Effects of Irbesartan on Phenotypic Alteration of Monocyte and Inflammatory Status of Hypertensive Patients with Left Ventricular Hypertrophy

Jingsi Zhang
Department of Cardiology, the Second Hospital of Dalian Medical University
Lina Yang
Department of Cardiology, the Second Hospital of Dalian Medical University
Yanchun Ding (yanchunding@aliyun.com)
Department of Cardiology, the Second Hospital of Dalian Medical University

Research Article

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Abstract

Background: Circulating monocytes and tissue macrophages play complex roles in pathogenesis of hypertension and its target organ damage. In this study we observed the alterations of monocyte phenotype and inflammatory state of hypertensive patients with left ventricular hypertrophy (LVH) and the effects of Irbesartan on it. We explored new mechanisms of Irbesartan to reverse LVH and provided new targets for the prevention and treatment of hypertensive target organ damage.

Methods: The CD163 and CD206 expressions on monocytes were detected as well as the IL-10 and TNF-α levels in serum of hypertensive patients with or without LVH and healthy volunteers. Furthermore, we treated monocytes of LVH group with different concentrations of Irbesartan, and then CD163, CD206, IL-10 and TNF-α were detected.

Results: We found for the first time that the expression of CD163, CD206 and IL-10 of LVH group was lower than that of non-LVH group and healthy control, but the TNF-α level of LVH group was significantly higher. Irbesartan could upregulate the expression of CD163 and CD206 of hypertensive patients with LVH in a concentration-dependent manner. Irbesartan could also increase the expression of IL-10 and inhibit the expression of TNF-α in monocytes culture supernatant in a concentration-dependent manner.

Conclusions: Our data suggests that inflammation was activated in hypertensive patients with LVH, the monocyte phenotype was mainly pro-inflammatory. The expression of pro-inflammatory factors increased while the expression of anti-inflammatory factors decreased. Irbesartan could alter monocyte phenotype and inflammatory status in hypertensive patients with LVH, which may be a new mechanism of Irbesartan to reverse LVH.

Trail registration: The study protocols were approved by the Ethical Committee of the Second Affiliated Hospital of Dalian Medical University. Each patient signed the informed consent.

Background

Hypertension is one of the most common chronic diseases, and the number of hypertensive patients is increasing year by year. According to report on cardiovascular disease in China 2016, there were about 270 million hypertensive patients in China, which accounting for about 1/5 of the global number of hypertension, and 30 % of the hypertensive patients were complicated with left ventricular hypertrophy (LVH) [1]. LVH is considered to be an important marker of target organ damage in hypertension and an important predictor of coronary heart disease, heart failure and stroke. Patients with LVH have a significantly increased risk of cognitive impairment, atherosclerosis, atrial fibrillation and other diseases. LVH is used as an independent risk factor for the assessment of the occurrence and prognosis of cardiovascular diseases nowadays [2]. As a result, reversal of LVH has become a long-term goal of hypertension treatment.

The occurrence of LVH is related to various mechanisms. And multiple factors are involved in the formation of LVH, including age, gender, obesity, heredity, hemodynamics, oxidative stress, endothelial function, neurohumoral factors, inflammatory immunity, etc [3]. The relationship between inflammatory response and LVH has attracted more and more attention in recent years.

Immune-inflammatory response persists throughout cardiovascular diseases and relates to the development of hypertensive target organ damages [4, 5]. The monocyte/macrophage system is the main effector of innate immunity and also plays an important role in mediating hypertensive target organ damage through blood pressure-independent mechanisms. When the inflammatory response is activated, reactive oxidants as while as many cytokines are produced, such as tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), interleukin-6 (IL-6), monocyte chemoattractant protein-1 (MCP-1), etc. These cytokines would then promote the aggregation and activation of monocyte/macrophage cells and other inflammatory cells in the target organs of hypertension, and further promote inflammatory response as well as the progress of hypertensive target organ damage.

Irbesartan is an Angiotensin II (Ang II) receptor blocker, which can specifically antagonize the Angiotensin type 1 receptor (AT1R). A meta-analysis suggested that Angiotensin receptor antagonists (ARB) could reverse LVH significantly, the left ventricular mass index (LVMI) significantly decreased by 3.2 %. Moreover, the effect of ARB was better than other antihypertensive drugs, including Angiotensin converting enzyme inhibitors, Calcium antagonists, Diuretics and β-blockers [6].

In this study, we observed the phenotype alterations of monocytes and the expressions of inflammatory cytokines in hypertensive patients with LVH, in order to explore the relationship between inflammatory immune response and hypertensive LVH. We further observed the effect of Irbesartan on the alteration of peripheral blood monocyte phenotype and inflammatory status in hypertensive patients with LVH, which might be a new mechanism of Irbesartan in LVH reversion.

Methods

Subjects and grouping

A total of 59 patients with primary hypertension admitted to our department from December 2016 to December 2017 were included. According to 2010 China Hypertension Guideline, high blood pressure (BP) was defined as a systolic blood pressure (SBP) of higher than or equal to 140mmHg and/or diastolic blood pressure (DBP) of higher than or equal to 90mmHg without antihypertensive drugs. Hypertensive subjects that already received antihypertensive drugs were included regardless of their BP values. The main exclusion criteria were the presence of clinical or laboratory evidence of congestive heart failure, atrial fibrillation, hyperthyroidism, renal insufficiency, sleep apnea-hypopnea syndrome previous stroke, significant cardiac valve disease, previous myocardial infarction, history of coronary by-pass, neoplastic disease and secondary hypertension. According to 2016 Asia Expert Consensus on Diagnosis and Treatment of Hypertension complicated with Left Ventricular Hypertrophy, patient with LVMI > 115 g/m^2

for male and LVMI≥95g/m^2 for female were considered as LVH. Among these hypertensive patients, there were 30 patients with LVH (21 males and 9 females), and 29 patients without LVH (13 males and 16 females, average age was 59.1 ± 11.9 years). In the same period, 30 healthy volunteers were admitted, including 16 males and 14 females. The study protocols were approved by the Ethical Committee of the Second Affiliated Hospital of Dalian Medical University. The project was carried out on the premise of protecting the rights and interests of the subjects according to the Declaration of Helsinki. All subjects were fully informed and signed informed consent. Participants were divided into three groups: LVH group as hypertensive patients with LVH, non-LVH group as hypertensive patients without LVH, normotensive control as healthy volunteers.

