Myocardial Fatty Acid Metabolism
Independent Predictor of Left Ventricular Mass in Hypertensive Heart Disease

Lisa de las Fuentes, Pilar Herrero, Linda R. Peterson, Daniel P. Kelly, Robert J. Gropler, Víctor G. Dávila-Román

Abstract—The expression of myocardial fatty acid β-oxidation enzymes is downregulated at the gene transcriptional level in animal models of left ventricular hypertrophy and of heart failure. Humans with idiopathic dilated cardiomyopathy have decreased myocardial fatty acid oxidation. The extent to which molecular mechanisms, such as a reduction in myocardial fatty acid oxidation, regulate the cardiac hypertrophic response in humans in vivo is unknown. Positron emission tomography was used to measure myocardial blood flow, oxygen consumption, fatty acid utilization, and oxidation in two groups of patients: (1) hypertensive left ventricular hypertrophy (n=19; left ventricular mass, 211±39 g; left ventricular ejection fraction, 67±4%) and (2) left ventricular dysfunction (n=9; left ventricular mass, 210±36 g; left ventricular ejection fraction, 31±10%); these were compared with a normal control group (n=36; left ventricular mass, 139±25 g; left ventricular ejection fraction, 66±6%). Left ventricular mass showed significant correlation with gender, diastolic and systolic blood pressure, myocardial fatty acid uptake, utilization and oxidation, myocardial blood flow, body mass index, and left ventricular ejection fraction (all P<0.02). Independent predictors of increased left ventricular mass were male gender (r=0.38, P<0.001), myocardial fatty acid oxidation (r=-0.24, P<0.018), systolic blood pressure (r=0.41, P<0.001), and left ventricular ejection fraction (r=-0.29, P=0.005). Thus, myocardial fatty acid metabolism is an independent predictor of left ventricular mass in hypertension and in left ventricular dysfunction. The extent to which reduced myocardial fatty acid metabolism affects cardiovascular morbidity and mortality and whether pharmacologic modulation results in improved outcomes remains to be determined. (Hypertension. 2003;41:83-87.)

Key Words: cardiac function ■ fatty acids ■ heart failure ■ hypertension, essential ■ hypertrophy ■ metabolism

Hypertension is the most common cause of pathologic left ventricular hypertrophy (LVH). It has been postulated that the development of hypertensive LVH may be an adaptive response to normalize ventricular wall stress and to maintain cardiac function; over time, however, LVH becomes maladaptive, leading to left ventricular enlargement and/or left ventricular dysfunction (LVD). Hypertensive LVH and LVD are characterized by an increase in left ventricular mass: Whereas patients with hypertension characterized by concentric hypertrophy, those with heart failure typically have eccentric remodeling. The molecular mechanisms mediating pathological remodeling in the hypertrophied and/or dysfunctional heart remain largely unknown.

Animal models of pressure-overload hypertrophy and of heart failure and humans with idiopathic dilated cardiomyopathy have decreased myocardial fatty acid utilization (MFAU) and oxidation (MFAO), suggesting a link between altered myocardial fatty acid metabolism and LVH. Children with mitochondrial defects in fatty acid β-oxidation (FAO) enzymes have cardiac hypertrophy and/or heart failure and are at risk for sudden cardiac death. A recent study in humans showed that variations in the peroxisome proliferator–activated receptor-α (PPAR-α) gene, a key transcriptional regulator of the expression of FAO pathways genes, influence the hypertrophic growth in response to both exercise and hypertension. This observation, along with those from animal studies, provides further evidence that maladaptive myocardial energy substrate utilization plays a causal role in the pathogenesis and/or modulation of the hypertrophic phenotype.

Thus, the metabolic phenotype of LVH and of LVD is characterized, at least in part, by decreased expression of the PPAR-α gene, a reduction in myocardial FAO enzyme levels, and a decrease in myocardial fatty acid (MFA) metabolism. The extent to which molecular mechanisms, such as decreased MFAO, influence the cardiac hypertrophic response in humans with acquired forms of heart disease is unknown.

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The purpose of this study was to determine clinical and/or phenotypic predictors of the hypertrophic response, and in particular to determine the extent to which MFA metabolism (ie, MFA uptake, utilization, and oxidation) correlates with left ventricular mass in humans with hypertensive LVH and/or LVD. Our hypothesis is that reduced MFA metabolism is an important molecular mechanism mediating the pathological hypertrophic phenotype in this particular population.

