Myocardial Oxygen Consumption Is Unchanged but Efficiency Is Reduced in Patients With Essential Hypertension and Left Ventricular Hypertrophy

Hanna Laine, MD; Chietsugu Katoh, MD; Matti Luotolahti, MD; Hannele Yki-Järvinen, MD; Ilkka Kantola, MD; Antti Jula, MD; Teemu O. Takala, MD; Ulla Ruotsalainen, PhD; Hidehiro Iida, DSc; Merja Haaparanta, Msc; Pirjo Nuutila, MD; Juhani Knuuti, MD

Background—Patients with hypertension and left ventricular hypertrophy (LVH) are prone to develop heart failure. We tested the hypothesis that compensatory LVH is associated with normalization of myocardial oxygen consumption and that this occurs at the expense of a decrease in the ratio between cardiac work and oxygen consumption (efficiency).

Methods and Results—Nine hypertensive men with LVH (LVH+) (age 42±2 years), left ventricular mass index (LVMI) 161±8 g/m², blood pressure (BP) 145±16/88±10 mm Hg (mean±SD); 8 hypertensive men without LVH (LVH−) (age 39±5 years, LVMI 107±15 g/m², BP 140±15/90±11 mm Hg); and 10 normotensive men (CONT) were studied. Myocardial blood flow, oxygen consumption, and glucose uptake were measured during euglycemic hyperinsulinemia using PET techniques. LV dimensions, volumes, and workload were determined by echocardiography, and efficiency was calculated. Myocardial workload (2.5±0.8 versus 3.0±0.6 versus 2.3±0.5 mm Hg·mL·min⁻¹·g⁻¹ for CONT versus LVH− versus LVH+; P<0.05, LVH− versus LVH+), myocardial blood flow (0.84±0.16 versus 1.06±0.22 versus 0.81±0.09 mL·g⁻¹·min, respectively; P<0.05, LVH− versus other groups) and oxygen consumption (0.09±0.02 versus 0.14±0.03 versus 0.11±0.01 mL·g⁻¹·min⁻¹, respectively; P<0.05, LVH− versus other groups) were increased in the LVH− group. Myocardial efficiency was reduced in the LVH+ group (18.1±4.1% versus 15.1±2.3% versus 13.5±1.9%, respectively; P<0.05, LVH+ versus CONT).

Conclusions—Myocardial oxygen consumption per unit weight is increased in hypertensive patients without LVH but is normal in those with LVH. The normalization of oxygen consumption via hypertrophy occurs at the expense of efficiency, which may predispose hypertensive patients with LVH to heart failure. (Circulation. 1999;100:2425-2430.)

Key Words: hypertension • hypertrophy • oxygen • metabolism • imaging
TABLE 1. Baseline Characteristics of the Study Groups

