Anemia and the Heart

Hematocrit and Left Ventricular Mass: The Framingham Heart Study

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OBJECTIVES
The goal of this study was to investigate the relationship between hematocrit (Hct) and left ventricular mass index (LVMI) and LV hypertrophy (LVH) in subjects without known hypertension or cardiovascular disease in the Framingham Heart study.

BACKGROUND
Anemia may be an independent risk factor for cardiovascular disease in the general population. One potential explanation for this finding could be an association between Hct with LVMI or LVH.

METHODS
Linear and logistic regression analyses were used to evaluate the association between Hct with LVMI and LVH. All analyses were stratified by gender and further according to menopausal status in women.

RESULTS
There were 1,376 men and 1,769 women who met the inclusion criteria. The mean Hct and LVMI were 46.5% and 41.9%, and 127.3 and 95.8 g/m, respectively, in men and women. After adjustment for confounders, each 3% lower Hct was associated with a 2.6 g/m higher mean LVMI in men, and a 1.8 g/m higher mean LVMI in postmenopausal women (p<0.05). There was a significant quadratic relationship between Hct and LVMI in premenopausal women (p<0.01). Subjects in the lowest quartile of Hct (compared with the rest of the sample) had an adjusted odds ratio of LVH of 2.0 (95% confidence interval [CI] 1.3 to 3.0) in men and 1.4 (95% CI 0.8 to 2.4) in postmenopausal women.

CONCLUSIONS
In a sample without known hypertension or cardiovascular disease, a lower Hct is associated with echocardiographically determined LVH in men and a small but significantly higher LVMI in men and postmenopausal women. The clinical importance of these findings remains unknown. (J Am Coll Cardiol 2004;43:1276–82) © 2004 by the American College of Cardiology Foundation

Anemia is an independent risk factor for adverse cardiovascular outcomes in patients with kidney disease (1), patients with left ventricular (LV) dysfunction (2,3), and possibly in the general population (4). The mechanisms underlying these relationships, however, are unknown.

One potential mechanism for the adverse health effects associated with chronic anemia may be an increased cardiac output, which may lead to the development of ventricular dilation, increased LV mass (LVM), and left LV hypertrophy (LVH) (5–7). In turn, LVM and LVH are well established predictors of cardiovascular morbidity and mortality (8,9). In fact, there is evidence to suggest that experimentally induced anemia causes myocardial hypertrophy in a rat model (10). Furthermore, several studies suggest that anemia is associated with increased LVM and LVH in patients with kidney disease (11–14), and treatment of anemia may result in regression of LVH in patients with end-stage renal disease (15–17).

There are limited data, however, that have evaluated the relationship between level of hematocrit (Hct) with LVM or LVH in the general population. Previous community-based studies examining correlates of LVM have shown that a higher Hct is associated with higher LVM (18–20), but two recent reports have also suggested that lower levels of Hct (hemoglobin) are associated with increased LVM as well as LV dilation (21,22).

To investigate the relationship between Hct with LVM and LVH, we studied subjects without known hypertension or cardiovascular disease in the Framingham Heart study. We also examined the association of Hct with LV chamber size and wall thickness to better characterize the pattern of LVH.

METHODS

Study population and design. The Framingham Heart study is a prospective study established in 1948 to evaluate potential risk factors for coronary heart disease. The original cohort consisted of 5,209 male and female residents of Framingham, Massachusetts, ranging from 28 to 62 years of age at study entry. An additional 5,124 individuals (off-
Abbreviations and Acronyms

- Hct = hematocrit
- IVST = interventricular septum thickness
- LV = left ventricle/ventricular
- LVD = left ventricular diameter
- LVDI = left ventricular diameter index
- LVH = left ventricular hypertrophy
- LVMI = left ventricular mass index
- PWT = left ventricular posterior wall thickness

spring of the original Framingham cohort and their spouses) were enrolled into the Framingham Heart study beginning in 1971. The study design and selection criteria for both cohorts have been previously described (23–28). The data for our analyses were obtained from the public use database.

