Link of Nonhemodynamic Factors to Hemodynamic Determinants of Left Ventricular Hypertrophy

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Abstract—Despite current evidence suggesting that hemodynamic load is the fundamental stimulus to begin the sequence of biological events leading to the development of left ventricular hypertrophy, genotype, gender, body size, and less easily recognizable environmental factors may contribute to generate the cascade of molecular changes that eventually yield the increase in protein synthesis needed to increase left ventricular mass. However, even nonhemodynamic factors such as gender and body size eventually regulate the growth of left ventricular mass by at least in part influencing loading conditions. Consideration of measurable factors, such as gender, body size, and hemodynamic load, allows evaluation of individual echocardiographic left ventricular mass as the deviation from the level that would be required to face a gender-specific hemodynamic load at a given body size. Values of left ventricular mass that are inappropriately high for individual gender, body size, and hemodynamic load are associated with a high cardiovascular risk phenotype, even independent of the presence of arterial hypertension. Thus, the condition of inappropriately high left ventricular mass may be recognized as a more advanced stage of pathological structural changes initially induced by overload, going beyond the compensatory needs. The biological process that yields inappropriate left ventricular mass is probably linked to the protracted activity over time of biological mediators of left ventricular hypertrophy, such as proto-oncogenes and other growth factors, neurohormones, and cytokines, inducing structural modifications that initially compensate imposed overload but eventually change the structure of myocardial tissue and the composition of motor units. (Hypertension. 2001;38:13-18.)

Key Words: hypertrophy • gender • genotype • growth factors • hemodynamics • blood pressure

Myocardial hypertrophy is the chronic adaptation of the left ventricle (LV) to increased cardiac load. Increased wall stress and strain provide a stimulus for signaling to cause mRNA transcription to increase muscular proteins. This prompt nuclear reaction is finalized to protect the myocardium from excessive wall tension by minimizing oxygen consumption and simultaneously producing sufficient strength to provide the body tissue with the required nutrient by maintaining or even increasing cardiac output. Thus, hemodynamic factors are at the basis of molecular changes that eventually yield the cascade of reactions needed to achieve those compensatory goals.1–4 Studies and experiments performed on the pathways that lead to the increased protein synthesis that ultimately causes LV hypertrophy have provided the assumption that LV hypertrophy might also occur in the absence of clear-cut, recognizable changes in cardiac loading conditions.5–9 Although this possibility appears to be true under experimental conditions in which direct exposures of cells to growth factors are investigated, independent of the hemodynamic factors known to be the stimuli for production of those substances, the applicability of those experiments to the intact circulation in humans remains to be proved. However, the difficulty of attributing most of the cross-sectional variability of LV mass in humans to the variability of blood pressure10,11 has led to the opinion that the entire process of the development of hypertensive LV hypertrophy is not necessarily associated with clearly identifiable hemodynamic alterations. Thus, the question of whether LV hypertrophy in human hypertension is a pure consequence of hemodynamic overload had been raised at the beginning of echocardiographic studies on cardiac adaptation to arterial hypertension.12

Despite the current evidence suggesting that hemodynamic load is the basic initial stimulus to begin the sequence of biological events that lead to the development of LV hypertrophy, there are at least 3 recognizable, potent stimuli for LV growth other than those generally considered as direct hemodynamic factors: genotype, gender, and body size. These factors do not appear to be immediately related to hemodynamics, although they eventually are. With these potent determinants, less easily recognizable environmental factors, especially those related to nutritional habits,13,14 might directly or indirectly contribute to the variability of LV mass.