<table>
<thead>
<tr>
<th></th>
<th>CONT (n=10)</th>
<th>LVH– (n=8)</th>
<th>LVH+ (n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>41±4</td>
<td>39±5</td>
<td>42±2</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>25±3</td>
<td>26±1</td>
<td>27±2</td>
</tr>
<tr>
<td>(V̇_O_{2\text{max}}), ml · kg⁻¹ · min⁻¹</td>
<td>37±3</td>
<td>33±5</td>
<td>31±4</td>
</tr>
<tr>
<td>BP systolic, mm Hg</td>
<td>127±16</td>
<td>140±15</td>
<td>145±16</td>
</tr>
<tr>
<td>BP diastolic, mm Hg</td>
<td>75±16</td>
<td>90±11</td>
<td>88±10</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>61±6</td>
<td>75±10†</td>
<td>68±7</td>
</tr>
<tr>
<td>RPP, mm Hg/min</td>
<td>7700±1800</td>
<td>10 600±2200*</td>
<td>9900±1600*</td>
</tr>
<tr>
<td>fP-glucose, mmol/L</td>
<td>5.5±0.5</td>
<td>5.7±0.5</td>
<td>5.6±0.3</td>
</tr>
<tr>
<td>fS-chol, mmol/L</td>
<td>5.2±0.4</td>
<td>5.0±0.3</td>
<td>5.0±0.5</td>
</tr>
<tr>
<td>fS-HDL chol, mmol/L</td>
<td>7±4</td>
<td>10±3</td>
<td>9±4</td>
</tr>
<tr>
<td>fS-HbA1c, %</td>
<td>0.48±0.26</td>
<td>0.59±0.11</td>
<td>0.57±0.19</td>
</tr>
<tr>
<td>fS-insulin, mU/L</td>
<td>5±0.7</td>
<td>5.6±0.8</td>
<td>5.4±0.9</td>
</tr>
<tr>
<td>fS-FFA, μmol/L</td>
<td>1.2±0.3</td>
<td>1.2±0.3</td>
<td>1.3±0.3</td>
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<tr>
<td>fS-tg, mmol/L</td>
<td>1.1±0.6</td>
<td>1.3±0.5</td>
<td>1.6±1.2</td>
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<tr>
<td>fS-LDL chol, mmol/L</td>
<td>3.7±0.6</td>
<td>3.8±0.6</td>
<td>3.4±0.7</td>
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<tr>
<td>Antihypertensive medication, y</td>
<td>...</td>
<td>4±3</td>
<td>5±4</td>
</tr>
</tbody>
</table>

TABLE 2. Echocardiographic Characteristics of the Study Groups at Baseline and During Euglycemic Hyperinsulinemia

<table>
<thead>
<tr>
<th></th>
<th>CONT (n=10) Basal</th>
<th>Ins</th>
<th>LVH– (n=8) Basal</th>
<th>Ins</th>
<th>LVH+ (n=9) Basal</th>
<th>Ins</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVMI, g/m²</td>
<td>109±14</td>
<td>ND</td>
<td>107±15</td>
<td>ND</td>
<td>161±8*</td>
<td>ND</td>
</tr>
<tr>
<td>LVDs, mm</td>
<td>32.4±2.2</td>
<td>30.5±2.6</td>
<td>31.5±2.8</td>
<td>30.4±4.2</td>
<td>35.6±2.4*</td>
<td>34.2±2.5*</td>
</tr>
<tr>
<td>LVDD, mm</td>
<td>52.2±2.2</td>
<td>52.0±2.7</td>
<td>51.0±4.6</td>
<td>51.8±4.9</td>
<td>57.3±3.0*</td>
<td>57.2±3.0*</td>
</tr>
<tr>
<td>SEs, mm</td>
<td>14.2±0.8</td>
<td>14.8±0.6</td>
<td>14.4±0.7</td>
<td>14.5±1.8</td>
<td>16.0±1.0*</td>
<td>16.7±1.3*</td>
</tr>
<tr>
<td>SEd, mm</td>
<td>9.5±0.7</td>
<td>9.6±0.5</td>
<td>9.8±1.3</td>
<td>10.0±1.2</td>
<td>11.5±0.2*</td>
<td>11.5±0.7*</td>
</tr>
<tr>
<td>PWs, mm</td>
<td>16.2±1.8</td>
<td>16.9±1.0</td>
<td>16.4±0.9</td>
<td>17.1±1.8</td>
<td>17.9±0.9*</td>
<td>18.5±1.3*</td>
</tr>
<tr>
<td>PWd, mm</td>
<td>9.0±0.7</td>
<td>9.3±0.6</td>
<td>9.4±0.9</td>
<td>9.2±1.1</td>
<td>11.3±0.7*</td>
<td>11.3±1.1*</td>
</tr>
<tr>
<td>EF, %</td>
<td>68±3</td>
<td>72±3†</td>
<td>68±4</td>
<td>72±5†</td>
<td>67±3</td>
<td>70±4†</td>
</tr>
<tr>
<td>SV, mL</td>
<td>89±8</td>
<td>93±10†</td>
<td>85±19</td>
<td>93±18</td>
<td>109±15*</td>
<td>114±15†</td>
</tr>
<tr>
<td>WS, mm Hg</td>
<td>62±9</td>
<td>54±17</td>
<td>64±9</td>
<td>60±24</td>
<td>69±11</td>
<td>61±9</td>
</tr>
</tbody>
</table>

