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Impaired flow-mediated vasodilatation is associated with increased left ventricular mass in a multi-ethnic population. The Northern Manhattan Study

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Abstract

BACKGROUND—Increased left ventricular (LV) mass and endothelial dysfunction are important risk factors for cardiovascular mortality and morbidity. However, it is not clear whether endothelial dysfunction is associated with increased LV mass. We tested the hypothesis that impaired flow-mediated vasodilatation (FMD) is associated with increased LV mass in a population-based multi-ethnic cohort.

METHODS—As a part of the Northern Manhattan Study, we performed two-dimensional echocardiography and FMD assessment during reactive hyperemia by high-resolution ultrasonography in 867 stroke-free community participants. LV mass was calculated according to an established method. LV hypertrophy was defined as the 90th percentile of sex-specific LV mass indexed for body surface area among normal subjects. Multivariable models were used to test the association of FMD with LV mass.

RESULTS—In multiple linear regression analyses adjusting for age, sex, body mass index, systolic blood pressure, antihypertensive medications, low-density lipoprotein cholesterol, diabetes, smoking, hematocrit, and race-ethnicity, FMD was inversely associated with LV mass ($\beta = -1.21 \pm 0.56$, $P = 0.03$). The association persisted after further adjustment for any component of blood pressure (systolic, mean, and pulse pressure). In univariate logistic regression analysis, each 1% decrease in FMD was associated with a 8% higher risk of LV hypertrophy [odds ratio (OR) 1.08, 95% confidence interval (CI) 1.03–1.13 per each FMD point $P< 0.01$].

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CONCLUSIONS—Impaired FMD is associated with LV mass, independent of other factors associated with increased LV mass. Endothelial dysfunction might be a potential risk factor for LV hypertrophy.

Increased left ventricular (LV) mass is one of the most important prognostic factors for cardiovascular mortality and morbidity.[1,2] LV mass is known to be determined by various factors, such as blood pressure,[3,4] body size,[3,5] age,[6,7] sex,[8] race,[9] and insulin resistance.[10,11] Aging, hypertension, and obesity are the most powerful factors in explaining LV hypertrophy, but a portion of LV mass variance not accounted for by conventional risk factors may still exist.[12] Indeed, LV hypertrophy is observed even in normotensive subjects, and the prognostic impact of LV hypertrophy in them is similar to that seen in hypertensive subjects even after adjustment for established cardiovascular risk factors.[13]

Flow-mediated vasodilation (FMD) is a well-established noninvasive method to estimate endothelial function. FMD is thought to reflect the regulation of vascular tone and diameter mediated by contracting and relaxing factors. Endothelial nitric oxide (NO) is the most important in the latter group. In an experimental study, endothelial NO synthase-deficient mice were shown to develop age-related myocardial hypertrophy.[14] Furthermore, some previous reports indicated that the inhibition of NO synthase induced LV hypertrophy independent of arterial blood pressure level,[15,16] suggesting that the increase in hypertrophic response of cardiac myocytes in response to stimuli such as angiotensin II might contribute to LV hypertrophy,[17] although the mechanism is not clear. Accordingly, impaired FMD, which predominantly reflects reduced production of endothelial NO, could be of importance in the development of LV hypertrophy. There have been a few reports showing a significant association between impaired FMD and increased LV mass,[18–21] whereas one report could not find the association.[22] However, in these studies the subjects were excluded if they had established CV risk factors, including diabetes and hyperlipidemia and obvious hypertension. In addition, the sample size of those studies was not sufficient to allow adjustment for a number of potential covariates. Thus, the aim of the present study was to evaluate the association between peripheral endothelial function and LV mass in a multiethnic community-based cohort.

METHODS

Study subjects

Subjects were selected from the Northern Manhattan Study (NOMAS), a population-based prospective cohort study designed to investigate cardiovascular and stroke incidence, risk factors, and prognosis in a multi-ethnic sample (white, black, and Hispanics) from northern Manhattan. Recruitment modalities have been previously published.[23–25] Briefly, random digit dialing of approximately 25000 households was performed. Community participants were enrolled in NOMAS if they 1) had never had a stroke; 2) were over age 40 years; and 3) resided in Northern Manhattan for at least three months in a household with a telephone. As a part of the study, a subsample of stroke-free participants underwent transthoracic echocardiography and endothelial reactivity by FMD. FMD assessment was performed in 1070 NOMAS participants from January 1998 to April 2001. Nine hundred and nineteen (86%) subjects had images that were of sufficient quality for analysis. Subjects who had not undergone transthoracic echocardiography were excluded (n = 30) from this analysis. Among the remaining 889 subjects, those of race-ethnicity other than Black, Hispanic and White were also excluded from this analysis due to their small number (n = 22). Written informed consent was obtained from all subjects, and the study was approved by the Institutional Review Board of Columbia University Medical Center.