Received September 15, 2000; first decision October 10, 2000; revision accepted December 13, 2000.
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Genotype
The number of human cardiac myocytes is genetically determined and reaches a final amount within the first year after birth, when mitotic activity ceases. Genotype is therefore very likely to be the primary stimulus for the construction of the myocardial architecture on which further stimuli will determine the degree of growth of cell size (hypertrophy). This genetic effect has been shown in studies of twins. Harshfield et al measured LV mass in 7 sets of monozygotic and 15 sets of dizygotic twins. After adjustments for gender, blood pressure, age, and caloric expenditure, monozygotic twins showed smaller within-pair differences \( (7 \pm 5 \text{ g/m}^2) \) and much higher intraclass correlation \( (\rho=0.90, P<0.01) \) than dizygotic twins \( (17 \pm 11 \text{ g/m}^2, P<0.03; \rho=0.33, P=\text{NS}) \), suggesting that the magnitude of LV mass was at least in part genetically determined. Recent studies in the cohort of the HyperGEN have confirmed that part of the variability of LV mass is in fact genetically determined.

The “normal” inherited genotype can, however, be altered by the signal transduction of mechanical stress, through the activation of protein kinase cascades of phosphorylation and the expression of immediate-early genes such as \( \text{c-fos, c-myc}, \text{c-jun}, \) and \( \text{Egr-1} \), inducing an increase in protein synthesis, and the late response of locally produced neurohormones and genes such as \( \beta\)-myosin heavy chain and skeletal \( \alpha\)-actin, altering the tissue structure.

Gender
LV mass does not differ between boys and girls during infancy and childhood, suggesting that the initial number of cardiac myocytes is likely to be similar in males and females. A clear-cut gender difference in LV mass becomes evident at puberty, when gender-specific hormonal influences are imposed on the original anatomic pattern established by the genetically determined number of cardiomyocytes. Gender difference in LV mass increases during adolescence and remains constant during adulthood. These gender differences are sustained by the symmetric increase in both chamber dimension and wall thickness, yielding no gender difference in relative wall thickness.

Body Size
The gender difference in LV growth evidenced during the pubertal period and then adolescence, and sustained during adulthood, however, is almost entirely due to covariance with body size. Despite a different rate of growth, because of the physiological decline in metabolic rate from birth to adulthood, a study performed in 341 twins demonstrated that genes common to LV mass and body weight significantly influence the covariability of these variables and that >90% of the correlation of LV mass and weight is indeed owing to common genes. In that study, univariate genetic analyses documented that genotype accounted for a significant proportion of the variance of LV mass in both boys and girls, even after removal of the effect of weight and sexual maturity through regression methods. These studies suggested that in the presence of “normal” cardiac loading conditions, body size is the most important bioassay of heart size, but it does not completely offset the effect of male hormones.

The impact of body size on LV mass is also a function of body composition. In the study from the Medical College of Virginia, Goble et al analyzed 243 children, aged 7 to 11, using stepwise regression models. They found that body weight, but not ponderosity, was a strong predictor of LV mass, whereas body fat was negatively associated with LV mass. The authors suggested that lean body mass can account for much of variability in cardiac growth seen in children, whereas the influence of hemodynamic variables was limited, in that study, to normotensive children. Daniels et al confirmed the speculation of Goble et al in a study in which 201 normotensive children (6 to 17 years old, 105 boys and 96 girls, 103 whites and 98 blacks) were studied using dual-energy x-ray absorptiometry to measure lean body mass and fat mass. In multiple regression analysis, lean body mass accounted for 75% of the variance of LV mass, with negligible additional contributions from fat mass and systolic blood pressure (1.5% and 0.5% of the variance, respectively).

In that study, lean body mass was the strongest determinant of LV mass in both males and females in both whites and blacks. With normalization for lean body mass, the gender difference in LV mass almost completely disappears.

For these reasons, when body weight increases because of increasing fat mass, the physiological relation between body size and LV mass, mostly due to covariance with lean body mass, is lost, because the variations in body weight are mostly due to an increase in fat mass. Because most of the resting energy expenditure depends on fat-free mass, with the contribution of fat mass being negligible, normalization of LV mass for body weight or other measures of body size that are body weight dependent (ie, body surface area) do not represent the real impact of body size when body composition is severely altered, as happens in obesity.