Basal indicates baseline; Ins, euglycemic hyperinsulinemia; LVDs, left ventricular diameter in systole; LVDD, left ventricular diameter in diastole; SEs, septal wall thickness in systole; SEd, septal wall thickness in diastole; PWs, posterior wall thickness in systole; PWd, posterior wall thickness in diastole; EF, ejection fraction; SV, stroke volume; WS, wall stress; and ND, not determined.

Methods

Subjects

A total of 27 men were studied: 9 had essential hypertension and left ventricular hypertrophy (LVH+), 8 essential hypertension and normal LV mass (LVH–), and 10 were normotensive with normal LV mass (CONT) (Tables 1 and 2). The hypertensive men were recruited from occupational outpatient clinics and the Research and Development Center in Turku. The inclusion criteria for the hypertensive subjects were: age 18 to 50 years, previously diagnosed hypertension, normoglycemia, no signs or symptoms of other cardiovascular disease, and no regular use of any drugs other than antihypertensive drugs. The hypertensive subjects were divided into LVH– and LVH+ groups using 131 g/m² as an upper limit of normal LV mass index.11 A complete medical examination was performed to exclude secondary forms of hypertension. The normal subjects were recruited among normotensive and normoglycemic males who used no medications and had no signs or symptoms of any disease. All study subjects had normal exercise echocardiograms and laboratory tests. To minimize the direct effects of high blood pressure on the results, the hypertensive subjects were studied while on metabolically neutral antihypertensive treatment (angiotensin-converting enzyme inhibitors and/or calcium channel blockers). The drugs were taken the morning of the PET study.

The nature, purpose, and potential risks of the study were explained to all subjects before they gave their voluntary consent to participate. The study was approved by the Ethical Committee of the Turku University Central Hospital.

Study Design

The PET studies were performed after a 10- to 12-hour overnight fast starting between 7:30 and 8 AM. Two catheters were inserted, 1 in an antecubital vein for all infusions and another in a contralateral hand vein for sampling of arterialized venous blood.12 Each study consisted of a 20-minute basal and a 140-minute hyperinsulinemic period. At 0 minutes, a primed continuous insulin infusion (1 mU · kg⁻¹ · min⁻¹) was started. Normoglycemia was maintained using infusion of 20% glucose. After 30 minutes of hyperinsulinemia, blood volume was quantified using [¹⁵Ο]CO inhalation. Thereafter, myocardial blood flow and oxygen consumption were measured using [¹⁵Ο]H₂O infusion and [¹⁵Ο] inhalation. At 100 minutes, [¹⁵Ο]FDG was injected and dynamic PET imaging was performed to determine the myocardial glucose uptake. Blood pressure and heart rate were monitored with an automatic oscillometric blood pressure monitor (HEM-705C, oscillometric blood pressure monitor, Omron Corp) every 15 minutes during the PET study.

The expense of efficiency. These data thus raise the possibility that the natural course of hypertensive heart disease is a gradual decrease in myocardial efficiency.

PET techniques allow quantification of myocardial perfusion and oxygen consumption in healthy individuals and asymptomatic hypertensive patients without cardiac catheterization. We combined PET and echocardiography to determine cardiac efficiency under standardized metabolic conditions in hypertensive patients with and without LVH, and in a group of matched normotensive subjects.

