

Association of white blood cell counts with left ventricular mass index in hypertensive patients undergoing anti-hypertensive drug therapy

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Abstract. Although studies using animal models have demonstrated that nonhemodynamic factors, including inflammatory cells and cytokines, contribute to left ventricular hypertrophy (LVH), there is little clinical data to confirm this association. Therefore in the present study, levels of circulating specific types of leukocyte were measured to determine the association between white blood cells and left ventricular mass index (LVMI) in hypertensive patients undergoing anti-hypertensive drug therapy. A total of 144 consecutive hypertensive patients taking anti-hypertensive drug therapy were enrolled in the current study. Subjects were divided into two groups: Those with normal geometry and those with left LVH. Total white blood cells and differentiated subtypes (neutrophils, lymphocytes, monocytes) were counted, and left ventricular end-diastolic diameter, left ventricular posterior wall thickness in diastole and inter-ventricular septal wall thickness in diastole

were all measured. Analysis revealed a significant correlation between LVMI and total white blood cell levels ($P=0.013$). The percentage of LVH in the highest tertile of WBC was increased compared with the middle tertile ($P=0.008$). Furthermore, a significant correlation between the highest tertile of neutrophil counts and LVH was observed ($P=0.039$). However, no significant associations between LVMI and monocyte or lymphocyte counts were detected. Therefore, the current study determined that increased total white blood cell and neutrophil subtype counts were associated with LVMI in hypertensive patients undergoing anti-hypertensive drug therapy. They may provide convenient and useful markers for further risk appraisal of LVH caused by nonhemodynamic factors of hypertension.

Introduction

The incidence of hypertension is increasing year by year and may cause severe organ damage and increase the risk of patient mortality (1,2). Hypertensive heart disease (HHD) may be associated with diastolic and systolic heart dysfunction, and eventually lead to heart failure (3,4).

The primary pathological characteristic of HHD is left ventricular hypertrophy (LVH), which is independently associated with a number of cardiovascular endpoints, including coronary heart disease and stroke (5). Therefore, hypertensive patients with LVH have an increased risk of experiencing cardiovascular events compared to hypertensive patients without LVH (6,7).

There is a strong correlation between high blood pressure and LVH (8,9). However, it has been indicated that nonhemodynamic factors, including transforming growth factor β 1, the renin-angiotensin system and tumor necrosis factor α may induce profibrotic effects and proinflammation, thus contributing to LVH (10,11). Furthermore, studies using

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animal models have demonstrated that macrophage, T cell and monocytic fibroblast precursors serve important roles in angiotensin II infusion-induced or pathological cardiac remodeling (12-15).

Although studies using animal models have demonstrated that nonhemodynamic factors, including inflammatory cells and cytokines, contribute to left ventricular hypertrophy (LVH) (12,14), there is little clinical data to confirm this association. Based on the aforementioned results, the present study aimed to determine whether circulating leukocyte subtypes are associated with LVH in hypertensive patients treated with anti-hypertensive drugs.

Patients and methods

Patients. A total of 144 consecutive hypertensive patients currently taking anti-hypertensive drug therapy were enrolled in the current study between January 2012 and December 2014 in the Department of Cardiology, Beijing Friendship Hospital, Capital Medical University (Beijing, China). All enrolled patients had a 5-20 year history of hypertension and had all previously taken anti-hypertensive drugs. Exclusion criteria included secondary hypertension, heart failure symptoms, idiopathic cardiomyopathy, ischemic heart disease and the presence of other heart diseases. Blood pressure (BP) was measured at an office at the Beijing Friendship Hospital on two separate occasions. A calibrated mercury sphygmomanometer was used while patients were seated following a 10 min rest. Normal BP was defined as systolic BP (SBP) of 90-140 mmHg or diastolic BP (DBP) of 60-90 mmHg (16,17). Patients were excluded from the current study if they had secondary hypertension, heart failure symptoms, idiopathic cardiomyopathy, ischemic heart disease or other heart diseases. Patient characteristics are summarized in Table I. The protocol of the current study was approved by the Institutional Committee of the Capital Medical University (Beijing, China) and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Written informed consent was given by all patients.

Laboratory analyses. Baseline clinical data was collected for all patients. Counts for total white blood cells (WBC) and differentiated subtypes (neutrophils, lymphocytes, monocytes, eosinophils and basophils) were measured immediately following presentation using peripheral venous blood in an automated blood cell counter (ADVIA 2120; Siemens Healthcare Diagnostics, Camberley, UK). The WBC count was treated as a continuous and categorical variable and was classified as low ($<6.65 \times 10^9/l$, <33 th percentile), intermediate ($6.65-10.11 \times 10^9/l$, 33th-66th percentiles) or high ($>10.11 \times 10^9/l$, >66 th percentile) (18,19). Alanine transaminase, creatinine, blood urea nitrogen, cholesterol, triglycerides, uric acid and glucose were measured using an established immunoassay (Biosite Inc., San Diego, CA, USA). Quantitative C-reactive protein determination was performed with the BN II Nephelometer (Siemens Healthcare Diagnostics). Cardiac troponin T was measured on the Elecsys 10/10 (Roche Diagnostics, Indianapolis, IN, USA).