Baseline clinical evaluation

Baseline evaluation was performed at enrollment as previously reported.[24] Briefly, race-ethnicity was defined by self-identification in response to a questionnaire modeled after the US census.[23] Race-ethnicity group was categorized into three groups: Hispanics, black (non-Hispanic), and white (non-Hispanic). Cardiovascular risk factors were collected by direct interview using standardized questions adopted from the Centers for Disease Control and Prevention Behavioral Risk Factor Surveillance System[26] or by medical record review. Blood pressure was measured twice with a mercury sphygmomanometer and cuff of appropriate size in the sitting position. Pulse pressure was calculated as the difference between systolic and diastolic pressure. Mean arterial pressure was calculated as diastolic pressure plus one third of pulse pressure. Anthropometric measurements were determined by the use of calibrated scales. Blood samples were obtained in the fasting state, and standard enzymatic methods were used to determine baseline levels of total cholesterol, high-density lipoprotein (HDL) cholesterol and triglycerides. The Friedwald equation was used to calculate low-density lipoprotein (LDL) cholesterol. Fasting glucose was determined by standard glucose dehydrogenase method. Analyses were carried out by the Core Laboratory of the Irving Center for Clinical Research at Columbia University Medical Center using Hitachi 912 automated spectrometer (Hitachi, OH). Hypertension was defined as either a systolic blood pressure ≥140 mmHg or a diastolic blood pressure ≥90 mmHg, a patient's self-report of a history of hypertension, or a use of antihypertensive medication. Diabetes mellitus was defined by one or more of the following: a patient's self-report of use of insulin or oral hypoglycemic agents, or a fasting glucose ≥126 mg/dl. Hypercholesterolemia was defined by a patient's self-report of taking lipid lowering therapy, or a fasting total cholesterol level ≥240 mg/dl. Body mass index was calculated as weight (kg) divided by height (m) squared.

Flow-mediated vasodilatation assessment

FMD was measured by a standard method[27,28] as follows. Participants fasted for 12 hours, and avoided exercise for at least four to six hours prior to FMD examination.[27] The brachial artery diameter was measured 6 cm above the antecubital crease using a 15 MHz linear array transducer (Phillips 5500, Andover, MA). FMD was measured as the dilator response to reactive hyperemia induced by five-minute blood pressure cuff occlusion of the upper arm. The cuff was inflated to at least 50 mmHg above a systolic blood pressure to occlude arterial flow.[27]

End-diastolic images were acquired and digitized by a frame grabber (model LG3, Scion Corporation) at baseline and one minute after deflation.[27,29] A blinded reader analyzed brachial artery diameters off-line using analysis software. Three consecutive cardiac cycles were analyzed for both baseline and hyperemia studies of each subject, and the measurements averaged. The percent change in vessel diameter after reactive hyperemia was calculated according to the following formula:

$$\text{FMD}\,(\%) = 100 \times (\text{brachial artery diameter at peak hyperemia} - \text{diameter at rest}) / \text{diameter at rest}$$

Intra- and interobserver variability for FMD measurement was 1.3% and 2.7%, respectively (n = 15).

Echocardiographic evaluation

Transthoracic two-dimensional echocardiography was performed. LV mass was calculated from the corrected American Society of Echocardiography method[30];

$$\text{LV mass (g)} = 0.8[1.04\{(\text{LVDD}+\text{IVS}+\text{PWT})^3 - \text{LVDD}^3\}] + 0.6$$

where LVDD indicates LV diastolic diameter; IVS, interventricular septum thickness; PWT, posterior wall thickness.