References

1. P<0.05 CONT vs other groups; †P<0.05 LVH– vs other groups.
Measurement of Myocardial Blood Flow, Oxygen Consumption, Oxygen Extraction Fraction, and Glucose Uptake

[15O] tracers and [18F]FDG were produced as previously described. [12,13] A six-ring ECAT 931/08–12 tomograph (Siemens/CTI Inc) was used. [15O]CO, [18O]H2O. [13] [18F]FDG studies were performed as previously described. All data were corrected for dead-time, decay, and measured photon attenuation. The [18F]FDG data were reconstructed into a 128×128 matrix using filtered back projection reconstruction method. The final in-plane resolution in filtered back projection–reconstructed and Hann-filtered (0.3 cycles/s) images was 9.5 mm full-width half-maximum. The data of [15O] studies was reconstructed with a new iterative reconstruction algorithm using median root prior. [15]

Regions of interest were drawn in the lateral, anterior and septal wall of the left ventricle in 4 representative transaxial slices in each study. Additionally a large horseshoe shaped region of interest was drawn in the same 4 slices and used to calculate the average values of metabolic parameters.

Calculation of Blood Flow, Oxygen Consumption, Oxygen Extraction Fraction, and Glucose Uptake

Values of regional myocardial blood flow (expressed in milliliters per gram of tissue per minute), oxygen consumption (expressed in milliliters per gram of tissue per minute), and extraction fraction were calculated according to previously published methods. Myocardial glucose uptake was calculated as previously described. [12] The lumped constant was assumed to be 1.0. [17]

Echocardiography

Two-dimensional guided M-mode echocardiography (Acuson 128XP/5, Acuson) was performed in all study subjects to determine end-diastolic and end-systolic wall thicknesses, LV dimensions, and volumes. LV mass was calculated according to the Penn convention and LV mass index by dividing LV mass by body surface area. Minute work (MINW) was calculated by mean blood pressure×cardiac output, MINW index by dividing MINW by body surface area, and MINW per gram of tissue by dividing MINW by LV mass. Meridional left ventricle wall stress was calculated according to the equation WS=(p · r)/[2Wth · (1+Wth/2r)], in which WS is wall stress, p is systolic blood pressure, r is systolic internal radius of left ventricle, and Wth is wall systolic thickness. [19]

Bicycle exercise echocardiograms were analyzed visually by an experienced physician (M.L.) to rule out silent myocardial ischemia. An upright bicycle-ergometer exercise test was performed by an experienced physician (M.L.) to rule out silent myocardial ischemia. An upright bicycle-ergometer exercise test was performed by an increasing workload by 20 W at 1-minute intervals. The test was continued until extreme fatigue or 90% of the predicted maximum heart rate. The echocardiograms were recorded before and immediately after the exercise. All subjects had a normal exercise capacity, were asymptomatic, had no diagnostic ST-changes in ECG, and no disturbances in wall motion either at rest or immediately after the maximal exercise.

Efficiency was calculated from the following equation:

\[
\text{Efficiency (\%) = } \frac{\text{MAP} \times \text{SV} \times \text{HR} \times 0.00136 \times 100}{\text{myocardial oxygen consumption of whole heart}} \times c
\]

where MAP is mean arterial pressure, SV stroke volume, and HR heart rate. The number 0.00136 represents a constant with units g · m⁻¹ · mL⁻¹ · mm Hg⁻¹ and c is a conversion factor representing energy equivalent per mL of oxygen metabolized equaling 2.059 kg · m⁻¹ · mL⁻¹ oxygen consumed.

Analytical Procedures

Plasma glucose was determined in duplicate by the glucose oxidase method, using an Analox GM7 (Analox Instruments) glucose analyzer. Serum insulin was measured by immunossay and serum free fatty acids (FFA) by fluorometric method. [12] Glycosylated hemoglobin was measured with fast-protein liquid chromatography (MonoS, Pharmacia) and serum cholesterol and triglycerides by enzymatic methods (Hibachi 717, Automatic Analyzer, Hibachi).

Statistical Analysis

All results are expressed as mean±SD. The differences between the 3 subject groups were compared using ANOVA and Tukey’s studentized range test. Paired samples were compared by paired comparisons t test. Pearson’s correlation coefficients were calculated when appropriate. The regional values were compared using the Mann-Whitney U test. ANCOVA was used to study the influence of hemodynamic parameters on myocardial blood flow, oxygen extraction fraction, and oxygen consumption. P<0.05 was considered significant. Statistical computations were performed with SAS statistical program package (SAS Institute).

