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Usefulness of the Blood Hematocrit Level to Predict Development of Heart Failure in a Community

Erin E. Coglianese, MD^{a,b}, Muhammad M. Qureshi, MBBS, MPH^{a,c}, Ramachandran S. Vasan, MD^{a,c}, Thomas J. Wang, MD^{a,d,†}, and Lynn L. Moore, DSc^{a,c,*}

^aFramingham Heart Study, Framingham, Massachusetts

^bCardiology Division, Loyola University Health System, Maywood, Illinois

^cPreventive Medicine and Cardiology Sections, Boston University School of Medicine, Boston, Massachusetts

^dCardiology Division, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts

Abstract

Current data suggest that increases in hemoglobin may decrease nitric oxide and adversely affect vascular function. In the preclinical setting, these changes could precipitate the development of heart failure (HF). We hypothesized that higher hematocrit (HCT) would be associated with an increased incidence of new-onset HF in the community. We evaluated 3,523 participants (59% women) from the Framingham Heart Study who were 50 to 65 years old and free of HF.

Participants were followed prospectively until an HF event, death, or the end of 20 years of follow up. HCT was subdivided into 4 gender-specific categories (women: HCT 36.0 to 40.0, 40.1 to 42.0, 42.1 to 45.0, >45.0; men: 39.0 to 44.0, 44.1 to 45.0, 45.1 to 49.0, >49.0). Gender-pooled multivariable Cox proportional hazards models were used to estimate the association of HCT with incident HF, adjusting for clinical risk factors. During the follow-up period (61,417 person-years), 217 participants developed HF (100 events in women). There was a linear increase in risk of HF across the 4 HCT categories (p for trend = 0.002). Hazards ratios for HF in the low–normal, normal, and high HCT categories were 1.27 (95% confidence interval 0.82 to 1.97), 1.47 (1.01 to 2.15), and 1.78 (1.15 to 2.75), respectively, compared to the lowest HCT category (p for trend <0.0001). Adjustment for interim development of other cardiovascular diseases and restriction of the sample to nonsmokers did not alter the results. In conclusion, higher levels of HCT, even within the normal range, were associated with an increased risk of developing HF in this long-term follow-up study.

Epidemiologic studies of the relation between hematocrit (HCT) and cardiovascular disease are inconsistent, and there are few data on the association of HCT with the development of heart failure (HF) in the community.^{1–3} We studied the association of HCT and HF in subjects in the Framingham Heart Study because investigating this relation in a primary prevention setting decreases the risk of confounding by active disease. We hypothesized that high HCT, even within the “normal range,” would be associated with a greater risk of new-onset HF.

Methods

The original Framingham Heart Study is a longitudinal cohort study focused on the epidemiology of cardiovascular disease. Subject selection and study design have been described previously.^{4,5} The targeted study population for these analyses included participants who were 50 to 65 years old and subjects were included whenever they first met the age criteria. Thus, the “baseline visit” ranged from biennial examinations 1 through 11. This age range was chosen so the baseline HCT studied would be reasonably proximate to any cardiovascular event.

Of the 5,209 participants enrolled at the first examination of the original cohort, 1,686 were excluded from the analyses because no data were available at ages 50 through 65 years (n = 147), data on HCT were missing (n = 308), follow-up data for HF were missing (n = 3), or data on potential confounders at the time of HCT measurement were missing (n = 789; 465 of whom were missing smoking data). Participants with prevalent HF (n = 34), cancer (n = 74), diabetes mellitus (n = 81), cerebrovascular accident (n = 21), or coronary heart disease (CHD; n = 154) were excluded, as were subjects with anemia (HCT <39 in men, <36 in women, n = 51) or who were underweight (body mass index <18 kg/m², n = 24). The final study sample consisted of 3,523 participants. All participants provided written informed consent and the study protocol was approved by the institutional review board of Boston University Medical Center.