Statistical analysis

The distributions of the variables of interest were examined. Means were calculated for continuous variables and proportions for categorical variables. Multiple linear regression analyses were used to determine the association between FMD and LV mass before and after adjusting for potential confounding demographic and clinical variables, including age, sex, race-ethnicity, body mass index, blood pressures (systolic blood pressure, mean blood pressure, and pulse pressure), antihypertensive medications, diabetes, past and current smoking, total cholesterol, HDL cholesterol, triglycerides, and LDL cholesterol levels. The variables that were considered to be associated with LVH in the previous studies or that were significantly associated with LV mass in the univariate analyses in our study were included in the multivariate models. For the categorical analyses, LV hypertrophy was defined as the 90th percentile of sex-specific LV mass, indexed for body surface area, among subjects who did not have hypertension, diabetes, coronary artery disease and had body mass index ≤30. These cutoff values were ≥113 g/m^2 for females and ≥125 g/m^2 for males. Multiple logistic analyses were also used to determine the odds ratio for LV hypertrophy before and after adjusting for potential variables as described before.

Statistical significance was determined at the $\alpha = 0.05$ level using two-sided tests. All analyses were conducted using SAS software, version 9.1 (SAS Institute, Cary, North Carolina).

RESULTS

Population characteristics

The mean age of the subjects was 67 ± 9 years; 43 % (n = 375) were men; 67% (n = 581) were Hispanic, 18% (n = 154) black non-Hispanic, and 15% (n = 132) white non-Hispanic. The baseline characteristics are shown in Table 1. Mean FMD for the overall study population was 5.7 ± 3.8%, and was similar among the various race-ethnic subgroups (5.8 ± 3.8 % in whites, 5.6 ± 3.7 % in Hispanics, and 5.8 ± 4.0 % in blacks, P = 0.965), and in both sexes (5.7 ± 3.6 % in males and 5.7 ± 3.9 % in females, P = 0.99).

FMD and LV mass in the overall population

Table 2 indicates coefficient correlations for FMD and LV mass in the overall population. Age, body mass index, systolic blood pressure, mean blood pressure, pulse pressure, and HDL cholesterol were significantly related to both FMD and LV mass.

In univariate linear regression analysis, FMD was significantly associated with LV mass as a continuous variable (β coefficient of LV mass per one percent increase in FMD = −2.59 ± 0.53, P < 0.001). In multiple linear regression analysis adjusting for age, gender, and race-ethnicity, the association between FMD and LV mass persisted (Table 3, Multivariate Model 1). The association remained statistically significant when additional cofactors were added to the model, including systolic blood pressure, mean blood pressure, and pulse pressure (Table 3, Multivariate Model 2–4). Since blood pressure levels are affected by antihypertensive treatment, we created a model adjusting for taking antihypertensive medications, which showed persisting inverse association between FMD and LV mass.

We also examined the relationship between FMD and LV hypertrophy. In univariate logistic regression analysis, each 1% decrease in FMD increased the risk of LV hypertrophy by 8% [odds ratio (OR) 1.08, 95% confidence interval (CI) 1.03–1.13 per each FMD point $P < 0.01$]. After adjusting for age, gender, and race-ethnicity, the relationship between FMD and LV mass persisted. After adjusting for cardiovascular risk factors and demographic factors (multivariate model in Table 3), FMD was no longer significantly associated with LV hypertrophy. Additionally, no significant interaction between FMD and systolic blood pressure was observed.

Subgroup analyses

Since both FMD and LV mass are strongly associated with hypertension, we performed a stratified analysis by hypertension status. In subjects with hypertension, an inverse trend between FMD and LV mass was observed in the multivariate linear regression analyses that included the covariates in the multivariate model 2 of Table 3, although it did not reach independent statistical significance, possibly because of the smaller sample size. (β coefficient of LV mass per one percent increase in FMD = -1.34 ± 0.74, $P = 0.07$). A significant trend was not observed in non-hypertensive subjects in the same multivariate model (β coefficient of LV mass per one percent increase in FMD = -0.71 ± 0.79, $P= 0.37$).

DISCUSSION

In this multiethnic community-based population, we demonstrated that impaired FMD was associated with increased LV mass, independent of well-known confounding factors. This relationship was observed regardless of arterial hypertension. Our study confirms the previous literature regarding this relationship, but expands the focus to a large sample of a multiethnic cohort, which allowed us to adjust for the effect for several variables associated with LV hypertrophy, which may have acted as confounders in previous studies.