Results

Metabolic Characteristics

Fasting glucose, FFA, and serum insulin concentrations were comparable between the groups (Table 1). The duration of antihypertensive medication was similar in both hypertensive groups (Table 1). During euglycemic hyperinsulinemia, serum-free insulin (67±9 versus 67±11 versus 61±6 mU/L, CONT versus LVH− versus LVH+, P=NS) and plasma glucose (5.1±0.4 versus 5.2±0.4 versus 5.0±0.4 mmol/L, CONT versus LVH− versus LVH+, P=NS) concentrations were comparable in all groups. Serum FFA were higher in the LVH− group (0.18±0.06 μmol/L) than in the CONT (0.08±0.04 μmol/L) or LVH+ (0.12±0.03 μmol/L) groups (P<0.05 for LVH− versus other groups).

Hemodynamic and Echocardiographic Characteristics

Hemodynamic and echocardiographic characteristics of the groups are shown in Tables 1 and 2. Blood pressures were slightly but not significantly higher in the hypertensive compared with the CONT group but similar in the 2 hypertensive groups (Table 1). LV mass index, LV diameters, and diameters of the septal and posterior walls (Table 2) were significantly higher in the LVH+ group than in the other groups. On the basis of the criteria presented in the Framingham study, [21] all hypertensive subjects in the LVH+ group had symmetric concentric LV hypertrophy (data not shown). Wall stress and ejection fraction were not different from each other between the groups (Table 2). MINW, calculated per unit weight, was significantly higher in the LVH− group (272±41 mL/min) than in the CONT group (180±23 mL/min, P<0.05 for LVH− versus other groups).

Myocardial Blood Flow, Oxygen Extraction Fraction, and Oxygen Consumption

Myocardial blood flow per unit weight was higher in the LVH− group than in the other groups (0.84±0.16 versus 1.06±0.22 versus 0.81±0.09 mL · g⁻¹ · min⁻¹, CONT versus LVH− versus LVH+, P<0.05 LVH− versus other groups). When calculated per total LV, mass myocardial blood flow was highest in the LVH+ group (225±31 mL/min) and lowest in the CONT group (180±23 mL/min, P<0.05 versus LVH− and LVH+ groups). Myocardial blood flow correlated significantly with MINW in each group (Figure 3).
The oxygen extraction fraction (fraction of oxygen used from that delivered) was increased in both hypertensive groups compared with the CONT group (0.59±0.02 versus 0.71±0.03 versus 0.73±0.04, CONT versus LVH− versus LVH+; P<0.05 CONT versus hypertensive groups).

Myocardial oxygen consumption calculated per unit weight (Figure 1) or per unit weight and per beat were higher in the LVH2 than in the other groups (0.15±0.03 versus 0.19±0.02 versus 0.17±0.02 mL · 100 g−1 · beat−1, CONT versus LVH− versus LVH+; P<0.05 LVH− versus other groups).

When calculated per total LV mass (Figure 2) or per total LV mass and per beat (0.32±0.06 versus 0.42±0.08 versus 0.58±0.09 mL · LV mass−1 · beat−1, CONT versus LVH− versus LVH+; P<0.05 CONT versus other groups, P<0.05 LVH+ versus LVH−), oxygen consumption was increased in both hypertensive groups compared with the controls and it was also significantly higher in the LVH+ than in the LVH− group (Figure 2). Differences in heart rate or blood pressure did not explain the differences in myocardial oxygen consumption, blood flow, or oxygen extraction fraction between the groups.

**Myocardial Efficiency**

Myocardial efficiency was lower in the LVH+ group (13.5±1.9%) than in the CONT group (18.1±4.1%, P<0.05). Efficiency in the LVH− group (15.1±2.3%) was between that in the LVH+ and CONT groups but not significantly different from either of the other groups (Figure 4).

