Association of Hemoglobin Delivery With Left Ventricular Structure and Function in Hypertensive Patients
Losartan Intervention For End Point Reduction in Hypertension Study


Abstract—Several studies have shown associations of high levels of hemoglobin (Hgb) or blood viscosity with cardiac events and with left ventricular (LV) hypertrophy (LVH). To assess the relations of LV mass and function with Hgb delivery (ie, the physiological carrier of oxygen), we calculated the product of Hgb concentration and Doppler-derived cardiac output in 864 hypertensive participants with electrocardiographic LVH (359 women) in the Losartan Intervention for End Point Reduction in Hypertension echocardiography substudy. Among women, Hgb delivery was positively related to internal dimension, septal and posterior wall thicknesses, LV mass, endocardial and midwall fractional shortening, and peak A wave velocity and negatively to total peripheral resistance index, E/A ratio, deceleration time, and the isovolumic relaxation time. Among men, Hgb delivery was positively related to LV internal dimension, LV mass, and A velocity, and negatively to LV midwall shortening, relative wall thickness, peripheral resistance index, and E/A ratio. In multivariable analyses that adjusted for age, diastolic blood pressure, body mass index, and total cholesterol, hemoglobin delivery in women was related positively to LV fractional shortening, midwall shortening, LV mass mitral valve A velocity, and LV internal dimension and negatively to mitral valve deceleration time and isovolumic relaxation time. Among men, Hgb delivery had positive independent relations to mitral valve A velocity, LV internal dimension, midwall shortening, and LV mass and negative relations to the E/A ratio and relative wall thickness. Thus, in hypertensive LVH, higher oxygen delivery capacity is associated with higher LV mass and impaired early diastolic LV filling. (Hypertension. 2006;47:868-873.)

Key Words: hypertension • hemoglobin • echocardiography

Hypertension is a known risk factor for future cardiovascular events. The risk of these events is further worsened in the presence of left ventricular (LV) hypertrophy. The development of hypertension depends on elevation of peripheral vascular resistance and/or cardiac output. This role of cardiac output has led to investigation of the contribution of hematocrit to the pathogenesis of hypertension. It has been recognized since the identification of the Poiseuille–Hagen relationship¹ that increased resistance to the flow of a fluid can be secondary to decreased vessel caliber or because of increased viscosity of the fluid, in this case, the blood. Several studies have shown evidence of increased blood viscosity in hypertensive patients.²⁻⁷ High viscosity affects peripheral vascular resistance, not only by increasing resistance to flow, but also by hindering vasodilatation. In a study in a canine model, high viscosity secondary to hypertriglyceridemia was found to impair coronary vasodilatation.⁸ Population-based studies have shown higher blood pressure in men than women, to which gender differences in hematocrit may contribute.⁹ Hematocrit can affect peripheral vascular resistance in 2 ways: primarily by affecting the blood viscosity¹⁰ and, secondly, by affecting the caliber of peripheral arterioles. Arteriolar caliber is affected by autoregulation being negatively related to the level of oxygen within tissues.¹¹ As hematocrit rises, tissue hypoxia is reduced, and hypoxia-mediated vasodilatation is diminished. As a result, peripheral vascular resistance increases. Interaction of hematocrit, tissue hypoxia, and hypertension is further supported by lower blood pressures in people living at high altitudes who, in spite of higher hematocrit values, do not have elevated tissue oxygen levels because of lower oxygen concentration in the atmosphere.¹²

A potential causal role of hematocrit in hypertension is supported by changes in blood pressure seen with treatment...
of anemia in many disease states with a rise in blood pressure levels in response to treatment of anemia with erythropoietin in chronically ill patients. However, there are conflicting results; one study found correlation between whole blood viscosity and LV mass, whereas another found that whole blood viscosity was related to LV wall thickness more than to LV mass. To our knowledge, there has been no previous investigation of the relation between systemic hemoglobin delivery and LV structure and function. The present study was undertaken to investigate the relations of hemoglobin level and the product of hemoglobin concentration multiplied by cardiac output as an index of oxygen delivery, with LV size and function in a large population of hypertensive patients with electrocardiographic LV hypertrophy enrolled in the Losartan Intervention For End point reduction in hypertension (LIFE) echocardiography substudy.