Evaluation of cardiac structure and function. Echocardiographic examination of the patients was performed

by two experienced cardiologists using a VIVID 7 cardiovascular ultrasound system (GE Healthcare Life Sciences, Uppsala, Sweden) with an M4S 1.5-4.0-MHZ matrix array probe (GE Healthcare Life Sciences) according to the guidelines of the American Society of Echocardiography (20). Echocardiographic examination was performed with patients in the left lateral decubitus position breathing slowly. The cardiologists were blinded to the patients' other data. The echocardiograph measurements included left ventricular end-diastolic diameter (LVEDD), left ventricular posterior wall thickness in diastole (LVPWT) and inter-ventricular septal wall thickness in diastole (IVST). Left ventricular systolic function was assessed using the left ventricular ejection fraction (LVEF) and left ventricular fractional shortening (LVFS). Left ventricular mass was calculated using the ASE-recommended formula: Left ventricular mass (g) = $0.8 \times \{1.04[(IVST + LVEDD + LVPWT)^3 - (LVEDD)^3]\}$ (21). Left ventricular mass was divided by body surface area to obtain the left ventricular mass index (LVMI). Body surface (m^2) was calculated using $(0.0061 \times \text{height} + 0.0124 \times \text{weight} - 0.0099)$. LVH was defined as previously described (22,23). Patients were divided into two different groups according to LVMI. One group consisted of patients with lower LVMI ($\leq 100 \text{ g}/m^2$) and the other group consisted of patients with higher LVMI ($>100 \text{ g}/m^2$).

Statistical analysis. Data analysis was performed using the SPSS statistical package ver. 16.0 for Windows (SPSS Inc., Chicago, IL, USA). Differences in the distribution of demographics, laboratory parameters and medical characteristics among hypertensive patients with lower LVMI, compared with those who had higher LVMI, were examined using the χ^2 test for categorized variables and either one-way analysis of variance for continuous variables, or non-parametric tests if distribution was skewed. Multivariate logistic regression analyses were performed to examine the associations of total white blood cell and other potentially confounding prognostic factors with LVMI. Other factors included in the multivariate analyses were age, gender, hypercholesterolemia, diabetes mellitus and medication (aspirin, β -blockers, calcium-channel blockers, angiotensin converting enzyme inhibitor and aldosterone receptor blocker). All P-values were the results of two-tailed tests. A value of $P < 0.05$ was considered to indicate a statistically significant difference.

Results

White blood cells are increased in patients with LVMI. Clinical characteristics of all patients are presented in Table I. At baseline, the 41% of the study population were male and the mean age was 53.7 years [range 44-66 years, standard deviation (SD) 5.8 years]. Out of all the patients, 10% had diabetes mellitus and 28% had hyperlipidemia. The mean SBP and DBP (mmHg) were 121.2 (SD 18.8) and 74.0 (SD 11.3). Blood platelet, hemoglobin, serum creatinine, urea nitrogen and uric acid levels did not significantly differ between the two groups. The drug treatments received by patients in the two groups were not significantly different.

Cardiac remodeling caused by hypertension is accepted as an inflammatory response (14,15) in which inflammatory cells

Table I. Clinical characteristics of patients in each group.

Characteristic	Lower LVMI	Higher LVMI	P-value
Age, years	59.4±12.8	61.9±12.6	0.301
Proportion of males, %	55.7	61.5	0.526
Systolic blood pressure, mmHg	138.2±23.6	145.8±23.7	0.086
Diastolic blood pressure, mmHg	87.0±12.6	84.1±14.6	0.384
Hyperlipidemia, %	12.3	15.8	0.582
Diabetes mellitus, %	23.6	13.2	0.174
Laboratory parameters			
Blood platelet, 10 ⁹ /l	218.0±57.4	228.3±60.8	0.354
Hemoglobin, g/l	136.7±14.9	131.7±12.4	0.065
Serum creatinine, μmol/l	83.7±37.6	88.6±37.3	0.493
Blood urea nitrogen, mmol/l	6.29±7.65	6.95±4.97	0.622
Blood uric acid, μmol/l	324.7±105.6	355.1±89.1	0.116
Medicine			
ACEI and/or ARB	67.0%	66.7%	0.945
Calcium-channel blockers	51.0%	51.3%	0.971
β-Blocker	47.2%	41.0%	0.510
Aspirin	52.8%	56.4%	0.701

Values are the mean ± standard error of the mean, unless otherwise indicated. ACEI, angiotensin converting enzyme inhibitor; ARB, aldosterone receptor blocker; LVMI, left ventricular mass index.

