# Hypertensive left ventricular hypertrophy is associated with abnormal myocardial fatty acid metabolism and myocardial efficiency

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*Background.* **Hypertension-induced left ventricular hypertrophy (LVH) is associated with an increased risk of cardiovascular morbidity and death by mechanisms not well characterized.**

*Methods and Results.* **Myocardial fatty acid (FA) metabolism and left ventricular (LV) mass were evaluated in 13 patients with hypertensive LVH with normal LV ejection fraction and 42 normal control subjects (primary cohort). Contractile performance was also evaluated in 5 hypertensive LVH patients and 5 matched normal control subjects (magnetic resonance [MR] substudy). Myocardial FA utilization (MFAU) and myocardial FA oxidation (MFAO) were assessed by positron emission tomography by use of 1–carbon-11 palmitate. Myocardial contractile function (strain and stress) was determined by cardiac MR imaging with tissue tagging and calibrated arterial pressure traces; myocardial external minute work and efficiency were derived. In the primary cohort decreased MFAO was predictive of increased LV mass (model $r^2 = 0.61$, $P = .03$). In the MR substudy decreased MFAO (corrected for myocardial oxygen consumption [$MVO_2$]) in the hypertensive LVH group compared with the normal group ($MFAU/MVO_2$, 26 ± 5 vs 37 ± 8; $MFAO/MVO_2$, 24 ± 6 vs 35 ± 7; both $P = .03$) was paralleled by decreased myocardial external minute work (0.13 ± 0.03 $J \cdot g^{-1} \cdot min^{-1}$ vs 0.17 ± 0.04 $J \cdot g^{-1} \cdot min^{-1}$, $P = .07$) and decreased myocardial efficiency (5.2% ± 1.4% vs 7.1% ± 1.0%, $P = .03$).**

*Conclusions.* **Abnormalities in myocardial FA metabolism are apparent in hypertensive LVH, and these abnormalities may be responsible, at least in part, for a reduction in myocardial efficiency. (J Nucl Cardiol 2006;13:369-77.)**

**Key Words: Hypertension-induced left ventricular hypertrophy • myocardial fatty acid metabolism • myocardial efficiency**

Arterial hypertension is a disease that affects more than 65 million Americans[1]; it is the most common cause of left ventricular hypertrophy (LVH), occurring in approximately 30% of the adult American population and in 50% to 60% of elderly persons. Although LVH represents a short-term compensatory response to normalize wall stress and maintain cardiac function in hypertensive patients, it may become maladaptive over time, leading to contractile dysfunction, ventricular enlargement, and heart failure. The precise mechanisms mediating the progression of hypertension-induced LVH to heart failure have not been completely elucidated. Animal studies of left ventricular (LV) pressure-overload hypertrophy have implicated alterations in myocardial energy substrate metabolism.[2-6]

Studies in animals have shown that in the progression from cardiac hypertrophy to ventricular dysfunction, the expression of genes encoding mitochondrial fatty acid transport and utilization enzymes is coordinately decreased.[7,8] The downregulation of fatty acid β-oxidation

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enzymes is associated with increased myocardial utilization of the more oxygen-sparing glycolytic pathways for the production of adenosine triphosphate (ATP).[9] Although this allows for reduced oxygen demands in the hypertrophied heart, over time, the reliance of the myocardium on glucose, a substrate that yields less ATP per mole than fatty acids, may produce a relative energy-deficient state, which eventually leads to a less efficient myocardium, resulting in decreased contractile performance. This hypothesis is supported by the development of myocardial hypertrophy, heart failure, or sudden cardiac death (or some combination thereof) in individuals with inherited defects in fatty acid β-oxidation enzymes.[10]

Positron emission tomography (PET) is a noninvasive, quantitative imaging technique that has been validated to accurately measure myocardial blood flow (MBF) with oxygen-15 water, myocardial oxygen consumption ($MVO_2$) with 1–carbon-11 acetate, and myocardial fatty acid metabolism with 1–C-11 palmitate under a wide range of hemodynamic and substrate environment conditions.[11-16] The hypothesis of the study was that in patients with hypertension-induced LVH (and normal LV ejection fraction [LVEF]), fatty acid metabolism is decreased, and this in turn is associated with decreased contractile performance. Accordingly, this study evaluated individuals with hypertension-induced LVH with normal LVEF and normal control subjects with a dual purpose: (1) to determine the association between myocardial fatty acid metabolism and LV mass (LVM) and (2) to determine whether decreased myocardial fatty acid metabolism is associated with decreased contractile performance.