The current retrospective analysis includes participants undergoing the 16th biennial examination of the original Framingham Heart Study and the second biennial examination of the offspring cohort. Subjects were excluded from our analysis if they met any of the following criteria: 1) echocardiograms of inadequate quality to estimate LV mass; 2) history or clinical evidence of coronary heart disease (myocardial infarction, angina pectoris), valvular heart disease, pulmonary disease, hypertension, diabetes mellitus, or congestive heart failure; 3) receiving medications for the treatment of hypertension; 4) absence of height, weight, blood pressure, or Hct measurements (29). These exclusion criteria allowed us to evaluate the relationship between Hct with both LVM and LVH with less confounding from other variables. Our study sample was, therefore, comprised of 486 original cohort participants and 2,659 offspring cohort participants.

**Variable measurement.** At the time of echocardiographic examination, the following variables were measured: Hct, height, weight, and blood pressure. Serum creatinine was not measured at the time of the 16th examination for subjects in the original cohort and, therefore, was not included in our analyses. Hematocrit was measured using the Wintrobe method in the original cohort (30) and using a Coulter Counter in the offspring cohort (31). Height and weight were used to calculate body mass index (in kg per square meter). Systolic blood pressure was measured in the left arm in the seated position using a mercury column sphygmomanometer. Two physician-measured systolic blood pressures were averaged to derive the variables used for analysis (29). Smoking status was defined as either currently smoking at the time of visit (offspring cohort) or currently smoking at the time of the previous visit (original cohort). Smoking status was not available at the 16th visit of the original cohort.

**Echocardiographic methods.** M-mode echocardiograms were obtained on original cohort subjects undergoing their 16th biennial examination and offspring cohort subjects undergoing their second biennial examination. Two-dimensional guided M-mode echocardiograms were performed with subjects in the left lateral decubitus position from a parasternal window with a Hoffrel 201 ultrasound receiver (Hoffrel Instruments), an Aerotech 2.25-MHz transducer (K. B. Aerotech), and a Jason thermographic printer (32,33). Echocardiograms were read by Framingham Heart study investigators, and three measurements were made and averaged. All measurements were made in accordance with the American Society of Echocardiography recommendations (34). End diastolic measurements of LV diameter (LVD), interventricular septum (IVST), and LV posterior wall (PWT) were used to calculate LVM (in grams) from the following formula: 

\[ LVM = 1.05 \cdot (\text{LVD} + \text{PWT} + \text{IVST})^3 - \text{LVD}^3 \]

Left ventricular hypertrophy was defined as a LVM normalized for height (LV mass index [LVMI]) two SDs or more above the mean for a previously defined healthy reference group within the Framingham Heart study (33). Wall thickness was defined as the sum of IVST and PWT, and relative wall thickness was calculated as the ratio of wall thickness to LV diameter at end-diastole. Among the subjects who met the above criteria for LVH, eccentric LVH was defined as a relative wall thickness less than 0.45 (21).

**Correction of LV parameters.** It is well appreciated that heart size differs with body size (36). Previous work from the Framingham Heart study has shown a significant association between height and LVM (33). Accordingly, LVM, wall thickness, and end-diastolic internal diameter have all been normalized for height.

**Statistical methods.** Means, SDs, and percentages were used to describe baseline demographic and clinical characteristics. Data were stratified by gender (37) and further by menopausal status for women. We chose to stratify by menopausal status in women because of well-recognized changes in LV structure after menopause (38) and the effect of menstruation on premenopausal Hct. Tests of differences between groups were performed using chi-square tests for categorical variables and t tests for continuous variables.