Impact of FMD on LV hypertrophy independent of hypertension

In the present study, impaired FMD was associated with increased LV mass, even after adjusting for any component of blood pressure (systolic blood pressure, mean blood pressure, and pulse pressure). In addition, the significant association between impaired FMD and LV mass was independent of antihypertensive medications. LV hypertrophy also exists in normotensive subjects, and the prognostic impact of LV hypertrophy in them is similar to that seen in hypertensive subjects.[13] In addition, although antihypertensive treatment is effective for the regression of LV hypertrophy, significant LV hypertrophy persists in some patients even after antihypertensive treatment.[31] Moreover, those who have LV hypertrophy while on appropriate antihypertensive treatment have higher risk of cardiovascular events than those who experience regression of LV hypertrophy during treatment.[31] These findings suggest that factors other than blood pressure levels are important in inducing the regression in LV hypertrophy, and impaired FMD might be one of the factors involved preventing such regression.

Potential explanation for the association between impaired FMD and LV hypertrophy

The reason why FMD is inversely related to LV mass is not immediately clear. Some previous reports indicated that the inhibition of NO synthase induced LV hypertrophy independent of arterial blood pressure levels,[15,16] suggesting that an increased hypertrophic response of cardiac myocytes to stimuli such as angiotensin II might contribute to LV hypertrophy.[17] Furthermore, other indirect mechanisms might exist. One plausible explanation for this association is that impaired FMD is associated with an increase in LV wall stress via increased arterial stiffness. Physiologically, the stiffness of the large artery depends on structural and functional factors, namely structural elements within the arterial

wall (such as elastin and collagen) and vascular smooth muscle cell tone, which is regulated mainly by endogenous NO.[32,33] Accordingly, impaired FMD, which predominantly reflects impaired NO formation, might be associated with increased arterial stiffness. Furthermore, increased systemic arterial stiffness may lead to LV hypertrophy through its impact on pulse wave velocity and the augmentation of systolic central pressure by early-reflected waves.[34] Therefore, impaired FMD might cause LV hypertrophy through the increase in LV wall stress. Interestingly, a previous report indicated that FMD is related to LV mass even when maximal dipyridamole-dependent coronary flow reserve is preserved.[35] In the present study, we demonstrated the association between FMD and LV mass independent of three components of blood pressure, suggesting that a mechanism other than a hemodynamic effect might be involved in the association.

Another explanation for the association between FMD and LV mass could be that other covariates are at play, and may interact with FMD. In this study, the association between FMD and LV mass remained significant after adjusting for established covariates. However, unidentified covariates may exist, of which inflammatory markers could be an example. Previous studies showed that elevated serum levels of C-reactive protein are associated with LV hypertrophy in diabetic[36] and hypertensive[37] patients. Similarly, elevated serum levels of C-reactive protein in patients with coronary artery disease were associated with systemic endothelial vasodilator dysfunction.[38,39] In a recent study, inflammation-mediated arterial stiffening appeared to lead to LV hypertrophy in patients with systemic lupus erythematosus.[40,41] Thus, inflammation might be one of the possible explanations for our results.

Study strength and limitations

A major strength of our study is its community-based multiethnic cohort with sufficient number of subjects and in-depth baseline assessment and medical history. Nevertheless, our study has some limitations. Due to the cross-sectional design, we cannot discuss cause-effect relationship of FMD and LV mass. Possible confounding factors, such as C-reactive protein, insulin resistance, and indices of subclinical atherosclerosis, were not included in the present study. The possible effect of previous cardiovascular events, and the influence of treatment with cardiovascular drugs, could both affect the results of the present study. Also, since most of the subjects in our population are elderly, the results cannot be applied to a younger population. Finally, as endothelium-independent vasodilatation with nitrates was not examined in the present study, we cannot determine the specific impact of endothelial dysfunction due to nitric oxide release/production deficit.

Conclusions

Impaired FMD was associated with LV mass, independent of other factors associated with increased LV mass. Endothelial dysfunction might be a potential risk factor for LV hypertrophy.