Methods

Study Population

The study population consisted of 2 groups of patients: (1) patients with hypertension, LVH, and with normal left ventricular function (HTN-LVH group, left ventricular ejection fraction [LVEF] ≥55%); and (2) patients with LVD (LVEF <50%); these were compared with a normal control group. Exclusion criteria for all groups were (1) a history of diabetes mellitus, (2) prior vascular surgery and/or a history of coronary artery disease, (3) noncardiac systemic disease (ie, malignancy, collagen vascular disease, and so on), (4) renal insufficiency (serum creatinine >190.7 μmol/L [2.5 mg/dL]), (5) hypercholesterolemia (fasting serum cholesterol >5.69 mmol/L [220 mg/dL]), and (6) active tobacco use. Normal subjects were excluded if they had a history of HTN or LVEF <55%. Exclusion criteria for the LVD group were other forms of cardiomyopathy, such as ischemic, restrictive, or hypertrophic forms or sarcoidosis, amyloidosis, hemochromatosis, pericardial, valvular and/or congenital heart disease.

All study subjects underwent a complete cardiovascular evaluation, including a history, physical examination, and an echocardiogram. Patients with LVH had normal coronary arteries based on coronary angiography; some of these patients and subjects were included in a previous report.11

The study was approved by the Human Studies Committee and the Radiotive Drug Research Committee, Washington University School of Medicine. Written informed consent was obtained from all patients and subjects before study enrollment.

Imaging Protocol

The imaging protocol has been previously described.11 A brief summary follows.

Echocardiography

All subjects underwent complete M-mode, 2-dimensional, and Doppler echocardiography to determine the LVEF, LV mass (LVM), and valve function. The HTN-LVH group and normal control group also underwent an exercise stress echocardiogram to exclude clinically significant coronary artery disease; those with an ischemic response were excluded.17 The LVEF was calculated according to the modified Simpson’s rule; normal left ventricular function was defined as an LVEF ≥55%.18,19 The LVM was determined by the modified Penn method (normal values: 148±26 g for men, 108±21 g for women); the presence of LVH was defined as an LVM >105 g/m² for women; the presence of LVH was defined as an LVM >105 g/m² for women). The LVM was indexed to the body surface area to derive the LVM index (g/m²).18,19

Cardiac Positron Emission Tomography

All studies were performed on conventional, commercially available tomographs (Siemens ECAT EXACT, Siemens Medical Systems). After a 12-hour overnight fast, all subjects underwent a positron emission tomography (PET) imaging protocol to measure myocardial blood flow (MBF, mL/L per minute), myocardial oxygen consumption (MVO₂, mmol/L per minute), MFAU (mmol/L per minute), and oxidation (MFAO, mmol/L per minute). After a positioning scan, a 15-minute transmission scan was performed for generation of attenuation correction factors used in emission-image reconstruction. The protocol to measure MBF involved an intravenous bolus of 0.4 mCi/kg (up to 25 mCi) of 15O-water with the immediate collection of a 5-minute dynamic scan. To measure MVO₂, an intravenous bolus of 0.40 mCi/kg of 11C-acetate was given followed by a 30-minute dynamic data collection for measurement of 11C-acetate myocardial kinetics. To measure MFAU and MFAO, an intravenous bolus of 0.4 mCi/kg of 11C-palmitate was given followed by a 30-minute dynamic data collection for measurement of 11C-palmitate myocardial kinetics. During the 11C-acetate and 11C-palmitate data collections, venous blood samples were obtained at predetermined intervals to measure plasma substrates. Plasma 11C-carbon dioxide (11CO₂) values were used to correct the arterial input function for compartmental modeling of 11C-acetate and 11C-palmitate myocardial kinetics. Heart rate was continuously monitored by 3-lead telemetry, and the brachial artery blood pressure was measured noninvasively every 5 minutes throughout the study.

PET Image Analysis

All PET-derived images were reoriented to generate standard short- and long-axis views. Myocardial time-activity curves were generated by placing a region of interest on 3 to 4 midventricular short-axis slices on the anterolateral wall (3 to 5 cm²) of composite 15O-water, 11C-acetate, and 11C-palmitate images, as previously described.20-24 To generate blood time-activity curves for each tracer, a small region of interest (1 cm²) was placed within the left atrial cavity on a midventricular slice in the vertical long-axis orientation of each composite image. Within these regions of interest, myocardial and blood time-activity curves were generated for 15O-water, 11C-acetate, and 11C-palmitate. To avoid contamination from right ventricular blood and liver radioactivity, septal and inferior regions were omitted.