## MATERIALS AND METHODS

### Study Population

The primary cohort consisted of (1) patients with hypertension and no other cardiovascular risk factors and (2) healthy volunteers. All primary cohort LVH subjects were invited to participate in the contractile performance part of the study (ie, MR substudy). Of these, 5 patients with hypertension-induced LVH agreed to participate; these were matched (by age, sex, and body mass index) to a cohort of normal control subjects. For the entire study, inclusion criteria for patients were as follows: (1) newly diagnosed or untreated hypertension or a history of hypertension treated only with diuretics, (2) LVH (LVM index [LVMI] >2 SDs above normal) by 2-dimensional echocardiography, (3) normal LVEF (>55%), and (4) no other systemic illnesses (discussed further as part of exclusion criteria). LVM was determined by the area-length method and was indexed to body surface area (LVMI); LVH was defined as an LVMI greater than 102 $g/m^2$ for men and greater than 88 $g/m^2$ for women.[17] Exclusion criteria were as follows: (1) treatment with antihypertensive agents other than diuretics; (2) ventricular hypertrophy due to restrictive or hypertrophic cardiomyopathy, sarcoidosis, amyloidosis, hemochromatosis, and pericardial, valvular (other than mild regurgitant lesions), or congenital heart disease; (3) diabetes mellitus or other systemic disease (eg, malignancy, collagen vascular disease); (4) smoker (current or past); (5) previous vascular surgery or known cardiovascular disease (eg, coronary artery disease, including an abnormal exercise stress echocardiogram [as discussed later]); (6) elevated levels of serum creatinine (>0.22 mmol/L [>2.5 mg/dL]), fasting blood sugar (>6.7 mmol/L [120 mg/dL]), or fasting serum cholesterol (>5.7 mmol/L [220 mg/dL]); (7) pregnancy; and (8) stage III hypertension (ie, systolic blood pressure >180 mm Hg or diastolic blood pressure >110 mm Hg [or both]).[18] All patients were treated with a diuretic (hydrochlorothiazide) for blood pressure control through the course of the cardiac imaging studies.

The study was approved by the Human Studies Committee and the Radioactive Drug Research Committee at Washington University School of Medicine, St Louis, Mo. Written informed consent was obtained from all patients before enrollment into the study.

### Imaging and Carotid Pressure Acquisition

**Echocardiography.** In all patients and normal control subjects, a complete 2-dimensional resting echocardiogram was obtained for determination of LVMI and ventricular and valvular function, and an exercise stress echocardiogram (Standard Bruce protocol) was obtained for detection of clinically significant exercise-induced myocardial ischemia.

**Cardiac PET.** All studies were performed on conventional commercially available tomographs (Siemens ECAT EXACT; Siemens Medical Systems, Iselin, NJ). After an overnight fast, all subjects underwent a PET imaging protocol to measure MBF (in milliliters per gram per minute), $MVO_2$ (in micromoles per gram per minute), and myocardial fatty acid utilization (MFAU) (in nanomoles per gram per minute) and the portion of the utilized fatty acids that undergo oxidation (MFAO) (in nanomoles per gram per minute) with O-15 water, 1–C-11 acetate, and 1–C-11 palmitate, respectively, by use of validated techniques as reported previously.[11-16] Plasma C-11-carbon dioxide values were used to correct the arterial input function for compartmental modeling of 1–C-11 acetate and 1–C-11 palmitate myocardial kinetics. All subjects were placed on telemetry and had blood pressures obtained at 5-minute intervals throughout the study. Each study was completed in approximately 5 hours.