All participants underwent clinical examination, measurement of anthropometry, electrocardiography, and laboratory examination, as described elsewhere.^{4,5} A single HCT (directly measured or converted from hemoglobin values) measured at the baseline examination was used in this study. HCT was measured at examinations 4 through 11 and hemoglobin at examinations 2 through 6. Data for hemoglobin and HCT from examination 4 were used to derive a conversion factor that was then applied to the hemoglobin data from examinations 2 and 3 to estimate HCT level at those examinations. Accuracy of the conversion factor was tested using data for subjects at examinations 5 and 6 as follows: HCT = hemoglobin × 3.2. The mean predicted HCT was virtually identical to the mean measured HCT and all differences between measured and predicted HCT values were very small. In addition, this conversion factor was very similar to that used in a previous study in the same sample.² HCT was measured using the Wintrobe method.²

Subjects were defined as having hypertension if they had a mean systolic blood pressure of 140 mm Hg or a mean diastolic blood pressure of 90 mm Hg on 2 consecutive Framingham examinations. In addition, all participants being treated with an antihypertensive medication were considered to have hypertension at the time of first report of such medications. Diabetes mellitus was defined as a fasting blood glucose level >125 mg/dl or use of insulin or oral hypoglycemic medications. Left ventricular hypertrophy was diagnosed based on electrocardiographic assessment. The physical activity index was calculated as the number of self-reported hours per day spent doing moderate or vigorous activities multiplied by a numeric weight derived from the oxygen consumption required (liters per minute) for that activity.⁶

Cigarette smoking is known to cause an increased HCT and is a strong predictor of cardiovascular disease risk.⁷ We included total pack-years of smoking as a potential confounder in the multivariable models. Because 461 participants were missing data for pack-years of smoking, we created a series of logical rules for data substitution in these cases. Such data substitution was used for approximately 9% of participants.

The primary end point of this study was incident HF. HF was defined by the presence of 2 major or 1 major and 2 minor criteria for HF (Framingham criteria). Major criteria included

paroxysmal nocturnal dyspnea, distended neck veins, rales, increasing heart size or pulmonary edema on chest x-ray, S₃, increased venous pressure (16 cm of water from the right atrium), and hepatjugular reflex. Minor criteria were bilateral ankle edema, night cough, dyspnea on ordinary exertion, hepatomegaly, pleural effusion, decrease in vital capacity by 1/3 from maximum recorded, or tachycardia (> 120 beats/min).⁸ Data were censored at 20 years of follow-up to minimize the effect of competing risks. Participants were followed until the first occurrence of HF, death, or the end of the 20-year follow-up.

Gender-specific quintiles of HCT were created. Because ranges of HCT in the third and fourth quintiles were narrow, HCT was collapsed into 4 distinct categories for analysis. For women, ranges of HCT within the 4 groups were 36.0% to 40.0% (low), 40.1% to 42.0% (low–normal), 42.1% to 45.0% (normal), and 45.1% (high). For men, ranges were 39.0% to 44.0% (low), 44.1% to 45.0% (low–normal), 45.1% to 49.0% (normal), and 49.1% (high). These gender-specific cutpoints were retained for all analyses.

Descriptive statistics were used to obtain baseline characteristics in the 4 HCT categories. Incidence of HF curves were created using the Kaplan–Meier method and differences among HCT categories were compared using log-rank test. We used multivariable Cox proportional hazards models to assess the association between baseline HCT and risk of developing HF, with adjustment for the following potential confounders that have been previously associated with HCT and risk of HF: age, gender, education level, body mass index, serum cholesterol, smoking history (pack-years), electrocardiographic left ventricular hypertrophy, prevalent hypertension, and physical activity level.⁹

We developed additional models incorporating time-dependent covariates to test whether associations with HCT were mediated by interim development of hypertension, CHD, cerebrovascular vascular accident (CVA), or diabetes. Definitions of CHD and CVA in the Framingham Heart Study have been described elsewhere.² We also repeated our analyses restricted to participants who were lifetime nonsmokers (0 pack-year at baseline examination) to minimize the likelihood of confounding by smoking-induced erythrocytosis.

All analyses were performed with SAS 9.1 (SAS Institute, Cary, North Carolina).

Results

Baseline characteristics of the sample are presented in Table 1 according to HCT category. Fifty-nine percent of participants were women. The average age of participants at baseline examination was 52 years. Subjects in the highest HCT category were younger, had higher systolic (statistically significant only in women) and diastolic blood pressures, higher cholesterol, and a higher prevalence of hypertension.