All multivariable regression analysis models evaluating the association between Hct and LVMI contained variables that are known determinants of LVMI. These included age (39), body mass index (29), systolic blood pressure (40), and smoking status (41). Study cohort (original vs. offspring) was also included into the multivariable model for all subgroups. Age, body mass index, and systolic blood pressure were treated as continuous variables. Using ordinary linear least-squares regression, adjusted increments in LVMI were estimated for decreasing values of Hct. Further analyses estimated the adjusted means of LVMI by quartiles of Hct. A sensitivity analysis was performed to find the optimal dichotomous cutoff Hct value and compared to the lowest quartile value for each subgroup. Similar analyses were used to assess the relationship between Hct and end-diastolic LV diameter, wall thickness, and relative wall thickness.

We fitted restricted cubic splines for Hct in order to
assess the functional form of Hct and its relationship with the various outcomes (42). If the plot indicated a threshold to transform Hct into a binary variable, we searched for the optimal break point that maximized the multivariable model’s log likelihood. If a significant quadratic relationship existed, adjusted parameter estimates or odds ratios (OR) were estimated using the middle 50th percentile of the sample as the reference group.

Logistic regression analysis was used to estimate the adjusted OR (adjusting for the same variables as listed above) for LVH by quartiles of Hct. For subjects with LVH and low Hct, mean relative wall thickness was calculated to determine the pattern of LVH.

We tested for interactions between Hct and study cohort in men, postmenopausal women, and premenopausal women by including a cross-product term in the final model and retaining it if significant (p < 0.05).

Finally, we performed a sensitivity analysis for all outcomes after additional adjustment for those subjects who had either a systolic blood pressure >140 mm Hg or diastolic blood pressure >90 mm Hg despite not having a clinical history of hypertension or undergoing treatment for hypertension.

All statistical tests were two-tailed, and analyses were performed using SAS (Cary, North Carolina) version 8.2, and nonlinear associations were explored using S-Plus (Insightful Corp., Seattle, Washington) version 6.1.

RESULTS

Study participants. There were 1,376 men, 760 postmenopausal women, and 1,007 premenopausal women who were included in the analysis. The mean Hct and LVMI were 46.5%, 42.9%, 41.1%, and 127.3, 101.6, 91.4 g/m in men, postmenopausal women, and premenopausal women, respectively. A total of 486 of the subjects were from the original cohort, and 2,659 from the offspring study.

Quartiles of Hct were the following (%): 44.5, 46.4, 48.3 in men, 40.7, 42.9, 44.9 in postmenopausal women, and 39.3, 41.1, 42.9 in premenopausal women. The mean (median) Hct values in the lowest 25th quartile were 42.9 (43.3) in men, 39.0 (39.4) in postmenopausal women, and 37.4 (37.9) in premenopausal women. The clinical characteristics of the study population are further summarized in Table 1.

Relationship between Hct and LVM. In univariate analysis, Hct was not significantly associated with LVMI in men (p = 0.32) or postmenopausal women (p = 0.09). After adjusting for previously described confounders, there was a significant, but small, association between Hct and LVMI in men and postmenopausal women (Table 2, Figs. 1A and 1B). Each 3% lower Hct was associated with a 2.55 g/m higher mean LVMI in men (p < 0.001) and 1.80 g/m higher LVMI in postmenopausal women (p = 0.03). There were significant (p < 0.01) univariate and multivariable quadratic relationships between Hct and LVMI in premenopausal women (Table 2, Fig. 1C).

Adjusted mean LVMI is shown by quartile of Hct in Figure 2. Mean LVMI was 4.7% higher in men (p < 0.001) and 1.1% higher in postmenopausal women (p = 0.55), when the lowest quartile was compared with the rest of the sample. Mean LVMI was 2.8% higher in premenopausal women (p = 0.03) when comparing the lowest quartile with the middle 50th percentile of the sample.