**Cardiac magnetic resonance imaging.** On a separate day, the magnetic resonance (MR) substudy cohort also underwent the cardiac MR imaging protocol, as described in detail elsewhere with exceptions noted.[19] MR images were acquired with a 1.5-T whole-body imaging system (Magnetom Vision; Siemens Medical Systems), gated by real-time electrocardiographic recordings at the time of scanning. Myocardial tissue tagging was performed by use of spatial modulation of magnetization, resulting in an orthogonal grid pattern of presaturations or "tag lines," followed by a 2-dimensional fast low flip-

angle shot cine component. Imaging parameters included the following: slice thickness, 8 mm; 15° excitation angle; 256 × 256 acquisition matrix; echo time, 20 to 40 milliseconds; repetition time, 58 milliseconds; and intertag spacing of 8 to 10 mm. The field of view was set to 350 × 350 $mm^2$ and 400 × 400 $mm^2$ for the short-axis and long-axis images, respectively. A series of images was acquired at mid-expiration, with each imaging plane at 29-millisecond intervals until the approximate completion of the cardiac cycle. Untagged MR images were also obtained at similar positions after acquisition of the tagged images. The arterial blood pressure was measured in the brachial artery with a Dinamap blood pressure recorder (GE Medical Systems, Waukesha, Wis) every 5 minutes throughout the study. Each study was completed in 1.5 hours.

**LV pressure data.** Individuals in the MR substudy cohort underwent measurements of LV end-systolic pressure while recumbent on the gantry of the MR scanner (immediately after the image acquisition) by means of the calibrated carotid artery pulse waveform via methods described in detail elsewhere.[20] In brief, a pencil-shaped high-fidelity Millar micromanometer (Micro-tip Pulse Transducer SSD-779; Millar Instruments, Inc, Houston, Tex) that works on the principle of applanation tonometry was positioned on the skin over the carotid artery. This technique has been validated previously as a noninvasive way to measure LV systolic pressure (interval from aortic valve opening to closure).[21-23] Characteristic carotid pulse tracing waveforms were acquired over a period of 3 minutes and digitized at a rate of 200 data points per second by use of customized data acquisition and manipulation software (LabView 4; National Instruments, Austin, Tex). The digitized waveforms were subsequently calibrated with the arterial blood pressure obtained by use of the Dinamap blood pressure recorder by assigning the systolic and diastolic blood pressure values to the peak and the nadir of the pulse tracing, respectively. Waveforms were analyzed, and the mean end-systolic pressure value was calculated for each subject.[20] This pressure measurement represents the LV load in calculation of myocardial end-systolic wall stress (LVESS).

## Image Analysis

**Myocardial PET imaging.** Myocardial O-15 water, 1–C-11 acetate, and 1–C-11 palmitate images were used to generate values for MBF, $MVO_2$, and MFAU and MFAO, respectively, by use of well-validated techniques.[11-16] Correction for partial-volume effects was performed as previously described.[11,17]

**Quantification of myocardial mechanical function.** Midventricular short-axis images were used for all myocardial stress and strain analyses.

For measurement of myocardial wall stress, endocardial boundaries determined from tagged and untagged cine MR images were considered with the calibrated carotid artery pressure tracings. LV circumferential end-systolic wall stress (LVESS) was calculated for the ejection phase of systole by use of a finite element analysis software package (StressCheck; Engineering Software Research Development, St Louis, Mo). This analysis involves a numeric approximation approach in which complex structures are divided into simple geometric subunits or elements.[17,24-26] Algebraic equations are derived that describe the relationship of forces and displacements within each element, and these equations are solved according to the boundary and loading conditions (ie, carotid artery pressure tracings) acting on each element. It is assumed that the mechanical properties of the myocardium are linear and isotropic. All values for LVESS are reported in kilodynes per square centimeter.

For measurement of myocardial wall strain, images were analyzed with custom software running on Silicon Graphic workstations (Silicon Graphics Inc, Mountain View, Calif), as described previously elsewhere.[27] Tracking software located tag line intersections on successive images with an automatic algorithm that was based on local pixel density. Once displacement vectors from the undeformed (ie, end-diastolic) to the maximally deformed (ie, end-systolic) images were generated, a finite element model of the ventricle was constructed. With a least squares fitting model, predicted displacement information was calculated for any point within the midventricular short-axis slice from known measured displacements by use of a finite element software package (StressCheck; Engineering Software Research Development).[24] Strain is a dimensionless measurement.