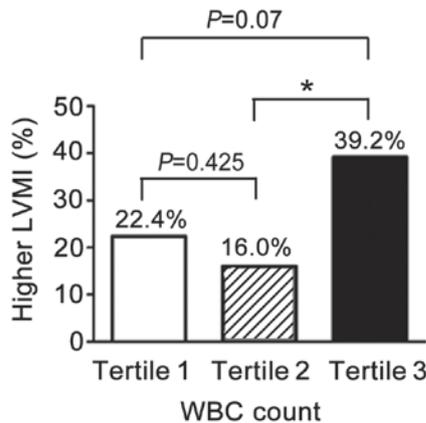


Figure 1. Proportion of patients with higher LVMI according to WBC count tertiles. Tertile 1, lowest tertile (n=48); tertile 2, middle tertile (n=48), tertile 3, highest tertile (n=48). *P<0.05, indicating a significant difference. LVMI, left ventricular mass index; WBC, white blood cell.

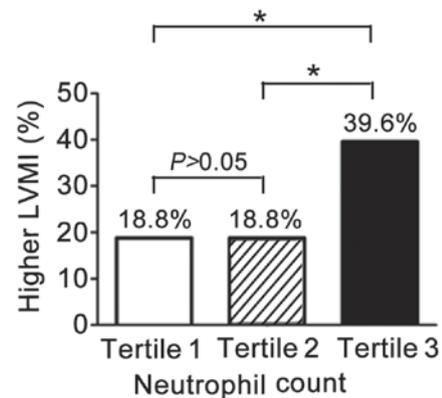


Figure 2. Proportion of patients with higher LVMI according to neutrophil count tertiles. Tertile 1, lowest tertile (n=48), tertile 2, middle tertile (n=48), tertile 3, highest tertile (n=48). LVMI, left ventricular mass index. *P<0.05, indicating a significant difference.

play a critical role. Therefore the current study measured levels of WBC. The LVMI of the study population by tertiles of total WBC level is presented in Fig. 1. In the middle tertile (Tertile 2, n=44), 16% of patients had higher LVMI, indicative of myocardial hypertrophy (MH), which was lower than that in the highest tertile (Tertile 3, n=51; P=0.012). Notably, in the lowest tertile (Tertile 1, n=49) 22.4% of patients had MH, higher than in the middle tertile (Tertile 2), however, this difference was not statistically significant (22.4% vs. 39.2%, P=0.425).

Neutrophil counts correlate with LVMI. To determine which specific leukocyte types have a critical role in

hypertension-induced MH, different WBC subtypes were measured. The LVMI of the study population by tertile of neutrophil counts is presented in Fig. 2. A high LVMI indicates the presence of MH. The proportion of patients with MH in both the lowest (n=48) and middle tertile (n=48) was 18.8%. However, a larger proportion (39.6%) of patients in the highest tertile had MH (18.8% vs. 39.6%, P=0.012) compared with the middle and lowest tertiles.

As presented in Fig. 3, other subtypes of WBC were detected. A slightly higher proportion of patients had MH (31.3%) in the middle tertile (n=48) compared with the other tertiles; the percentages in the lowest tertile (n=46) and highest tertile (n=50) were 25.0 and 22.0% respectively (P=0.582;

Table II. Multivariate logistic regression analyses for left ventricular mass index in hypertensive patients.

Variable	B	OR	95.0% C.I. for EXP (B)		P-value
			Lower LVMI	Higher LVMI	
Total WBC count					0.013 ^a
WBC Tertile (lowest)	0.364	1.439	0.478	4.338	0.518
WBC Tertile (highest)	1.415	4.117	1.452	11.693	0.008 ^a
Old age (>65 years)	0.865	2.374	1.037	5.473	0.042 ^a
Male (%)	-0.314	0.731	0.312	1.716	0.469
Hypercholesterolemia	0.414	1.512	0.493	4.636	0.469
DM	-0.934	0.395	0.126	1.237	0.111
ACEI or ARB	-0.047	0.955	0.507	1.796	0.885
CCB	-0.011	0.989	0.444	2.203	0.979
Aspirin	0.165	1.179	0.517	2.693	0.695
β-blocker	-0.277	0.758	0.339	1.695	0.511

^aP<0.05, high LVMI group vs. low LVMI group. WBC, white blood cell; DM, diabetes mellitus; ACEI, angiotensin converting enzyme inhibitor; ARB, aldosterone receptor blocker; CCB, calcium-channel blockers; LVMI, left ventricular mass index; C.I., confidence interval; OR, Odds Ratio; EXP, Exponential; B, Basic data.