Subsequently, blood and myocardial time-activity curves were used in conjunction with well-established kinetic models to measure MBF, MVO₂, MFAU, and MFAO in each myocardial region analyzed and averaged to obtain one value of each per subject. Correction for partial volume effects was implemented in the 15O-water kinetic model. The partial volume correction factor obtained from the 15O-water kinetic model was subsequently used in the kinetic modeling for all the other PET-derived measurements (ie, MVO₂, MFAU, and MFAO). Blood-to-myocardium count spillover was accounted for in each one of the models by estimating the spillover fraction along with the model transfer-rate constants.

Measurement of MBF

Myocardial 15O-water time-activity curves for each segment were generated by applying the image-analysis routine to the time-segmented data. From these data, MBF was quantified through the use of a previously validated compartmental modeling approach.20

Measurement of MVO₂

After correcting PET-derived blood activity for 11CO₂ contribution, blood and myocardial time-activity curves were used in conjunction with a 1-compartment kinetic model to estimate the rate at which 11C-acetate is converted to 11CO₂ (kₗ, min⁻¹). Values for MVO₂ were determined by means of a previously published relation between kₗ and MVO₂.21-25

Measurement of MFAU and MFAO

After correcting the PET-derived blood 11CO₂ activity, blood and myocardial 11C-palmitate time-activity curves were used in conjunction with a 4-compartment kinetic model to measure fractional myocardial palmitate extraction and oxidation.24 Substrate uptake (in mL/L per minute) is the product of the substrate extraction fraction and myocardial blood flow (Equation 1). Substrate uptake thus represents the rate at which the substrate is taken up by the myocardium and is independent of the level of substrate in blood. Substrate utilization (in mmol/L per minute) is the product of substrate uptake and the concentration of substrate in blood (Equation 2) and thus reflects the amount of substrate taken up by the myocardium. Changes in substrate utilization may be due to changes in extraction fraction, MBF, and/or plasma substrate levels.

The tracer extraction fractions are used in conjunction with MBF and plasma levels of free fatty acid to calculate the total tracer uptake and utilization (ie, MFAO), as follows:

Myocardial tracer uptake (mL/L per minute) = MBF×Tracer extraction fraction (Equation 1)
TABLE 1. Clinical Characteristics, Echocardiographic Parameters, Hemodynamics, and Plasma Substrate and Insulin Levels

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normal Control (n=36)</th>
<th>HTN-LVH (n=19)</th>
<th>LVD (n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>49±21</td>
<td>60±13</td>
<td>39±6‡</td>
</tr>
<tr>
<td>Female, % (n)</td>
<td>58.3 (21)</td>
<td>36.8 (7)</td>
<td>44.4 (4)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>25±5</td>
<td>28±4†</td>
<td>31±6‡</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>66±6</td>
<td>67±4</td>
<td>31±10‡</td>
</tr>
<tr>
<td>LVM, g</td>
<td>139±25</td>
<td>211±39*</td>
<td>210±36*</td>
</tr>
<tr>
<td>LVMI, g/m²</td>
<td>77±9</td>
<td>106±18*</td>
<td>109±20*</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>65±9</td>
<td>62±9</td>
<td>74±16‡</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>123±18</td>
<td>156±25*</td>
<td>115±24‡</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>69±8</td>
<td>81±14‡</td>
<td>69±17</td>
</tr>
<tr>
<td>Free FA, nmol/mL</td>
<td>631±180</td>
<td>634±233</td>
<td>563±138</td>
</tr>
<tr>
<td>Glucose, µmol/mL</td>
<td>4.8±0.5</td>
<td>4.6±1.3</td>
<td>4.9±0.4</td>
</tr>
<tr>
<td>Lactate, mmol/mL</td>
<td>789±428</td>
<td>792±351</td>
<td>560±127</td>
</tr>
<tr>
<td>Insulin, µU/mL</td>
<td>4.3±1.9</td>
<td>6.0±3.9</td>
<td>12.6±11.1§</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; HTN-LVH, hypertensive left ventricular hypertrophy group; LVD, left ventricular dysfunction group; LVEF, left ventricular ejection fraction; LVM, left ventricular mass; LVMI, left ventricular mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; and FA, fatty acids.

*Mindt is significant vs normal control; †P<0.001 vs HTN-LVH; ‡P<0.001 vs normal control; §P<0.05 vs normal control; ‡‡P<0.05 vs HTN-LVH.

Myocardial substrate utilization (nmol/g per minute) = myocardial tracer uptake × Plasma substrate level (Equation 2).

MFAO was measured from the kinetics of 11C-palmitate by calculating from the model transfer-rate constants the portion of total tracer extraction that is converted to 11CO₂ (fast turnover pool) and is assumed to be oxidized. This fractional oxidation was then used in Equations 1 and 2 to measure MFAO.