With regard to calculation of myocardial external work and myocardial efficiency, the circumferential component of the myocardial external minute work (MEMW) (in joules per gram per minute) was calculated as the product of LVESS, myocardial strain, and heart rate, corrected for the specific mass of the myocardium (1.055 $g/cm^3$). Myocardial efficiency was calculated as the ratio of MEMW to $MVO_2$. Because $MVO_2$ was converted to its energy equivalent ($4.523 \cdot 10^6$ dyne · cm per μmol $O_2$), myocardial efficiency is expressed as a percentage.

**Measurements of cold plasma substrates and insulin.** Serum was collected during the 1–C-11 palmitate image acquisition to provide free fatty acid levels necessary for calculation of the MFAU and MFAO, as well as glucose and insulin levels for comparison of the substrate environment. Plasma glucose and lactate levels were measured by use of a commercially available glucose-lactate analyzer (YSI, Yellow Springs, Ohio). Plasma fatty acid levels were determined by capillary gas chromatography and high performance liquid chromatography.[13] Plasma insulin levels were measured by radioimmunoassay.[28]

## Statistical Analysis

Results for each parameter were averaged and expressed as mean ± SD. Variables not normally distributed were logarithmically transformed for analyses (LVM, LVMI, body mass index, and insulin). Comparisons between patient groups were performed by 2-tailed unpaired Student *t* tests, the $\chi^2$ test, and the Fisher exact test as appropriate. Measurements were adjusted for the effects of age by performing multiple stepwise regressions for each dependent variable by use of age, age squared, age cubed, log(age), and exp(age), retaining only those terms significant at the $P < .05$ level. Additional potential

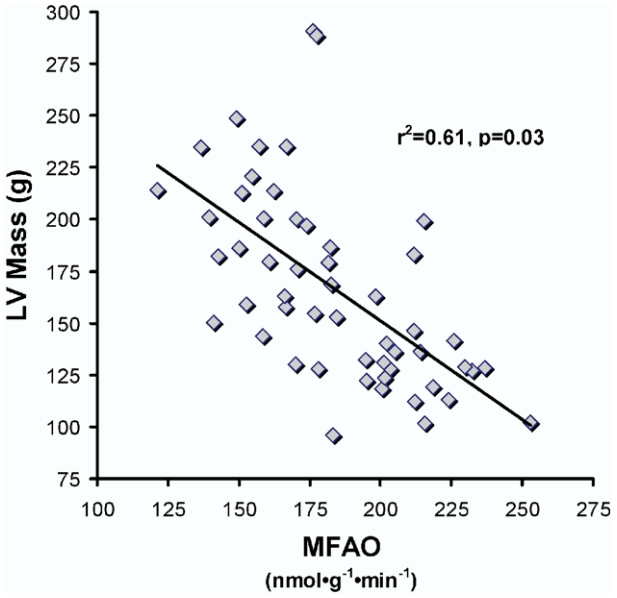


**Figure 1.** MFAO measurements (after adjustment for sex and body mass index) are shown plotted against LVM. MFAO exhibited a statistically significant inverse correlation with LVM. The *P* value reflects the significance of MFAO in the regression model.

covariates (sex, body mass index, $MVO_2$, LVEF, insulin level) were tested for significance in stepwise multivariate regression analyses; variable entry into the model required a *P* value $<$ .15. Once significant covariates were identified, they were regressed on MFAO to generate adjusted values for plotting against LVM in Figure 1; $P < .05$ was considered significant.

## RESULTS

### Patient Characteristics

Characteristics of the hypertension-induced LVH and normal control groups for the primary cohort and the MR substudy are shown in Table 1. In the primary cohort age, body mass index, and blood pressure were significantly higher in the hypertension-induced LVH group compared with the normal control group. Age and body mass index were similar between groups in the MR substudy; the systolic and diastolic blood pressures, though slightly higher in the hypertension-induced LVH group than in the MR substudy, were not significantly different compared with the control group. By design, the LVM and LVMI of the hypertension-induced LVH groups in both the primary cohort and the MR substudy were significantly greater than those in the normal control groups. There were no significant differences in the LVEF or LV cavity diameters between the groups (data not shown).