During 20 years of follow-up (61,417 person-years), 217 HF events occurred (100 events in women). Incidence of HF was highest in the high HCT category and lowest in the low HCT category (Figure 1). The log-rank p value for the difference between HCT categories was 0.03. Crude incidence rates per 10,000 person-years in each HCT category are presented in Table 2.

Table 3 presents the results of multivariable Cox proportional hazards analyses. Multivariable-adjusted hazard ratios (HRs) for HF were 1.27 (95% confidence interval [CI] 0.82 to 1.97), 1.47 (95% CI 1.01 to 2.15), and 1.78 (95% CI 1.15 to 2.75) for increasing HCT categories compared to the lowest HCT category that served as the referent (p for trend < 0.001). To compare these HRs with those for covariates, the HR for HF for prevalent hypertension was 2.01 (95% CI 1.51 to 2.68), the HR for female gender was 0.65 (95% CI

0.47 to 0.89), the HR for a 50-pack-year smoking history was 1.57 (95% CI 1.11 to 2.21), and the HR for development of CHD during follow-up was 3.65 (95% CI 2.72 to 4.91).

To evaluate whether the association between HCT and HF was mediated by hypertension, diabetes, CHD, or CVA occurring during the follow-up period, we performed analyses adjusting for these co-morbidities as time-dependent variables. Although the trend remained similar, only the high HCT group remained statistically significant (Table 3).

We performed additional analyses restricted to subjects who were lifelong nonsmokers. In total 1,584 subjects had a 0-pack-year smoking history at baseline examination (45% of study sample). Multivariable-adjusted HRs for HF were 1.62 (95% CI 0.82 to 3.19), 1.86 (95% CI 0.98 to 3.50), and 2.25 (95% CI 1.06 to 4.77) for increasing HCT categories compared to the lowest HCT category (p for trend <0.001). HRs after additional adjustment for interim hypertension, coronary disease, cerebrovascular disease, and diabetes in nonsmokers were 1.29 (95% CI 0.75 to 2.96), 1.73 (95% CI 0.92 to 3.28), and 2.22 (95% CI 1.04 to 4.74) for increasing HCT categories.

Discussion

We observed that higher HCT was associated with an increased risk of developing HF, even after adjusting for conventional HF risk factors. In lifetime nonsmokers, those in the highest HCT category (>45.0 for women, >49.0 for men) had >2 times the risk for HF. The strength of the association that we found is supported by the large well-characterized study sample, several decades of longitudinal follow-up, routine surveillance for HF with adjudication using standardized criteria, a sufficient number of events, and extensive characterization of and adjustment for potential confounders.

Although an association between HCT and incident HF has not been previously established, several previous studies have related baseline HCT to risks of cardiovascular disease, hypertension, and left ventricular remodeling. The association of HCT with cardiovascular events has been investigated by several groups, with varied results. In the Puerto Rico Heart Health Program, increased HCT in men (HCT $>49\%$) was associated with increased coronary events even after adjusting for risk factors such as smoking.¹ In a previous Framingham report, Gagnon et al² used a 2-year pooled observation method to evaluate the short-term effect of HCT on cardiovascular disease risk and found that low and high HCT levels were associated with increased risk. In contrast, investigators from the Honolulu Heart Study found no association between HCT and CHD.³ Our analysis differs from those studies in several important ways. In our analyses, we evaluated the long-term effect of HCT on incident HF risk using time-dependent survival modeling, accounting for interim development of conditions such as CHD, diabetes, and hypertension. The significant effect of high HCT on HF risk persisted after accounting for these factors, which suggests that the association between HF and HCT is not fully mediated by these other conditions. An additional strength of our analysis is the careful control of potential confounding by smoking. In addition to controlling for long-term pack-years smoked, we carried out subanalyses restricted to lifelong nonsmokers, thus eliminating potential confounding by this variable. This study confirms that high HCT is associated with an increased long-term risk of HF that is independent of smoking history.