A surrogate of fat-free mass is body height. In mammals, height (or length) is determined by skeletal size, which is in turn related to muscle mass. Skeletal structure is therefore built for a given amount of muscle. As a consequence, body length or height is a strong biological correlate of the “ideal” lean body mass, and in fact, a close relation between skeletal and lean body mass has been demonstrated in humans with the use of dual-energy x-ray absorptiometry. Because of the geometric disproportion between height (a linear measure) and LV mass (a 3-dimensional variable generated by a cubic function), the relation is linear only when height is raised to an exponent close to 3, which is called “allometric signal.” This exponent has been identified to be between 2.7 and 3 in different epidemiological studies. Indexation of LV mass for height \( (\text{m}^{2.7}) \) can be useful when attempting to measure the impact of abnormalities of body composition on LV anatomy, such as in obesity or anorexia nervosa, although it is not necessarily better for prognostic purposes.

The mechanisms through which the metabolically active lean body mass influences the magnitude of LV mass is related to the metabolic requirements to maintain the resting energy balance, but it is also genetically determined, although this genetic link might be more complex than suggested in available studies.
Nonhemodynamic Factors Are Also Hemodynamic Stimuli

In addition to affecting body build and LV weight, genotype influences cardiac loading conditions. Genetic factors that determine within-family similarities of blood pressure may be observed with a design able to discriminate the importance of shared rearing environments and genetic effects. Genetic factors were observed to play an important role in individual differences in blood pressure, but substantial influences of shared family effects were also demonstrated. In another study, systolic and diastolic blood pressures were measured in 254 monozygotic and 260 dizygotic middle-aged male twin pairs and then remeasured twice during a follow-up. Heritability was 0.5 at each time point. Genetic variation present at middle age contributed ~60% to the variability detected 9 years later, with the remaining 40% being new. Significant genetic covariances were also reported for systolic and diastolic blood pressure during cold-pressor test in 91 monozygotic and 41 dizygotic normal twin pairs aged 34±14 years. Most recently, Snieder et al reported a higher heritability for augmentation index (radial waveform, measured by applanation tonometry) than for blood pressure traits in 225 monozygotic and 594 dizygotic female white twin pairs aged 18 to 73 years. This study was implemented on the assumption that <50% of the variance in LV mass is accounted for by conventional factors such as age, blood pressure, and body size, but hemodynamic volume load was not considered. This is in fact the case when only the pressure component of cardiac load is considered, which is not necessarily the most important hemodynamic predictor of LV mass.

Cardiac work is indeed caused by displacement of a given volume of blood through development of a pressure able to overcome aortic impedance. This work, sustained by a given amount of LV mass, can be represented by the product of stroke volume and mean systolic pressure and can be approximated by multiplying stroke volume by cuff brachial systolic (or mean) blood pressure. Stroke work is closely related to LV mass, as well as to body size, as was recently demonstrated in a large normotensive, normal-weight population study that encompassed the entire lifespan (Figure). In an age-weighted regression model generated in the entire study population (n=766), gender, body size (height in m²), and stroke work accounted for up to 86% of variability of LV mass, with only 14% of variance unexplained. In this study, the ability of body size to accurately predict LV weight was very high at birth and decreased progressively toward adolescence to reach a stable scatter during adulthood. Age was identified as the source of such increasing error of body size prediction (heteroscedastic distribution of residuals), and its effect was attributed, in the hypothesis of the study, to the increasing variability of loading conditions, because of the superimposition of unmeasured factors. Interestingly, although stroke work increased markedly during childhood and adolescence, body growth remained the main determinant of LV mass in this age stratum, and until puberty, male gender also had a lower impact than body size. In contrast, after puberty, during adulthood, when body size was more stabilized by the completion of physiological growth, the influence of changes in body size was minimal, whereas the variability of stroke work became the overwhelming correlate of LV mass and the effect of male gender became more important.

