symptoms and signs of pulmonary venous congestion. As noted above, the clinical definition of diastolic dysfunction is the signs and

symptoms of congestive heart failure plus simultaneous or near simultaneous documentation of LVEF > 45%

Medical therapies for congestive heart failure may need to be modified somewhat in the setting of LVH with diastolic dysfunction, depending on the therapeutic objective. For example, Patients with pulmonary venous hypertension and pulmonary congestion are ordinary treated with diuretics and often nitrates, especially if coronary disease is also present. Diuretics are required in virtually all symptomatic patients, but, since LVH is associated with myocardial fibrosis and impaired relaxation, both nitrates and diuretics should be used cautiously, since rapid reduction of left ventricular filling pressure and cardiac output may lead to orthostatic hypotension and renal insufficiency. ACE inhibitors and angiotensin II subtype 1 (AT1) blockers also relieve elevated pulmonary capillary wedge pressure, although not as rapidly as diuretics. Both classes of agents also may cause hypotension and renal insufficiency. Thus, management of pulmonary venous congestion will usually involve a combination of an ACE inhibitor and a diuretic, but symptoms, blood pressure, exam, weights and renal function must be closely monitored.

Digoxin has no role in therapy of diastolic dysfunction in the setting of sinus rhythm.

Patients with a rapid ventricular rate due to either atrial fibrillation or sinus tachycardia plus LVH may tolerate the combination quite poorly. Aggressive treatment of abrupt atrial fibrillation with rapid ventricular response may be required. In spite of the fact that beta agonists improve myocardial relaxation, the overall benefit of beta blockers is to slow the heart rate and improved ventricular filling. Amiodarone may be quite helpful in maintaining sinus rhythm among patients with LVH and atrial fibrillation. If amiodarone and beta blockers are ineffective among patients with atrial fibrillation, AV node ablation and DDD pacing may be an option.

Finally, the combination of LVH, significant coronary disease, and diastolic dysfunction is a particularly challenging combination. Close attention to reduction of oxygen demand with beta blockers and control of hypertension is required, as is judicious antiischemic therapy with nitrates. Revascularization is an option, but the long-term prognosis for patients with severe diastolic dysfunction, LVH and coronary disease is not good.

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