Methods
All of the patients were participants in the LIFE study, aged 55 to 80 years, with stage II to III essential hypertension and evidence of LV hypertrophy defined by Cornell voltage-duration criteria (SV1 + RaVL × QRS duration ≥2440 mV·ms) or Sokolow-Lyon voltage criteria (SV1 + R5V5/R6V6 >38 mm). After signing ethics committee-approved informed consent, patients were taken off all antihypertensive medications and entered into a 2-week, single-blind placebo phase, after which baseline measurements were obtained. These included laboratory blood samples for hemoglobin and serum chemistry, and a 12-lead ECG.

A subset of ~10% of the total LIFE patient population participated in the LIFE-echocardiographic study and had M-mode, 2D, and Doppler echocardiograms performed as described previously. Doppler echocardiographic recordings were made with the patients in the left decubitus position, following previously published and standardized protocols. LV chamber dimensions and wall thicknesses were measured following the American Society of Echocardiography standards. Relative wall thickness was calculated at end diastole as posterior wall thickness (PWT)/internal radius, the ratio of LV mass/body surface area was calculated as [(1/2)×(PWT+diameter)] × body surface area and indexed for body surface area, were

### Statistical Analysis
Data were analyzed using SPSS 12.0.1 statistical software (SPSS, Inc). Results are mean±SD or 95% confidence interval, when appropriate, and frequencies are expressed as percentages. Differences in continuous variables between 2 groups were assessed by Student t test for parametric data, with log transformation when needed to satisfy the assumption of normality and χ² analysis for categorical data. Independent correlates of continuous measures of LV geometry were identified by multiple linear regression analysis using an enter procedure with assessment of colinearity diagnostics. Two-tailed P<0.05 was considered statistically significant.

### Results
Patient Characteristics
A total of 864 patients, 359 women and 505 men, were included in the present study; these patients were similar to the entire LIFE population with the exception of including higher proportions of men (58% versus 46%) and blacks (14% versus 6%). There were no significant differences in age or ethnicity between women and men (Table 1). Compared with women, men had larger body size but lower body mass index, heart rate, and systolic and pulse pressure but higher diastolic blood pressure. Mean levels of both hemoglobin and oxygen delivery capacity were ~8% higher in men than women (Table 2). There was no gender difference in mean glucose level, but men had higher plasma creatinine levels and exhibited trends toward greater albuminuria compared with women. Men also had lower mean values than women for total and especially for high-density lipoprotein (HDL) cholesterol concentration.

### Echocardiographic Findings
Echocardiographic variables are described in Table 3. As expected, LV wall thicknesses, chamber size, and mass, both in absolute terms and indexed for body surface area, were

### TABLE 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Men (N=505)</th>
<th>Women (N=359)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>66±7</td>
<td>66±7</td>
<td>NS</td>
</tr>
<tr>
<td>White race, n (%)</td>
<td>407 (81)</td>
<td>312 (87)</td>
<td>0.166</td>
</tr>
<tr>
<td>Height, cm</td>
<td>175±7</td>
<td>162±7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>82±13</td>
<td>74±14</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>26.8±3.6</td>
<td>28.1±3.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body surface area, m²</td>
<td>1.97±0.17</td>
<td>1.78±0.16</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heart rate, min⁻¹</td>
<td>66±11</td>
<td>70±12</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>173±14</td>
<td>175±14</td>
<td>0.064</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>99±9</td>
<td>97±9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pulse pressure, mm Hg</td>
<td>74±15</td>
<td>78±16</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

NS indicates not significant.

### TABLE 2. Laboratory Parameters

<table>
<thead>
<tr>
<th>Variable</th>
<th>Men (N=505)</th>
<th>Women (N=359)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin, g/dL</td>
<td>14.7±1.2</td>
<td>13.6±1.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hemoglobin delivery, g/min</td>
<td>761±205</td>
<td>709±177</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum glucose, mmol/L</td>
<td>6.1±2.5</td>
<td>6.0±2.3</td>
<td>0.442</td>
</tr>
<tr>
<td>Serum creatinine, mmol/L</td>
<td>98±23</td>
<td>80±18</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Urine albumin/creatinine, mg/mmol</td>
<td>9.8±34.4</td>
<td>6.8±26.7</td>
<td>0.186</td>
</tr>
<tr>
<td>Log₁₀ urine albumin/creatinine</td>
<td>0.32±0.70</td>
<td>0.23±0.62</td>
<td>0.064</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>5.8±1.0</td>
<td>6.3±1.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.4±0.4</td>
<td>1.7±0.5</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
higher in men; there was no gender difference in LV relative wall thickness. Stroke volume was larger in men than women, but there was no gender difference in cardiac output because of the higher heart rate in women. Peripheral resistance index was higher and cardiac index lower in male than female LIFE patients. Measures of LV systolic chamber and midwall function were higher in women than men, as were the peak velocities of blood flow across the mitral valve in early diastole and with atrial systole.