### PET Imaging Studies

**MBF, $MVO_2$, and substrate environment.** Measurements of MBF, $MVO_2$, and serum levels of free fatty acids and glucose were similar between groups in both the primary cohort and the MR substudy (Table 2). Serum insulin levels were significantly greater in the hypertension-induced LVH group in the primary cohort only.

**MFAU and MFAO.** In both the primary cohort and the MR substudy the uncorrected rates of myocardial fatty acid metabolism (MFAU and MFAO) were lower in the hypertension-induced LVH group, but these differences only reached statistical significance for MFAO in the primary cohort (Table 2). Because myocardial substrate utilization is highly dependent on $MVO_2$, both MFAU and MFAO were corrected for $MVO_2$. After correction for $MVO_2$, MFAU was significantly lower in the hypertension-induced LVH group compared with the normal control group in the primary cohort ($P < .05$), with MFAO demonstrating a similar trend. In the MR substudy both MFAU and MFAO showed significantly lower values in the hypertension-induced LVH group compared with the normal control group ($P = .03$ and .02, respectively). Thus hypertension-induced LVH (with normal resting LV function) is characterized by abnormalities in myocardial metabolism, including reduced rates of MFAU per unit of $O_2$ consumed.

**Myocardial fatty acid metabolism predicts LV mass.** To further explore the relationship between myocardial fatty acid metabolism and LV structure, regression analyses tested the hypothesis that MFAO is predictive of LVM in this cohort with normal LVEF. Among all covariates tested in the univariate models, age, sex, body mass index, and insulin level were significantly associated with LVM and therefore retained in the stepwise multivariate regression analyses. MFAO was found to be predictive of LVM (model $r^2 = 0.60$, partial $r^2 = 0.042$, $P = .03$ for MFAO in model); sex-adjusted and body mass index–adjusted values for MFAO are plotted against LVM in Figure 1. This figure shows that, in this cohort with normal LVEF and a wide range of LVM values (ie, normal control subjects and hypertension-induced LVH patients), a lower rate of MFAO is predictive of greater LVM.

### MR Imaging Substudy

**Myocardial wall stress and wall strain.** The purpose of the MR substudy was to characterize contractile performance by use of cardiac MR. The overall LV end-systolic stress (LVESS in dynes per square centimeter) was similar between the two groups. However, myocardial strain (a dimensionless value) was signifi-

**Table 1.** Characteristics of normal control subjects and hypertension-induced LVH patients

| | Primary cohort | | MR substudy | |
|---|---|---|---|---|
| | Normal control subjects (n = 42) | Hypertension-induced LVH patients (n = 13) | Normal control subjects (n = 5) | Hypertension-induced LVH patients (n = 5) |
| Age (y) | 51 ± 21 | 58 ± 9‡ | 64 ± 4 | 65 ± 7 |
| Male [n (%)] | 18 (43) | 10 (77) | 4 (80) | 4 (80) |
| BMI (kg/m$^2$) | 24 ± 4 | 28 ± 5‡ | 26 ± 6 | 26 ± 4 |
| SBP (mm Hg) | 124 ± 18 | 166 ± 24* | 132 ± 26 | 159 ± 27 |
| DBP (mm Hg) | 69 ± 9 | 87 ± 9* | 74 ± 9 | 79 ± 8 |
| HR (beats/min) | 64 ± 8 | 64 ± 11 | 62 ± 4 | 58 ± 11 |
| LVEF (%) | 67 ± 6 | 67 ± 4 | 67 ± 4 | 69 ± 4 |
| LVM (g) | 148 ± 32 | 223 ± 34* | 140 ± 11 | 249 ± 49† |
| LVMI (g/m$^2$) | 81 ± 11 | 113 ± 15* | 74 ± 6 | 124 ± 17* |

Data are given as mean ± SD.
*BMI,* Body mass index; *SBP,* systolic blood pressure; *DBP,* diastolic blood pressure; *HR,* heart rate; *LVMI,* left ventricular mass indexed to body surface area.
*$P \leq .0001$.
†$P < .001$.
‡$P < .05$.