Statistical Analysis
All statistical analysis was performed with the use of SPSS (SPSS Inc., release 11.0). Continuous variables were reported as mean±SD. Comparison between the three groups (ie, HTN-LVH, LVD, and normal control) were performed with the use of ANOVA with the Tukey post hoc tests. The Fisher exact test was used to compare gender differences between the groups. Pearson correlation coefficients were obtained to determine variables that showed significant correlation with LVM. Multivariate linear regression analysis was performed by means of a forward stepwise method. Variable entry into the model required a probability value <0.05. Variables included in the analysis were gender, age, body mass index, LVEF, blood pressure and heart rate, plasma substrate (ie, free fatty acids, glucose, and lactate), and insulin levels, MVO₂, and MFAO. For both regression analyses, the listed unstandardized regression coefficients represent the change in LVM per unit change in the variable being evaluated (assuming that all other variables remain constant). The Pearson correlation coefficients reflect the strength and direction of the relation. For the multivariate analysis, the regression coefficients are weighted to have a mean of 0 and a standard deviation of 1, listed as the standardized regression coefficients. Probability values <0.05 were considered statistically significant.

Results
Study Population
The patient characteristics, echocardiographic parameters, hemodynamics, plasma substrate, and insulin levels of the study population are shown in Table 1. By design, the left ventricular function in both the HTN-LVH and the normal control group were normal; it was significantly lower in the LVD group. Although hypertension was probably the etiology of LVD among 4 patients in the LVD group, it was less certain in the remaining patients. The HTN-LVH and LVD groups had significantly greater LVM and LVMI index compared with the normal control group (P<0.001 for both). The LVD group had a significantly higher mean heart rate compared with the HTN/LVH group. The systolic and diastolic blood pressures were significantly higher in the HTN-LVH group compared with the normal control group and the LVD group. There were no significant differences in the plasma free fatty acid, glucose, or lactate levels among the 3 groups. The plasma insulin levels were higher in the LVD group, probably reflecting the association of insulin resistance with LVD.

MBF, MVO₂, and MFA Metabolism
The PET-derived measurements of MBF, MVO₂, and MFA uptake, utilization, and oxidation are shown in Table 2. There were no significant differences in MBF or MVO₂ among the 3 groups. The 3 measured parameters of MFA metabolism (ie, uptake, utilization, and oxidation) were significantly lower in both the HTN-LVH and the LVD groups compared with the normal control group. Furthermore, these 3 parameters were lower in the LVD group compared with the HTN-LVH group; however, these did not achieve statistical differences.

Variables that showed a significant correlation with LVM are listed in Table 3. The Pearson correlation coefficient shows that...
in addition to known predictors of the cardiac hypertrophic response, such as gender, systolic and diastolic blood pressure, body mass index, and LVEF, all measurements of MFA metabolism (ie, MFAO, MFAU, and MFA uptake) and MBF showed statistically significant correlations with LVM. The regressions for the 3 MFA metabolism variables (ie, MFAO, MFAU, and MFA uptake) are as follows: LVM = (−0.30 × MFAO) + 225, r² = 0.43, P < 0.001; LVM = (−0.30 × MFAU) + 222, r² = 0.43, P < 0.001; LVM = (−0.21 × MFA uptake) + 222, r = −0.37, r² = 0.14, P = 0.003.

This analysis indicates that between 14% and 18% of the LVM variability is determined by MFA metabolism (ie, MFAO, MFAU, or MFA uptake).

Multivariate regression analysis showed that male gender, systolic blood pressure, LVEF, and MFAO are the most important clinical predictors of LVM, and together these variables account for 62% of the LVM variability (r² = 0.62, F = 46.29, P < 0.001, Table 4). This regression model implies that a man with decreased MFAO, LVD, and increased systolic blood pressure would have the most severe degree of cardiac hypertrophy. The regression coefficient of 36 implies that male gender is associated with a 36-g higher LVM compared with female gender. Likewise, for every unit (ie, mmol/g per minute) decrease in MFAO, there is an associated 0.17-g increase in LVM; stated more clinically relevant terms, a decrease of 50 mmol/g per minute in MFAO is associated with an 8.5-g increase in LVM.