Relationship between Hct and LVH. Criteria for LVH were met in 140 men (10.2%), 127 postmenopausal women, and 1,007 premenopausal women who were included in the analysis. The mean Hct and LVMI were

<table>
<thead>
<tr>
<th>Subject Characteristic</th>
<th>Men (n = 1,376)</th>
<th>Postmenopausal Women (n = 760)</th>
<th>Premenopausal Women (n = 1,007)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>45.2 (12.4)</td>
<td>58.7 (9.7)</td>
<td>38.1 (7.1)</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>46.5 (2.9)</td>
<td>42.9 (3.1)</td>
<td>41.1 (2.9)</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>123.1 (12.7)</td>
<td>125.6 (15.7)</td>
<td>112.4 (12.1)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>26.8 (3.3)</td>
<td>25.9 (4.2)</td>
<td>24.5 (4.2)</td>
</tr>
<tr>
<td>Height (meters)</td>
<td>1.8 (0.1)</td>
<td>1.6 (0.1)</td>
<td>1.6 (0.1)</td>
</tr>
<tr>
<td>Current smoking status (%)</td>
<td>33.8</td>
<td>30.4</td>
<td>35.3</td>
</tr>
<tr>
<td>Left ventricular mass, ASE (g)</td>
<td>223.2 (47.6)</td>
<td>161.2 (39.2)</td>
<td>147.9 (30.7)</td>
</tr>
<tr>
<td>Left ventricular mass adjusted for height (g/m)</td>
<td>127.3 (26.4)</td>
<td>101.6 (24.2)</td>
<td>91.4 (18.3)</td>
</tr>
<tr>
<td>Left ventricular diameter (mm)</td>
<td>51.0 (3.9)</td>
<td>45.0 (3.7)</td>
<td>46.4 (3.2)</td>
</tr>
<tr>
<td>Left ventricular wall thickness (mm)</td>
<td>19.2 (2.5)</td>
<td>17.6 (2.5)</td>
<td>15.8 (1.7)</td>
</tr>
<tr>
<td>Relative wall thickness</td>
<td>0.38 (0.06)</td>
<td>0.39 (0.07)</td>
<td>0.34 (0.04)</td>
</tr>
<tr>
<td>Prevalence of LVH (%)</td>
<td>10.2</td>
<td>16.7</td>
<td>5.6</td>
</tr>
</tbody>
</table>

All data are presented as means (SD) with exception of smoking and prevalence of left ventricular hypertrophy (LVH), which are presented as percentages.

ASE = American Society of Echocardiography.
The results of sensitivity analyses identifying optimal Hct cutoff values for men and postmenopausal women by maximizing the log likelihood ratio were similar to the 25th quartile cutoff values. Subjects in the lowest quartile of Hct (compared with the rest of the sample) had an adjusted OR for LVH of 2.0 (95% confidence intervals [CI] 1.3 to 3.0) in men, and 1.4 (95% CI 0.8 to 2.4) in postmenopausal women. Subjects in the lowest quartile of Hct (compared with the middle 50% percentile) had an adjusted OR of 1.4 (95% CI 0.6 to 3.0) in premenopausal women (Fig. 3).

Among subjects with LVH in the lowest quartile of Hct, the mean relative wall thickness was 0.42, 0.45, and 0.38 for men, postmenopausal, and premenopausal women, respectively.

### Table 2. Relationship of Hematocrit to LVM, End-Diastolic Dimension, and Wall Thickness

<table>
<thead>
<tr>
<th></th>
<th>LVM/ht</th>
<th>LVD/ht</th>
<th>SWT/ht</th>
<th>RWT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Men</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCT</td>
<td>0.72</td>
<td>0.18*</td>
<td>−0.06</td>
<td>−0.01*</td>
</tr>
<tr>
<td>HCT&lt;sub&gt;A&lt;/sub&gt;</td>
<td>2.55*</td>
<td>0.26*</td>
<td>0.03</td>
<td>−0.002</td>
</tr>
<tr>
<td>HCT&lt;sub&gt;25%&lt;/sub&gt;</td>
<td>5.88*</td>
<td>0.43*</td>
<td>0.19*</td>
<td>0.0006</td>
</tr>
<tr>
<td><strong>Postmenopausal Women</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCT</td>
<td>−1.43</td>
<td>0.17*</td>
<td>−0.21*</td>
<td>−0.01*</td>
</tr>
<tr>
<td>HCT&lt;sub&gt;A&lt;/sub&gt;</td>
<td>1.80*</td>
<td>0.25*</td>
<td>0.07</td>
<td>−0.001</td>
</tr>
<tr>
<td>HCT&lt;sub&gt;25%&lt;/sub&gt;</td>
<td>1.10</td>
<td>0.37</td>
<td>0.06</td>
<td>−0.003</td>
</tr>
<tr>
<td><strong>Premenopausal Women</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCT&lt;sub&gt;25%&lt;/sub&gt;U</td>
<td>2.57*</td>
<td>0.17</td>
<td>0.13</td>
<td>0.002</td>
</tr>
</tbody>
</table>