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Table 1

Population characteristics

	Mean ± s.d. or Number (%)				
Characteristic	**Overall**	**Subgroups stratified by FMD**			**P for trend**
		1st tertile	**2nd tertle**	**3rd tertile**	
Total sample	867	289	289	289	
Age (yrs)	67 ± 9	68 ± 9	66 ± 9	66 ± 8	<0.01
Male sex (%)	375 (43.3)	119 (41.2)	139 (48.1)	117 (40.5)	0.12
Race-ethnicity					0.93
White (%)	132 (15.2)	44 (15.2)	40 (18.0)	48 (16.6)	
Hispanic (%)	581 (67.0)	194 (67.1)	197 (68.2)	190 (65.7)	
Black (%)	154 (17.8)	51 (17.7)	52 (13.8)	51 (17.7)	
Body mass index (kg/m^2)	28 ± 5	29 ± 5	28 ± 5	27 ± 5	<0.01
Systolic blood pressure (mmHg)	143 ± 19	146 ± 20	143 ± 19	140 ± 18	<0.01
Diastolic blood pressure (mmHg)	84 ± 10	84 ± 11	85 ± 10	83 ± 11	0.28
Mean blood pressure (mmHg)	104 ± 12	105 ± 12	104 ± 12	102 ± 12	0.050
Pulse pressure (mmHg)	59 ± 16	63 ± 17	59 ± 16	57 ± 15	<0.01
Hypertension (%)	588 (67.8)	225 (77.9)	194 (67.1)	169 (58.5)	<0.01
Total cholesterol (mg/dl)	202 ± 40	204 ± 39	200 ± 40	203 ± 40	0.50
LDL cholesterol (mg/dl)	131 ± 36	132 ± 36	128 ± 36	131 ± 36	0.30
HDL cholesterol (mg/dl)	46 ± 14	45 ± 13	45 ± 14	47 ± 15	0.10
Fasting glucose (mg/dl)	105 ± 49	109 ± 50	105 ± 51	101 ± 46	0.15
Diabetes (%)	199 (23.0)	78 (27.0)	68 (23.5)	53 (18.3)	0.045
Ever smoked (%)	469 (54.2)	142 (49.3)	164 (56.8)	163 (564)	0.13
Current smoking (%)	139 (16.2)	34 (12.0)	60 (21.0)	45 (15.6)	0.01
Hematocrit (%)	41 ± 4	41 ± 4	42 ± 4	41 ± 4	0.047
LV mass (g)	179 ± 60	188 ± 66	184 ± 61	166 ± 49	<0.01
LV mass index (g/m2)	100 ± 31	104 ± 35	103 ± 33	94 ± 25	<0.01
LV hypertrophy (%)	170 (19.6)	69 (23.9)	58 (20.1)	43 (14.9)	0.02
FMD (%)	5.7 ± 3.8	1.6 ± 1.3	5.4 ± 1.1	10.0 ± 2.2	<0.01
Taking any medicine	698 (80.8)	244 (84.7)	232 (80.6)	222 (77.1)	0.02
Taking anti-hypertensive medicine	382 (53.2)	159 (63.6)	126 (52.7)	97 (42.4)	<0.01

	Mean ± s.d. or Number (%)				
Characteristic	**Overall**	**Subgroups stratified by FMD**			**P for trend**
		1st tertile	**2nd tertle**	**3rd tertile**	
Medications at entry					
Beta-blocker (%)	41 (4.8)	19 (6.6)	13 (4.5)	9 (3.1)	0.14
ACE-inhibitor (%)	42 (4.9)	19 (6.6)	14 (4.9)	9 (3.1)	0.15
Calcium channel blocker (%)	39 (4.5)	21 (7.3)	11 (3.8)	7 (2.4)	0.01
Diuretics (%)	122 (14.1)	51 (17.8)	32 (11.1)	39 (13.5)	0.07
Cholesterol lowering agents (%)	160 (18.5)	62 (21.6)	49 (17.0)	49 (17.0)	0.26
Aspirin (%)	238 (27.6)	86 (30.0)	74 (25.7)	78 (27.1)	0.51
Insulin (%)	36 (4.2)	18 (6.3)	11 (3.8)	7 (2.4)	0.07
Oral hypoglycemic (%)	126 (14.6)	57 (19.9)	37 (12.9)	32 (11.2)	<0.01

LV hypertrophy was defined as the 90th percentile of sex-specific LV mass, indexed for body surface area, among subjects who did not have hypertension, diabetes, coronary artery disease and had body mass index ≤30. Data are expressed as mean ± s.d.