**Relations of Hemoglobin to Clinical Characteristics**
Among women, hemoglobin concentration had a significant positive relation with total cholesterol level and a negative relation with plasma creatinine (Table 4) but was not significantly related to age, systolic or diastolic blood pressure, age, body mass index, log urine albumin/creatinine, serum glucose, or HDL cholesterol levels (all \( P > 0.20 \)). Among men, hemoglobin concentration had significant positive relations with diastolic blood pressure, total cholesterol level (both \( P < 0.001 \)), and body mass index \( (P = 0.03) \) and negative relations with plasma creatinine and age \( (P < 0.001; \text{Table 4}) \), but not with log urine albumin/creatinine, serum glucose, or systolic blood pressure (all \( P > 0.10 \)).

**Relations of Hemoglobin to Echocardiographic Findings**
Among women, there was a weak negative relation of hemoglobin level with LV internal dimension \( (P < 0.05) \) but not with LV wall thicknesses, mass, or relative wall thickness. Similarly, there was no significant relation between hemoglobin level and stroke volume, cardiac output, peripheral resistance, or measures of LV systolic chamber or midwall function (Table 4).

Among men, the hemoglobin level was negatively related to stroke volume \( (r = -0.13; P = 0.005) \) but not other measures of LV geometry or function or of systemic hemodynamics, whereas hemoglobin delivery was positively related to LV internal dimension \( (r = 0.23; P < 0.001) \) and LV mass \( (r = 0.17; P < 0.001) \) and negatively related to relative wall thickness and LV midwall shortening (both \( r = -0.14; P = 0.004 \)).

**Relations of Hemoglobin Delivery to Clinical and Echocardiographic Findings**
Among women, hemoglobin delivery was positively related to systolic blood pressure and negatively to serum creatinine and HDL cholesterol levels among clinical variables (Table 5). There were also positive relations between hemoglobin delivery and LV internal dimension, septal and PWTs, LV mass, endocardial and midwall FS, and cardiac index and a negative relation with total peripheral resistance index. Among measures of LV diastolic filling, hemoglobin delivery was positively

### TABLE 3. Echocardiographic Variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Men</th>
<th>Women</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left ventricular posterior wall, cm</td>
<td>1.10±0.13</td>
<td>0.14±0.12</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Interventricular septal thickness, cm</td>
<td>1.19±0.15</td>
<td>1.12±0.14</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Left ventricular internal dimension, cm</td>
<td>5.44±0.57</td>
<td>5.04±0.47</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Left ventricular mass, g</td>
<td>253±56</td>
<td>207±47</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Left ventricular mass/body surface area, g/m²</td>
<td>129±27</td>
<td>117±23</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Left ventricular mass/height, g/m²²</td>
<td>56.4±13.1</td>
<td>56.4±12.8</td>
<td>0.941</td>
</tr>
<tr>
<td>Relative wall thickness</td>
<td>0.41±0.07</td>
<td>0.42±0.06</td>
<td>0.104</td>
</tr>
<tr>
<td>Cardiac output, L/min</td>
<td>5.18±1.34</td>
<td>5.20±1.22</td>
<td>0.783</td>
</tr>
<tr>
<td>Cardiac index, L/min/m²</td>
<td>2.63±0.63</td>
<td>2.94±0.69</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stroke volume, mL</td>
<td>80±18</td>
<td>74±16</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stroke index, mL/m²</td>
<td>41±9</td>
<td>42±9</td>
<td>0.055</td>
</tr>
<tr>
<td>FS, %</td>
<td>33±6</td>
<td>35±6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Midwall shortening, %</td>
<td>15.2±2.1</td>
<td>15.7±2.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peak E velocity, cm/s</td>
<td>63±17</td>
<td>69±19</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peak A velocity, cm/s</td>
<td>77±19</td>
<td>87±22</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total peripheral resistance, dynes×s×cm⁻⁵</td>
<td>2008±618</td>
<td>1972±516</td>
<td>0.397</td>
</tr>
<tr>
<td>Total peripheral resistance index, dynes×s×cm⁻³</td>
<td>3916±1142</td>
<td>3482±896</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