All values are parameter estimates, which refer to the coefficient for the hematocrit variable in the linear regression model. *p value <0.05.

HCT = parameter estimates for a decrease in hematocrit of 3% in univariate analysis; HCT<sub>A</sub> = parameter estimates for a decrease in hematocrit of 3% in multivariable analysis after controlling for age, systolic blood pressure, body-mass index, smoking status, and study cohort (original vs. offspring); HCT<sub>25%</sub> = fully adjusted parameter estimates comparing lowest quartile to rest of sample population; HCT<sub>25%M</sub> = fully adjusted parameter estimates comparing lowest quartile to middle 50% percentile; LVD/ht = end-diastolic left ventricular diameter indexed for height; LVM/ht = left ventricular mass indexed for height; RWT = relative wall thickness; SWT/ht = the sum of posterior wall and interventricular wall thickness at end-diastole indexed for height.

### Table 2. Relationship of Hematocrit to LVM, End-Diastolic Dimension, and Wall Thickness

### Figure 1.
(A) Relationship between hematocrit and left ventricular mass (LVM) index in men. (B) Relationship between hematocrit and LVM index in postmenopausal women. (C) Relationship between hematocrit and LVM index in premenopausal women. Hematocrit is treated as a continuous variable; LVM index is LVM normalized for height (g/m). All relationships shown are fully adjusted restricted cubic spline estimates for the relationship between hematocrit and LVM index. Other covariates in the multivariable model include: age, systolic blood pressure, body mass index, smoking status, and study cohort (original vs. offspring). Dashed lines = 95% confidence intervals.
Relationship between Hct and relative wall thickness.
After adjusting for confounders, there was no association between Hct and relative wall thickness in men, postmenopausal women, or premenopausal women (Table 2).

Interactions and sensitivity analysis. There were no significant interactions between Hct and study cohort with LVMI, LVDI, or LVH as outcomes in any of the subgroups.

In a sensitivity analysis after additional adjustment for subjects with a systolic blood pressure >140 mm Hg or diastolic blood pressure >90 mm Hg, the results did not significantly change (data not shown).

DISCUSSION
Chronic severe anemia is known to result in increased cardiac output that may lead to the development of LVH (5). The latter has been well appreciated in patients who are anemic secondary to kidney disease (11,43) and sickle cell disease (44). To the best of our knowledge, however, this association has not been demonstrated at less severe degrees of anemia in the general population. The results of our study suggest that, in subjects without known hypertension or cardiovascular disease, lower levels of Hct are associated with a small increase in LVMI in men and postmenopausal women, and increased LVH in men.

Previous studies evaluating the relationship between chronic anemia and adaptive changes in cardiac geometry have primarily focused on patients with kidney disease or other extreme forms of anemia. In fact, there are limited published data regarding this topic in the general population. Astor and colleagues (22) recently evaluated middle-aged African American participants of the Atherosclerosis Risk in Communities study and noted that lower levels of hemoglobin are associated with elevated LVMI and LV dilation (22). This analysis, however, included subjects with potentially confounding pre-existing conditions (e.g., hypertension and cardiovascular disease) and used hemoglobin values taken an average of three to six years before the time of echocardiogram. Our study evaluated subjects free of preexisting cardiovascular comorbidity who had Hct values taken at the time of echocardiography, and, therefore, allows for a more direct evaluation of the relationship between Hct and LVMI. In a smaller retrospective analysis, Schunkert and colleagues (21) demonstrated an association between lower Hct levels and LV dilation, suggesting a pattern of eccentric LVH at the lowest Hct extreme. The results of our study are consistent with these findings, and support the notion that chronically low levels of Hct may contribute to LV remodeling and potentially to the development of LVH in the general population.