ACE, angiotensin converting enzyme; FMD, flow-mediated vasodilatation; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Table 2

Coefficient correlations for LV mass and FMD

Valuables	For LV mass		For FMD	
	r	P	r	P
FMD (%)	−0.163	<0.01	n/a	
LV mass (g)	n/a		−0.163	<0.01
Age (yrs)	0.067	0.049	−0.148	<0.01
Body mass index (kg/m^2)	0.165	<0.01	−0.141	<0.01
Systolic blood pressure (mmHg)	0.187	<0.01	−0.126	<0.01
Diastolic blood pressure (mmHg)	0.098	<0.01	−0.009	0.79
Mean blood pressure (mmHg)	0.160	<0.01	−0.074	0.03
Pulse pressure (mmHg)	0.160	<0.01	−0.145	<0.01
Total cholesterol (mg/dl)	−0.155	<0.01	0.244	0.489
LDL cholesterol (mg/dl)	−0.116	<0.01	0.009	0.80
HDL cholesterol (mg/dl)	−0.086	0.01	0.088	0.01
Fasting glucose (mg/dl)	0.016	0.64	−0.070	0.04
Hematocrit (%)	0.061	0.08	0.026	0.46

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Table 3

Association between left ventricular mass, flow-mediated vasodilatation, other demographic and clinical variables

Variables	Univariate		Multivariate 1		Multivariate 2		Multivariate 3		Multivariate 4	
	β ± s.e.	P	β ± s.e.	P	β ± s.e.	P	β ± s.e.	P	β ± s.e.	P
FMD (%)	−2.59 ± 0.53	<0.01	−2.47 ± 0.50	<0.01	−1.21 ± 0.56	0.03	−1.31 ± 0.57	0.02	−1.20 ± 0.57	0.03
Age (yrs)	0.46 ± 0.23	0.049	0.42 ± 0.22	0.06	0.36 ± 0.25	0.14	0.54 ± 0.25	0.03	0.34 ± 0.26	0.19
Male sex	42.09 ± 3.85	<0.01	43.95 ± 3.77	<0.01	50.28 ± 4.76	<0.01	49.96 ± 4.78	<0.01	50.30 ± 4.76	<0.01
Race-ethnicity										
Hispanic vs White	−2.77 ± 5.73	0.63	3.83 ± 5.41	0.48	−0.55 ± 6.00	0.93	−1.39 ± 6.05	0.82	−0.39 ± 6.04	0.95
Black vs White	18.80 ± 7.05	<0.01	26.80 ± 6.52	<0.01	10.99 ± 7.58	0.15	11.78 ± 7.60	0.12	11.01 ± 7.59	0.15
Body mass index (kg/m^2)	1.95 ± 0.40	<0.01			1.81 ± 0.44	<0.01	1.81 ± 0.44	<0.01	1.81 ± 0.44	<0.01
Systolic blood pressure (mmHg)	0.57 ± 0.10	<0.01			0.49 ± 0.11	<0.01				
Mean blood pressure (mmHg)	0.81 ± 0.17	<0.01					0.69 ± 0.19	<0.01	0.45 ± 0.21	0.04
Pulse pressure (mmHg)	0.59 ± 0.12	<0.01							0.36 ± 0.16	0.02
Anti-hypertensive medication	19.87 ± 4.54	<0.01			9.94 ± 4.46	0.03	9.74 ± 4.55	0.03	10.14 ± 4.54	0.03
LDL cholesterol (mg/dl)	−0.19 ± 0.06	<0.01			−0.11 ± 0.06	0.048	−0.12 ± 0.06	0.048	−0.11 ± 0.06	0.051
Fasting glucose (mg/dl)	0.02 ± 0.04	0.64								
Diabetes	17.84 ± 4.80	<0.01			6.01 ± 4.86	0.22	6.64 ± 4.88	0.17	5.95 ± 4.87	0.22
Ever smoked	13.94 ± 4.06	<0.01			7.05 ± 4.23	0.10	7.71 ± 4.24	0.07	6.97 ± 4.24	0.10
Hematocrit (%)	1.00 ± 0.56	0.08			−1.29 ± 0.64	0.04	−1.37 ± 0.64	0.03	−1.27 ±0.64	0.047