### TABLE 4. Relations of Hemoglobin Level to Clinical and Echocardiographic Variables in Hypertensive Women and Men

<table>
<thead>
<tr>
<th>Variable</th>
<th>Women ( r )</th>
<th>( P )</th>
<th>Men ( r )</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.016</td>
<td>0.77</td>
<td>-0.18</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>0.022</td>
<td>0.68</td>
<td>-0.045</td>
<td>0.32</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>0.063</td>
<td>0.24</td>
<td>0.21</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body mass index</td>
<td>-0.042</td>
<td>0.45</td>
<td>0.10</td>
<td>0.022</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>-0.14</td>
<td>0.009</td>
<td>-0.23</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>0.14</td>
<td>0.011</td>
<td>0.20</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Left ventricular end-diastolic diameter</td>
<td>-0.11</td>
<td>0.04</td>
<td>-0.013</td>
<td>0.77</td>
</tr>
<tr>
<td>Left ventricular mass</td>
<td>-0.083</td>
<td>0.12</td>
<td>-0.033</td>
<td>0.47</td>
</tr>
<tr>
<td>Stroke volume</td>
<td>0.002</td>
<td>0.97</td>
<td>-0.13</td>
<td>0.005</td>
</tr>
</tbody>
</table>
related to the peak A wave velocity and negatively related to the 
E/A ratio, deceleration time of early diastolic LV inflow, and the 
isovolumic relaxation time.

Among men, hemoglobin delivery was positively related to 
diastolic blood pressure, body mass index, and glucose level 
and negatively to age and plasma creatinine level but was 
statistically unrelated to systolic blood pressure, total cholesterol, 
log urine albumin/creatinine, or HDL cholesterol level 
(Table 5). There were also positive relations of hemoglobin 
delivery with LV internal dimension, LV mass, and cardiac 
index, and negative relations between hemoglobin delivery 
and LV midwall shortening and relative wall thickness, as 
well as total peripheral resistance index. Among indices of 
LV diastolic filling, the peak A wave velocity was positively 
and the E/A ratio negatively related to hemoglobin delivery in 
men, without relations with other diastolic filling variables.

Multivariate Analyses of Hemoglobin Delivery

A series of regression models were developed that included 
clinical variables associated with hemoglobin level or 
hemoglobin delivery in either gender, including diastolic blood 
pressure, total cholesterol, body mass index, and age as 
covariates based on their univariate associations with 
hemoglobin level. Among women, hemoglobin level had indepen-
dent negative relations to mitral valve E velocity ($\beta = -0.188$; 
$P = 0.001$) and A velocity ($\beta = -0.132$; $P = 0.027$) but was not 
independently related to septal or PWT, LV internal diameter, 
LV mass, relative wall thickness, FS, midwall shortening, 
mitral valve E/A ratio, deceleration time, or isovolumic 
relaxation time. Among men, hemoglobin level was not 
independently related to any of the LV geometric or 
functional variables under consideration.

Multivariate Analyses of Hemoglobin Delivery

Hemoglobin delivery in women had positive relations, 
independent of the same covariates, with LV FS ($\beta = 0.229$), 
midwall shortening ($\beta = 0.223$; both $P < 0.001$), LV mass 
($\beta = 0.159$; $P = 0.008$), mitral valve A velocity ($\beta = 0.137$; 
$P = 0.021$), and LV internal dimension ($\beta = 0.121$; $P = 0.037$) 
and was negatively related to the mitral valve deceleration 
time ($\beta = -0.203$; $P < 0.001$) and isovolumic relaxation time 
($\beta = -0.130$; $P = 0.028$). No independent relation existed be-
tween hemoglobin delivery in women and septal or PWT, 
relative wall thickness, or mitral valve E or A ratio.