**Table 2.** Myocardial blood flow, oxygen consumption, and substrate environment

| | Primary cohort | | MR substudy | |
|---|---|---|---|---|
| | Normal control subjects (n = 42) | Hypertension-induced LVH patients (n = 13) | Normal control subjects (n = 5) | Hypertension-induced LVH patients (n = 5) |
| MBF (mL · g$^{-1}$ · min$^{-1}$) | 1.0 ± 0.3 | 1.0 ± 0.2 | 1.1 ± 0.4 | 1.0 ± 0.2 |
| $MVO_2$ (μmol · g$^{-1}$ · min$^{-1}$) | 5.1 ± 1.4 | 5.5 ± 1.8 | 5.3 ± 0.7 | 6.0 ± 2.6 |
| MFAU (nmol · g$^{-1}$ · min$^{-1}$) | 211 ± 75 | 174 ± 68 | 194 ± 30 | 151 ± 53 |
| MFAO (nmol · g$^{-1}$ · min$^{-1}$) | 194 ± 65 | 149 ± 79† | 184 ± 23 | 137 ± 48 |
| MFAU/$MVO_2$ | 43 ± 17 | 33 ± 13† | 37 ± 7 | 26 ± 5* |
| MFAO/$MVO_2$ | 40 ± 16 | 31 ± 13‡ | 35 ± 7 | 23 ± 5* |
| Serum substrates | | | | |
| Free fatty acids (nmol · mL$^{-1}$) | 626 ± 178 | 670 ± 260 | 556 ± 56 | 509 ± 242 |
| Glucose (μmol · mL$^{-1}$) | 4.7 ± 0.9 | 4.9 ± 0.6 | 5.0 ± 0.7 | 4.7 ± 0.3 |
| Insulin (μU · mL$^{-1}$) | 4.2 ± 2.0 | 6.8 ± 4.0† | 4.2 ± 1.1 | 5.8 ± 2.5 |

Data are given as mean ± SD.
*$P \leq .03$.
†$P < .05$.
‡$P \leq .07$.

cantly lower in the hypertension-induced LVH group compared with the normal control group ($P = .03$) (Table 3).

**MEMW and myocardial efficiency.** Measurements of MEMW tended to be lower in the hypertension-induced LVH group compared with the normal control group (0.13 ± 0.03 J · g$^{-1}$ · min$^{-1}$ vs 0.17 ± 0.04 J · g$^{-1}$ · min$^{-1}$, $P = .07$) (Figure 2). Myocardial efficiency, calculated as the ratio of MEMW to $MVO_2$, showed significantly lower values in the hypertension-induced LVH group than in the normal control group (5.2% ± 1.4% vs 7.1% ± 1.0%, $P = .03$). Thus these

**Table 3.** Myocardial fatty acid utilization and oxidation and mechanical function

| | MR substudy | |
|---|---|---|
| | Normal control subjects (n = 5) | Hypertension-induced LVH patients (n = 5) |
| LVESS (kdynes · $cm^{-2}$) | 113 ± 15 | 123 ± 37 |
| Myocardial strain | 0.26 ± 0.02 | 0.21 ± 0.04* |

Data are given as mean ± SD.
*$P$ = .03.

differences suggest that in patients with hypertension, the hypertrophied myocardium has decreased contractile function at rest (despite normal LVEF) and, compared with the normotensive, nonhypertrophied heart, is less energy-efficient.

## DISCUSSION

The results of this study provide compelling evidence in support of the hypothesis that in human beings, hypertension-induced LVH (and with normal resting LVEF) is associated with abnormalities in myocardial metabolic function, manifested by reduced rates of MFAU and MFAO. Furthermore, these abnormalities in myocardial fatty acid metabolism are coupled with abnormalities in myocardial work and efficiency.

Decreased rates of MFAU and MFAO have been described in patients with idiopathic forms of cardiomyopathy.[29,30] Our group has previously shown that rates of myocardial fatty acid metabolism correlate with measures of LVM in a diverse cohort that included patients with idiopathic cardiomyopathy.[29,30] In that prior work, LVEF contributed significantly to the model predicting LVM. We now provide incremental data by extending these observations to patients with hypertension-induced LVH and normal LVEF. By evaluating a cohort with normal LV systolic function, we minimize the potentially confounding relationships between LVEF and LVM, as well as between LVEF and MFAO. Regression models in this normal LVEF cohort demonstrate that MFAO is still predictive of LVM. Furthermore, we also show significant differences between normal control subjects and those with hypertension-induced LVH for both MFAU and MFAO after correction for $MVO_2$, a more robust measure, given that myocardial substrate utilization is highly dependent on $MVO_2$.