**Discussion**

Hypertensive heart disease is characterized early on by pathologic LVH, followed by ventricular enlargement and/or dysfunction. Epidemiologic studies have shown that hypertensive LVH is a significant predictor of increased cardiovascular morbidity and mortality rates.2–3 Despite the known association between increased LVM and adverse clinical outcomes, the molecular mechanisms mediating the hypertrophic response are not well understood. In this study, we showed that along with increased systolic blood pressure, decreased left ventricular function and male gender, a molecular determinant of MFA metabolism (ie, MFAO) is also an independent predictor of the cardiac hypertrophic response. These findings are important because they complement a wide body of studies in animal models of pressure-overload hypertrophy and/or dysfunction as well as studies in humans with idiopathic dilated cardiomyopathy that have shown that alterations in MFA metabolism play a role in the development of cardiac hypertrophy and/or dysfunction.5–14 The gender dependency of the hypertrophic response in humans has been previously shown.26 Altered MFA metabolism may be responsible for the gender-specific survival differences seen in animal models of LVH.27–28

**MFA Metabolism and LVH**

The association between altered myocardial metabolism, particularly fatty acid metabolism, and LVH and/or LVD has been previously discussed and is briefly summarized in this report.27 First, the results of studies in animal models have shown that the progression from cardiac hypertrophy to ventricular dysfunction is associated with decreased expression of genes encoding mitochondrial FAO enzymes and that these changes are associated with reduced rates of MFAO.8–9 Second, human studies have also linked alterations in MFAO with cardiac hypertrophy and/or dysfunction. Patients with idiopathic dilated cardiomyopathy have downregulation of FAO enzymes and/or decreased MFAO (as assessed by PET).8,11 Third, children with inborn errors of FAO enzymes develop LVH and/or heart failure and are at risk for sudden cardiac death.12–14 Fourth, inhibition of mitochondrial FAO in animals results in cardiac hypertrophy.29 Thus, alterations in MFA metabolism, and in particular MFAO, have been linked to both ventricular hypertrophy and/or dysfunction. The precise molecular mechanisms by which alterations in MFAO play a role in the development of hypertrophy and how these alterations contribute to the progression to ventricular dysfunction remain uncertain. However, the strong association between metabolic alterations in FAO and the development of cardiac hypertrophy suggest that genes involved in the regulation of MFA metabolism play a role in the development of cardiac hypertrophy. The evidence is at present circumstantial, but it is strongly supported on several fronts. PPAR-α is a transcription regulator governing the expression of enzymes involved in the transport and metabolism of long-chain fatty acids in the heart.15,16,28–32 Under normal conditions, increased intracellular MFA levels activate the PPAR-α gene. In PPAR-α null (−/−) mice, basal and induced expression of peroxisomal and mitochondrial β-oxidation enzymes is reduced, leading to massive intracellular lipid accumulation in the heart (ie, lipotoxicity).29,31,32 Finally, a recent study in humans linked an Intron 7 G/C PPAR-α gene polymorphism to alterations in the hypertrophic phenotype: Hypertensive male patients with the PPAR-α CC polymorphism had a hypertrophic response significantly greater than those with the more common GG or GC genotypes, a finding that was independent of blood pressure control.15

**Gender Influences the Expression of the Hypertrophic Phenotype**
The survival of PPAR-α–deficient mice after pharmacological stress has been found to be influenced by gender; however, the precise mechanisms mediating this interaction remain unknown.28 Although hypertension and heart failure are common diseases among both men and women, men have a greater degree of cardiac hypertrophy, even after correcting for their larger body habitus.1,19,26 The results of the current study are in support of these observations showing gender-related differences in the phenotypic expression of myocardial hypertrophy, although the mechanisms responsible for this difference remain unclear. Among individuals with PPAR-α gene variants, gender-related differences in the hypertrophic phenotype have been described.15 Further stud-
ies are warranted to evaluate whether differences in PPAR-α expression lead to altered MFA metabolism, thereby influencing the hypertrophic response.

Limitations of the Study
Factors known to influence the development of LVH, such as duration and/or treatment of hypertension, were not evaluated in this study. Furthermore, genetic variants of key MFA metabolism enzymes, such as PPAR-α and other potential candidate genes that regulate the hypertrophic phenotype, were not evaluated.

Perspectives
Hypertension and the resulting ventricular hypertrophy constitute important public health problems associated with high cardiovascular morbidity and mortality rates. Although the clinical variables responsible for the hypertrophic phenotype have been known for some time, molecular mechanisms mediating cardiac hypertrophy have not been shown in humans. Therefore, this is the first study to show, in vivo, in humans, that MFA metabolism (i.e., MFAO) is a significant independent predictor of the cardiac hypertrophic response. Animal studies, and more recently human studies, have shown that MFAO declines in the setting of hypertensive LVH and/or LVD. The extent to which reduced MFA metabolism affects cardiac morbidity and mortality rates and whether pharmacologic modulation results in improved clinical outcomes remains to be determined.

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