Among men, hemoglobin delivery had positive independent 
relations to the mitral valve A velocity ($\beta = 0.186$; $P < 0.001$), 
LV internal dimension ($\beta = 0.188$; $P < 0.001$), midwall shorten-
ing ($\beta = 0.146$; $P = 0.001$), and LV mass ($\beta = 0.115$; $P = 0.016$) 
and negative relations to the mitral valve E/A ratio ($\beta = -0.144$; 
$P = 0.002$) and relative wall thickness ($\beta = -0.135$; $P = 0.003$) 
but was not related to septal or PWT, FS, E velocity, deceler-
tation time, or the isovolumic relaxation time.

Discussion

In the present study, we provide new evidence of several notable 
correlates of the level of systemic hemoglobin delivery. In both 
men and women, higher hemoglobin delivery was associated 
with more abnormal LV geometry, higher cardiac output, and 
Doppler evidence of less impaired LV relaxation. If the focus 
had been only on the level of hemoglobin, many of these 
correlations would have been missed, because most echocardio-
graphic parameters were not significantly related to hemoglobin 
level. Because it has been shown in previous studies that it is not 
just blood viscosity but also the level of oxygenation that 
determines the adequacy of the peripheral circulation, this study 
provides unique data that tie the 2 factors together. The present 
demonstration of a negative relation between hemoglobin deliv-
ery, with its attendant capacity to deliver oxygen to tissues, and 
peripheral resistance suggests that higher oxygen delivery does 
not lead to peripheral vasoconstriction in hypertensive patients 
who are well enough to participate in a long-term clinical trial.31

The association of higher hemoglobin delivery with larger LV 
chamber size and higher LV mass observed in both women and 
men in the present study is primarily because of the strong 
contribution of higher cardiac output to greater hemoglobin 
delivery. These findings help draw together several lines of 
evidence obtained in previous studies. First, a strong positive 
relation between Doppler stroke volume and LV mass, indepen-
dent of the level of blood pressure and other covariates, has been 
documented in a large, population-based sample.32 Second, 
higher cardiac output has been demonstrated in both mildly 
hypertensive patients19 and LIFe participants with more elevated 
blood pressure20 compared with age- and sex-matched
normotensive adults. Finally, higher fat-free mass, a major determinant of greater tissue oxygen demand, has been documented in hypertensive members of a population-based sample and related to higher cardiac output in that setting. Although fat-free mass was not measured in the LIFE study, it is attractive to speculate that greater tissue mass would have been present in patients with higher hemoglobin delivery and greater LV chamber size and mass in the population of this study.

Another novel and potentially important finding of the present study is that of negative relations between indices of impaired LV diastolic relaxation and hemoglobin delivery. Although Doppler features of abnormal LV filling, including reduced E/A ratio, and prolonged deceleration and isovolumic relaxation times, are detected in many hypertensive patients, the clinical significance of these findings is often unclear. The present observations suggest that impaired LV diastolic filling might, by reducing oxygen delivery, lead to greater fatigue and reduced exercise tolerance. Because these were not measured in the LIFE study, further research will be needed to address this possibility. These observations may be relevant to a spectrum of medical conditions. It is common for patients with renal disease and with anemia from diverse etiologies to be treated to improve hemoglobin levels. Whereas such interventions improve hemoglobin and may increase exercise tolerance, it is a clinical observation that blood pressure rises. Our study suggests that enhancement of hemoglobin delivery to peripheral tissues may contribute to this rise in blood pressure by increasing blood viscosity because of higher hemoglobin, as well as by a direct vasoconstrictive effect of administered erythropoietin. Further studies are needed to identify the optimal hemoglobin level and capacity to deliver oxygen for sound cardiovascular health with optimum cardiovascular outcomes.

Perspectives

Results of this study reveal that greater hemoglobin delivery is associated with more abnormal parameters of LV structure but also less abnormal diastolic function in patients with hypertension and LV hypertrophy. Most of the echocardiographic parameters did not, per se, correlate with the hemoglobin level; thus, it is important to look at both viscosity as determined by hematocrit level and the level of tissue oxygenation, as reflected by hemoglobin delivery, when determining the possible outcomes of therapies aiming to improve hemoglobin levels and oxygenation in patients with anemia of chronic disease.

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References


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