There are several mechanisms by which HF and HCT could be associated. In studies of primary polycythemia vera, very high levels of HCT have been associated with increased blood pressure and risk of thrombosis.¹⁰ Although polycythemia vera represents an extreme, experimental studies have suggested that more modest increases in HCT could lead to vascular perturbations. One mechanism is nitric oxide (NO) scavenging by

hemoglobin.^{11–14} Because hemoglobin may act as a sink for NO, higher hemoglobin concentrations may result in decreased NO bioavailability. Decreased NO availability impairs flow-mediated dilation and may link increased HCT to the pathogenesis of hypertension and related disorders. For example, Madsen et al¹³ reported that hemoglobin concentration is inversely correlated with radial artery luminal diameter. Despite attenuation of the association of HCT with HF when incident hypertension was added to the model, the high HCT group remained significantly associated. Further work is needed to clarify the role that hypertension may play in the HCT–HF association.

Aside from associations with blood pressure and NO handling, increased HCT may be directly related to changes in cardiac structure and function, including left ventricular mass and diastolic function.^{15, 16} In the Multinational Monitoring of trends and determinants in cardiovascular disease (MONICA) Augsburg study, higher HCT levels were associated with a higher prevalence of concentric left ventricular hypertrophy¹⁵ and abnormal indices of diastolic function.¹⁶ In the study of diastolic function, the results were not attenuated by addition of blood pressure or body mass index to the models.

The relation between HCT and cardiovascular risk may be mediated by erythropoietin (EPO). In transgenic mice, overexpression of the EPO gene results in extremely high HCTs and leads to increased heart weight, left ventricular dilation, and decreased survival compared to wild-type mice.¹⁷ It has been proposed that erythropoietin-induced hypertension is a result of acquired NO resistance, increased cytosolic calcium concentration, or vascular cell hyperplasia and may be independent of increases in HCT.^{18, 19}

There are several limitations to our study. First, the Framingham Heart Study participants are primarily white and thus our findings may not be readily generalizable to other races and ethnicities. Second, despite attempting to address possible confounding factors and because of the observational design of our study, it is possible that unaccounted confounders are present in our analysis. Third, at the examinations used in this study, erythropoietin levels are not available. As mentioned previously, increased erythropoietin may be the factor that is associated with increased HF risk and increased HCT may simply be a marker of this finding. Further work to clarify the association between HCT and HF may provide important insights into the development of HF.

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Figure 1.

Kaplan–Meier curves for the incidence of heart failure. The referent group (*bottom curve*) consists of participants with low hematocrit. Low hematocrit: women 36% to <40%, men 39% to <44%; low–normal hematocrit: women 40.1% to <42%, men 44.1% to <45.1%; normal hematocrit: women 42.1% to <45%, men 45.1% to <49.0%; high hematocrit: women 45%, men 49.1%.

Table 1

Baseline characteristics of study population in gender- and hematocrit-specific categories

Variable	Men				Women			
	Low (n = 384)	Low–Normal (n = 219)	Normal (n = 594)	High (n = 240)	Low (n = 510)	Low–Normal (n = 503)	Normal (n = 727)	High (n = 355)
Age (years)	53.2 ± 3.7	52.3 ± 3.2	52.1 ± 3.1	51.2 ± 2.4	52.9 ± 3.7	53.3 ± 3.8	52.2 ± 3.2	51.9 ± 3.0
p Value	<0.001				<0.001			
Hematocrit (%)	42.2 ± 1.5	45.0 ± 0	47.2 ± 1.1	51.4 ± 1.6	39.0 ± 1.1	41.5 ± 0.5	43.9 ± 0.8	47.5 ± 1.9
p Value	<0.001				<0.001			
Body mass index (kg/m ²)	26.2 ± 3.4	26.4 ± 3.5	26.5 ± 3.4	26.7 ± 3.7	25.6 ± 3.9	26.0 ± 4.3	26.1 ± 4.5	26.5 ± 5.3
p Value	0.316				0.040			
Systolic blood pressure (mm Hg)	133 ± 20	133 ± 22	134 ± 20	136 ± 19	136 ± 23	137 ± 23	136 ± 23	140 ± 26
p Value	0.222				0.022			
Diastolic blood pressure (mm Hg)	83 ± 11	84 ± 12	85 ± 11	88 ± 11	83 ± 12	84 ± 12	84 ± 12	87 ± 14
p Value	<0.001				<0.001			
Pack-years smoked (years)	23.5 ± 22.0	23.8 ± 21.9	26 ± 22.8	27.6 ± 23	4.5 ± 9.3	4.8 ± 10.1	7.0 ± 11.9	12.1 ± 15.2
p Value	0.084				<0.001			
Serum total cholesterol (mg/dl)	227 ± 39	231 ± 39	236 ± 43	243 ± 41	239 ± 45	249 ± 44	251 ± 43	257 ± 46
p Value	<0.001				<0.001			
Physical activity index (hours)	9.5 ± 9.6	9.4 ± 10.4	9.2 ± 9.5	7.2 ± 7.7	5.0 ± 5.7	4.7 ± 4.9	5.2 ± 5.5	5.0 ± 5.6
p Value	0.014				0.493			
Education								
Less than high school	51%	43%	41%	35%	40%	43%	36%	32%
High school	26%	26%	31%	34%	34%	34%	33%	36%
More than high school	23%	32%	29%	31%	26%	24%	31%	32%
p Value	0.003				0.013			
Left ventricular hypertrophy								
No electrocardiographic left ventricular hypertrophy	95.6%	99.1%	96.1%	96.7%	97.4%	96.4%	96.8%	96.1%
Possible electrocardiographic left ventricular hypertrophy	1.6%	0.0%	1.2%	1.2%	0.8%	1.2%	0.7%	0.8%
Definite electrocardiographic left ventricular hypertrophy	2.9%	0.9%	2.7%	2.1%	1.8%	2.4%	2.6%	3.1%
p Value	0.373				0.848			
Hypertension								
Baseline	35%	34%	43%	50%	34%	40%	39%	47%
p Value	<0.001				0.001			
Follow-up	27%	28%	26%	21%	33%	29%	28%	27%
p Value	0.327				0.243			