Using the unweighted regression equation from the entire study population, we could determine that after consideration of the hemodynamic load, body height (as a measure of fat-free mass) accounts for 37% of the explained variance of LV mass, whereas male gender accounts for only 5% of variability. The 18% of variance of LV mass that remained statistically unexplained in the unweighted regression model could be because of either intrinsic error of measurements or, perhaps mainly, undetected (in this study) genetic influences other than those affecting cardiac workload and body size, which were estimated to be ~9%.

The real limitation of these studies in relating LV mass to stroke work might be the fact that both LV mass and stroke volume are computed with the same primary echocardiographic measurements. The consequent obvious colinearity might reduce the impact of those findings, making at least part of the relation spurious, because of mathematical tautology. The obvious method to partially overcome this tautology is to measure LV mass or stroke volume with different primary measures, a procedure that has been used. However, in symmetrically contracting hearts, this risk of tautology is possibly minimized.

With these limitations taken into account, an evaluation of gender-specific LV mass in relation to cardiac workload at a given body size theoretically allows the need to use normal distribution–based partition values for the identification of LV hypertrophy to be overcome and allows a “qualitative” estimation of the increase in LV mass. Theoretically, every value of observed LV mass that exceeds 100% of the
predicted value should be considered as abnormally elevated, but the probability that this excess might have biological relevance can be graduated according to a reference normal distribution (Table).

**Biological Mediators for LV Hypertrophy**

The pathways through which different stimuli yield increase in LV mass are most likely common and involve immediate stretch-induced expression of early proto-oncogenes and intramyocardial transcription of neurohormones (angiotensin II, aldosterone, endothelin, bradykinin, and so on). Neurohormones have hemodynamic activity, but being produced locally, they are also direct growth factors. The regulation of other mediators of cell growth, including cytokines, growth hormone (GH), and insulin-like growth factor I (IGF-1), also plays an important role in LV remodeling by modulating cardiac structural changes. Two factors might have particular biological relevance to many shared neurohormonal mediators. Two factors might have particular biological relevance to many shared neurohormonal mediators.

Insulin influences many biological pathways in addition to the glucose metabolism. Hemodynamic effects (vasodilation) and is a potent growth factor. Resistance to the utilization of glucose, occurring to some extent in hypertension and obesity, does not imply that the other hormone effects are also blunted, but it causes a substantial increase in insulin production in the attempt to maintain a normal rate of utilization of glucose. Both insulin resistance and the resulting hyperinsulinemic status have consequences on the cardiovascular system, although this effect might not be independent of other demographic and hemodynamic correlates.

An indirect mechanism through which insulin might also influence LV growth is related to its ability to increase sodium retention, therefore coupling another important (although not unanimously considered) stimulus for LV growth. Sodium intake has been shown to be a potent determinant of LV growth in hypertensive as well as in normotensive experimental animal models, through complex mechanisms that involve circulating volume expansion and possible activation of the tissue renin-angiotensin system. In humans, the effect of high sodium intake is more difficult to isolate from other biological determinants of LV mass, the most important of which is obesity. The overall high caloric intake of overweight individuals tracks a high sodium intake. Studies that compare the effect of a reduction in sodium and/or caloric intake have shown that the decrease in blood pressure can be optimized by combining low sodium with low caloric intake, suggesting that the same might happen for LV mass.

**Conclusions**

LV growth depends on hemodynamic load influenced by genetic and environmental factors. The extent to which an individual LV reacts to hemodynamic stimuli is related to the ability to produce a cascade of events that start at the level of the cell membrane, yielding eventually increased production of growth factors. This ability is most probably under direct genetic control but also is independently related to the magnitude of body size and to the influence of gender-specific hormones, raising their activity at the time of adolescence. Because of the individual specificity of LV weight, the recognition of individual gender-specific ideal LV mass appropriate for cardiac work, at a given body size, might
help discrimination of pathological from compensatory LV hypertrophy.

References


12. de Simone et al. Nonhemodynamic Factors and Cardiac Hypertrophy


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*Hypertension*. 2001;38:13-18
doi: 10.1161/01.HYP.38.1.13

*Hypertension* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2001 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

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