Downregulation of genes involved in mitochondrial fatty acid β-oxidation has been shown in animals with pressure-overload cardiac hypertrophy, in animals with heart failure, and in human cardiac transplant recipients.[8] Animal models with underexpression or pharmacologic inhibition of genes involved in fatty acid transport have been shown to be associated with myocardial hypertrophy.[31-34] Furthermore, a number of inherited genetic enzymatic defects of myocardial fatty acid β-oxidation in human beings have been associated with cardiac hypertrophy, cardiomyopathy, or sudden cardiac death (or some combination thereof) in childhood.[10] Taken together, these findings strongly suggest that alterations in myocardial fatty acid metabolism play an important role in the development of cardiac hypertrophy and possibly heart failure. The findings of our study have important implications with regard to the molecular pathogenesis of hypertensive heart disease because they show that abnormalities in myocardial fatty acid metabolism occur relatively early in the disease (ie, at a time when the LV cavity size and systolic function appear normal) and that these metabolic changes are coupled with alterations in contractile function and energy efficiency.

### Fatty Acid Metabolism in Normal, Hypertrophied, and Failing Heart

Animal and human studies have shown that fatty acid β-oxidation decreases and glycolysis increases in association with ventricular hypertrophy and systolic heart failure.[29,30,35-39] Recent animal studies have shown that the switch in myocardial substrate utilization during the development of pressure-overload LVH and heart failure recapitulates the fetal heart phenotype, a developmental period when glucose is the primary energy substrate for the production of ATP.[8] Thus activation of the fetal gene program may initially represent an adaptive structural and metabolic response of the overloaded ventricle to maximize efficiency and decrease oxygen consumption by the hypertrophied myocytes. However, in the long term, particularly under conditions of chronically increased myocardial wall stress, these changes likely become maladaptive, resulting in decreased myocardial efficiency and, ultimately, impaired contractile performance, underscoring the importance of cardiac energy transduction in modulating the cardiovascular phenotype.[10]

### Assessment of Myocardial Metabolic Function in Human Beings by Use of PET

The ability to quantify myocardial fatty acid metabolism by use of PET has been validated at our institution in animals subjected to a wide range of hemodynamic and substrate environment conditions.[11] Myocardial PET imaging allows for noninvasive quantitative assessment of the rates of uptake, utilization, and clearance of metabolic

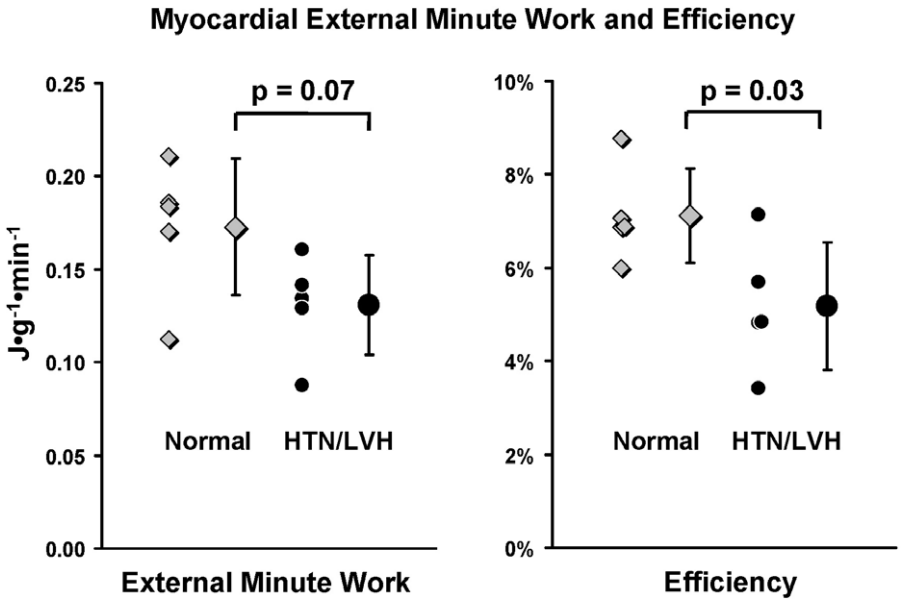


**Figure 2.** MEMW and myocardial efficiency are shown for normal control and hypertension (*HTN*)–induced LVH groups of MR substudy. Individual data points are given with the mean and SD shown to the right of each group.