**Myocardial Glucose Uptake**

Myocardial glucose uptake per unit weight was not different between the groups (54±14 versus 62±11 versus...
Also, these studies included hypertensive patients with symptoms or signs of hypertensive microvascular heart disease and were divided into LVH− and LVH+ groups on the basis of their echocardiographically determined LV masses. Oxygen consumption was found to be significantly lower per unit mass of myocardium in patients with than without LVH. This result is consistent with previous data in rats in which a pressure-induced increase in myocardial mass is accompanied by a decrease in oxygen consumption and a shift in myosin isoenzymes from a faster V1 to a slower V3 enzymatic form.22 Thus, LVH may be viewed as a structural adaptation, which aims at restoring oxygen consumption per unit mass of myocardium toward normal.

In the present study, glucose uptake per gram of myocardial tissue was not different between the groups. Serum FFA were, however, slightly higher in the LVH− than in the CONT and LVH+ groups. Because it is more costly to burn fatty acids than glucose, one could speculate that the decreased efficiency, ie, increased oxygen cost of myocardial work found in the LVH+ group, might be due to increased myocardial fatty acid usage. In this study, FFA uptake was not quantified, but it can be estimated by multiplying the FFA concentrations measured in the present study by previously (under similar metabolic conditions than in our study) quantified FFA uptake rates of normal myocardium.23 Assuming all FFA are oxidized, the percent of oxygen maximally used for FFA oxidation24 can be estimated. These calculations reveal that 6% of total myocardial oxygen uptake could have maximally been used for FFA oxidation in the control group, 8% in the LVH−, and 7% in the LVH+ group. These data imply that decreased efficiency in the LVH+ group cannot be simply attributed by increased use of FFA.

An exaggerated interstitial and perivascular deposition of fibrillar collagen is found in hypertrophied left ventricles of hypertensive subjects,25 and increased amount of myocardial collagen has been held responsible for impaired ventricular pumping capacity.26 In addition to the increment of myocardial collagen, media hypertrophy of intramyocardial coronary arterioles has also been found in myocardial biopsies of hypertensive patients.7 Such structural alterations might partly explain the present finding of reduced myocardial efficiency in patients with LVH. In concentric hypertrophy, an increment of the LV diastolic diameter, which characterized the LVH+ group in the present study, combined with only slightly elevated LV end-diastolic pressure would be consistent with initial heart failure.27 Because LV end-diastolic pressures were not measured in the present study, we cannot exclude this possibility in the LVH+ group.

In the present study all hypertensive subjects used an ACE inhibitor as antihypertensive medication, with the exception of 1 patient in the LVH− group who used a calcium channel blocker. To achieve normotension, a calcium channel blocker was combined with an ACE inhibitor in 1 patient in the LVH− group and in 5 patients in the LVH+ group. Long-term antihypertensive treatment using both ACE inhibitors and calcium channel blockers have been shown to reduce LV hypertrophy and to exert a favorable effect on the matching between myocardial mass and perfusion.28 A recent study in dogs suggested that ACE inhibitors might also play a role in matching myocardial oxygen supply to oxygen demands, because ACE inhibitors were found to reduce oxygen consumption in coronary microvessels and increase cardiac nitric oxide release.29 Consequently, lack of measurements performed in the absence of antihypertensive medication could be viewed as a limitation of the present study. On the other hand, because the LVH patients used more medication than those without LVH, one could argue that differences in efficiency and oxygen consumption between the hypertensive...
groups would have been even greater if untreated patients had been studied. Because only asymptomatic, middle-aged, hypertensive men with normal stress echocardiographies were studied, our data can obviously not be directly extrapolated to hypertensive patients with symptoms of angina or to women.

In conclusion, the present data demonstrate that myocardial oxygen consumption per unit weight is increased in hypertensive patients without LVH but normal in those with LVH. This apparent normalization in oxygen consumption is accompanied by reduced efficiency, ie, the ratio of myocardial work to oxygen consumption. LV failure is invariably characterized by reduced efficiency. The present data raise the possibility that a decrease in efficiency also predisposes patients with hypertension and LVH to develop heart failure.

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References


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