Variable	Men				Women			
	Low (n = 384)	Low–Normal (n = 219)	Normal (n = 594)	High (n = 240)	Low (n = 510)	Low–Normal (n = 503)	Normal (n = 727)	High (n = 355)
Occurrence of coexistent diseases during follow-up								
Diabetes mellitus	6.2%	7.3%	8.2%	10.8%	4.1%	5.7%	4.9%	9.5%
p Value		0.221				0.005		
Coronary heart disease	18%	18%	22%	20%	11%	11%	13%	12%
p Value		0.371				0.668		
Cerebrovascular disease	3%	5%	5%	7%	4%	3%	3%	4%
p Value		0.131				0.827		

Values are expressed as mean $\pm$ SD or percentage. Low hematocrit: women 36% to <40%, men 39% to <44%; low–normal hematocrit: women 40.1% to <42%, men 44.1% to <45.1%; normal hematocrit: women 42.1% to <45%, men 45.1% to <49.0%; high hematocrit: women 45%, men 49.1%.

Table 2

Heart failure incidence according to hematocrit category

HCT Category*	Participants	Person-Years of Follow-Up	HF Cases	Rate per 10,000 Person-Years
Low	894	16,301	41	25.2
Low-normal	722	13,029	40	30.7
Normal	1,321	23,737	89	37.5
High	595	10,350	47	45.4

* Low: women 36% to <40%, men 39% to <44%; low-normal: women 40.1% to <42%, men 44.1% to <45.1%; normal: women 42.1% to <45%, men 45.1% to <49.0%; high: women 45%, men 49.1%.

Table 3

Results of multivariable analyses

HCT Category [*]	Multivariable-Adjusted HR (95% CI) [†]	Multivariable-Adjusted + Interim CVD Development [‡] HR (95% CI)	p Value for Trend
Low	Referent	Referent	
Low-normal	1.27 (0.82–1.97)	1.21 (0.78–1.87)	
Normal	1.47(1.01–2.15)	1.38(0.95–2.01)	
High	1.78(1.15–2.75)	1.58(1.02–2.44)	<0.0001

CVD = cardiovascular disease.

^{*} Low: women 36% to <40%, men 39% to <44%; low-normal: women 40.1% to <42%, men 44.1% to <45.1%; normal: women 42.1% to <45%, men 45.1% to <49.0%; high: women 45%, men 49.1%.

[†] Model adjusts for age, gender, education, physical activity, pack-years smoked, total cholesterol, electrocardiographic left ventricular hypertrophy, body mass index, and prevalent hypertension.

[‡] In addition to the above model, incident hypertension, diabetes, coronary heart disease, and cerebrovascular disease are included as time-dependent variables during follow-up.