substrates. Positron-emitting tracers of long-chain fatty acids (eg, 1–C-11 palmitate) and short-chain fatty acids (eg, 1–C-11 acetate) were among the first tracers used for the external assessment of regional myocardial metabolism.[40]

In patients with genetic defects of fatty acid β-oxidation (long-chain acyl-dehydrogenase deficiency), PET with 1–C-11 palmitate and 1–C-11 acetate was used to show decreased rates of myocardial oxidation of long-chain fatty acids; the extent of decreased clearance of palmitate correlated with the clinical severity of long-chain acyl-dehydrogenase deficiency.[41] Studies of patients with hypertrophic cardiomyopathy and with dilated cardiomyopathy, many using analog PET tracers (eg, iodine 123–labeled 15-[p-iodophenyl]-3-[*R*,*S*] methylpentadecanoic acid), have also shown abnormalities in fatty acid metabolism.[29,42-45]

## Assessment of Myocardial Mechanical Function and Energetics by Cardiac MR Imaging

In addition to characterizing the metabolic substrate environment of the myocardium in hypertension-induced LVH, this study also assessed myocardial mechanical function. Cardiac MR–tagged cine images allowed quantification of circumferential myocardial strain via finite element analyses. When the LVESS measurements derived from calibrated carotid artery pressure tracings were combined with measures of strain, the resultant values for circumferential MEMW tended to be lower in the hypertension-induced LVH hearts compared with age- and sex-matched normal control subjects ($P = .07$). Furthermore, when calculated as a ratio of MEMW to $MVO_2$, myocardial efficiency was significantly decreased in the hypertension-induced LVH group ($P = .03$) despite similar LVEF, MBF, and $MVO_2$ values between groups. This decline in the mechanical efficiency of contraction represents an imbalance between LV performance and myocardial energy consumption and may signal a preclinical deterioration in cardiac function in hypertension-induced LVH.

A previous study attempted to characterize the rates of myocardial glucose uptake using the glucose analog fluorine 18 fluorodeoxyglucose.[46] Although no differences in F-18 fluorodeoxyglucose uptake were found between the groups, this previous study (as in our investigation) noted rates of MBF and $MVO_2$ that were similar between those with hypertension-induced LVH and the normal control subjects, with lower myocardial efficiency noted in the hypertension-induced LVH group. Unfortunately, myocardial fatty acid metabolism was not characterized in the previous study, precluding further comparisons.

## Study Limitations

The highly restrictive study entry criteria and the intensive imaging protocol limited the number of patients eligible for the MR substudy. Although representative of patients with hypertension-induced LVH, the small cohort size of the MR substudy may limit the generalization of the results. Despite the limited sample

size, the results of this study are consistent with previous animal and human data implicating alternations in myocardial fatty acid metabolism in the development of hypertrophy and heart failure in the setting of ventricular pressure overload. Lactate metabolism and glucose metabolism represent significant sources of energy for the myocardium; neither was assessed in this study. The higher insulin levels in patients with hypertension-induced LVH have been previously described.[47,48] Although insulin could favor a shift in substrate utilization away from fatty acids, insulin was not a significant independent predictor of LVM or MFAO. Future studies characterizing myocardial carbohydrate metabolism may further elucidate the substrate utilization switches that occur in hypertension-induced LVH.

## Conclusions

The results of this study suggest that abnormalities in myocardial fatty acid metabolism are apparent in hypertension-induced LVH, a relatively early stage in the development of hypertensive heart disease, and that these abnormalities in metabolic function may be responsible, at least in part, for a reduction in myocardial efficiency. These findings may provide insight as to the possible molecular mechanisms mediating the transition from LVH to systolic dysfunction and heart failure.

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