Fig. 3A). As presented in Fig. 3B for the monocyte count, a marked increase (37.8%) of MH in the highest tertile (n=45) was observed, while the proportion of patients with MH in the other two tertiles were 19.6% and 22.6% respectively. However, none of these differences were statistically significant.

Table II presents the results from the logistic analysis. Total WBC counts differed significantly between the two LVMI groups (the lowest and the highest; P=0.013). Additionally, accompanied by an increase in total WBCs particularly over the middle tertile, the percentage of patients with higher LVMI (or MH) was significantly increased (P=0.008). Furthermore, Table II indicated that older patients (>65 years old) had higher LVMI than those ≤65 years (P=0.042). However, there were no significant differences in gender, DM, hypercholesterolemia and cardiovascular drug treatment between the groups.

Discussion

In the present study, a correlation was detected between white blood cell count and LVMI in hypertensive patients undergoing anti-hypertensive drug therapy. Hypertension is an important risk factor for cardiovascular diseases including atherosclerosis and myocardial hypertrophy, and is independent of age, gender and ethnicity (24,25). The incidence of hypertension is an important basis for the progress of cardiovascular diseases, which itself is a result of many interacting factors. There is evidence that nonhemodynamic factors, which possibly lead to profibrotic effects and proinflammation, may influence LVH (10,11).

Hypertension is a chronic disease (26,27). Active drug therapy may reduce and delay the organ damage caused by hypertension (27). Excluding the impact of other factors, there are significant differences in LVH among patients receiving the same drug therapy (28,29). LVH is closely associated with the plasma levels of white blood cells in patients, which gives

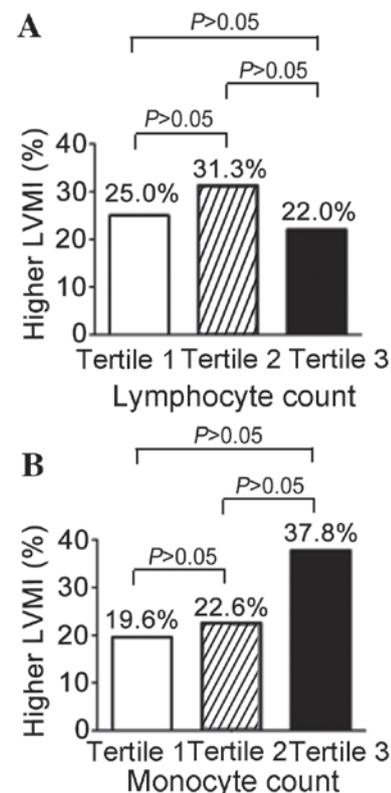


Figure 3. Proportion of patients with higher LVMI. (A) Proportion of patients with higher LVMI according to lymphocyte count tertiles. Tertile 1, lowest tertile (n=46); tertile 2, middle tertile (n=48); tertile 3, highest tertile (n=50). (B) Proportion of patients with higher LVMI according to monocyte count tertiles. Tertile 1, lowest tertile (n=46), tertile 2, middle tertile (n=53), tertile 3, highest tertile (n=45). LVMI, left ventricular mass index.

an indication of hypertension (17,19). Thus practitioners can focus on the level of white blood cell intervention required, further reducing the patient's long-term target organ damage.

The current study detected a strong correlation between white blood cell counts (particularly neutrophil counts) and LVMI in hypertensive patients undergoing anti-hypertensive drug therapy. It demonstrates that modulating neutrophil number to a moderate level for hypertensive patients alongside anti-hypertensive drug therapy may benefit the long-term prognosis of patients. Inflammation is an indicator for the progression of myocardial remodeling underlying the pathogenesis of LVH (30-34). Inflammatory factors are typically derived from white blood cells, particularly neutrophils (35-39). Myocardial expression of inflammatory mediators, including monocyte chemoattractant protein-1 or fractalkine, is significantly increased in experimental myocarditis or dilated cardiomyopathy (40,41). The infiltrating inflammatory cells and/or cardiomyocytes may account for enhanced LVH. Inflammatory cells and cytokines participate in the pathological process of cardiovascular remodeling and are a double-edged sword; they can clear necrotic cells and foreign antigens and promote angiogenesis and scar repair (42). However, excessive inflammatory cell infiltration may seriously upset the balance of the body microenvironment, causing organ damage (42-44).

To the best of our knowledge, the present study is the first to demonstrate that circulating specific types of leukocyte may be associated with LVH in hypertensive patients currently taking anti-hypertensive drugs and thus may provide a novel preventative strategy for LVH by modulating myocardial inflammation.

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