Our study demonstrates a significant, albeit small, association between lower levels of Hct and higher LVMI in both men and postmenopausal women, a U shaped relationship between Hct and LVMI in premenopausal women, and an association between low levels of Hct and LVH in men. Although some of these differences may be due to power limitations, differences in cardiac remodeling between pre- and postmenopausal women and between men and women may be playing a role (38,45–47).

Given that LVH in the general population predicts cardiovascular morbidity and mortality (8), the association we have demonstrated between lower levels of Hct and LVH in men may be important. Furthermore, values in the lowest quartile of Hct were not as low as values previously thought to induce cardiac remodeling. For example, the
mean (median) Hct value in the lowest quartile in men was 42.9% (43.3%). This association raises the question as to whether a chronic Hct in the low-normal range may result in alterations in LV morphology.

Classically, anemia has been associated with eccentric LV growth, which is characterized by a proportionate increase in LV diameter and wall thickness. Most of the published data in support of this association has been derived in patients with kidney disease and patients with extreme forms of anemia (48–51). Our results suggest that the pattern of LVH associated with low Hct involves both an increase in wall thickness and an increase in LV cavity size. That is, the mean relative wall thickness did not change across levels of Hct supporting an association with eccentric LVH (Table 2). Furthermore, the mean relative wall thickness of those with LVH and low Hct remains less than or equal to 0.45 in all subgroups, which, by definition, is consistent with eccentric LVH (21). Thus, our findings are consistent with known physiologic processes in specific subpopulations and suggest a similar relation in otherwise healthy subjects.

Study limitations. There are potential limitations to the present study results. First, given the observational nature of our study, it is possible that the association between Hct and echocardiographic parameters of LVM is due to unrecognized confounding factors that affect both Hct and LVMI. We have attempted to address this limitation by excluding individuals with a history of diabetes, cardiovascular disease, or pulmonary disease. The observational design of the study, however, precludes our ability to ascribe cause and effect relationships. Second, our analysis only takes into account measurement of Hct at one point in time and, thus, duration of anemia is unknown. This may be less of a consideration for relatively healthy men and postmenopausal women who presumably have more stable blood counts. Hematocrit measurements in premenopausal women, however, inherently fluctuate more and are, thus, less reliable. In this respect, we note that the association between Hct and LVMI was different in the premenopausal subgroup.

Third, Hct was measured using different methods in the two Framingham Heart study cohorts. For each outcome, however, there was no significant interaction between Hct and cohort in men, postmenopausal women, or premenopausal women. Furthermore, we found similar parameter estimates for all continuous outcomes and similar adjusted ORs for LVH in all subgroups when stratifying by cohort (data not shown). Thus, we believe the difference in the method of Hct measurement between Framingham Heart study cohorts is less concerning. Moreover, any artificial variability in Hct values due to laboratory measurement would likely reduce, rather than enhance, the observed relationships between Hct and LVM.

Finally, the generalizability of our results is also limited in that all of the participants were Caucasian. Recent data from Astor et al. (22), however, describe a similar association between hemoglobin and LVMI in African American participants of the Atherosclerosis Risk in Communities study (22), suggesting a consistency of this relationship among different races.

Conclusions. The results of this study suggest that, in a large well-characterized sample without known hypertension or cardiovascular disease, a lower Hct is associated with echocardiographically determined LVH in men and a small, but significantly higher, LVM in men and postmenopausal women. The clinical importance of these findings remains unknown. Future studies are required to confirm this finding and to evaluate whether the relationship between Hct and LVM is due to a cause and effect relationship.

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REFERENCES