Study design

The patient characteristics including gender, age, height and body weight of all participants were recorded and body mass index (BMI) was calculated on the basis of weight and height ($kg.m^{-2}$). Total cholesterol (TC), triglyceride (TG), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), homocysteine (Hcy), high sensitivity creative protein (hs-CRP), β-2 microglobulin (β-2MG) were determined. Two-dimensional guided M-mode recording was performed through the parasternal window according to the guidelines of the American Society of Echocardiography. The following parameters on the M-mode echocardiogram were evaluated: left ventricular end diastolic diameter (LVEDd, mm), interventricular septal diastolic thickness (IVSTd, mm), left ventricular posterior wall diastolic thickness (LVPWTd, mm). Left ventricular mass (LV mass) was calculated according to Devereux's adjusted formula: LVM (g) = 0.8 × 1.04 × $[(LVEDd + LVPWTd + IVSTd)^3 - LVEDd^3] + 0.6$. Left ventricular mass index (LVMI) (g/m^2) = LVM (g) / body surface area (BSA) (m^2). BSA was calculated according to the formulas: BSA for male = 0.0057 × height (m) + 0.0121 × body weight (kg) + 0.0882, BSA for female = 0.0073 × height (m) + 0.0127 × body weight (kg) − 0.2106. The monocytes in peripheral blood were isolated by Ficoll-Hypaque density separation method (Sigma, Germany). The expression of CD163 and CD206 in monocytes was detected by Flow cytometry (BD, USA). The concentrations of IL-10 and TNF-α in serum and supernatant of monocytes cultures were detected by ELISA (Abcam, UK).

Statistical analyses

SPSS 22.0 software was used for the statistical analysis. Normal distribution was tested for all continuous variables. The data that were normally distributed were presented as mean ± standard deviation. Comparisons inter-groups for normally distributed data were performed with Student's t-test. Analysis of Variance (ANOVA) was used for comparison among multiple groups, and LSD method was further used for pairwise comparison. The data that were not normally distributed were tested using the non-parametric test and were presented as median.Values of $P < 0.05$ were considered to be statistically significant.

Results

Patients characteristics

There were no statistical differences in the age, BMI, TC, LDL-C, HDL-C, TG among the three groups (P > 0.05). Hcy, β-2MG in LVH group were higher than control group (P < 0.05). Serum hs-CRP of LVH group was higher than that of non-LVH group and control group, and non-LVH group was higher than that of control group (P < 0.05) (Table 1).

Table 1
Patient characteristics of three groups

	Control (n = 30)	non-LVH (n = 29)	LVH (n = 30)	F	P
Age(years)	58.53 ± 10.17	59.07 ± 11.79	58.03 ± 14.93	0.28	0.755
BMI(kg/m^2)	23.13 ± 1.23	24.62 ± 2.21	24.51 ± 4.06	0.23	0.801
TC(mmol/L)	4.17 ± 0.79	4.69 ± 0.91	4.79 ± 1.03	0.89	0.416
LDL-C(mmol/L)	1.29 ± 0.19	1.39 ± 0.34	1.47 ± 0.54	1.24	0.296
HDL-C(mmol/L)	2.48 ± 0.31	2.83 ± 0.76	2.55 ± 0.74	1.21	0.304
TG(mmol/L)	1.79 ± 1.43	1.89 ± 1.24	1.84 ± 1.01	0.01	0.987
Hs-CRP(mg/L)	11.50 ± 1.29	12.42 ± 3.09*	14.12 ± 4.32*#	2.01	0.143
Hcy(umol/L)	1.43 ± 0.65	1.37 ± 0.98	2.87 ± 1.87*	7.82	0.001
β-2MG(mg/L)	1.85 ± 0.47	1.98 ± 0.53	2.70 ± 0.72*	10.69	< 0.001
* P < 0.05 vs. control, # P < 0.05 vs. non-LVH group					

Comparison of CD163 and CD206 expression

The expression of CD163 and CD206 in monocytes of LVH group was lower than that of non-LVH group and control group (P < 0.05). The expression of CD163 in non-LVH group was lower than control group (P < 0.05) (Table 2, Fig. 1).

Table 2
Expressions of CD163 and CD206

	Control (n = 30)	non-LVH (n = 29)	LVH (n = 30)	F	P
CD163(%)	87.75 ± 25.32	75.29 ± 18.30*	65.73 ± 17.89*#	13.18	< 0.001
CD206(%)	32.32 ± 7.82	30.81 ± 8.29	12.19 ± 6.07*#	8.45	0.002
* P < 0.05 vs. control, # P < 0.05 vs. non-LVH group					

Comparison of IL-10 and TNF-α

The concentration of TNF-α in serum of LVH group was significantly higher than that of non-LVH group and control group, and non-LVH group was higher than control group ($P < 0.05$). The concentration of IL-10 in serum of LVH group and non-LVH group was lower than that of control group ($P < 0.05$), but there was no significant difference between LVH group and non-LVH group (Table 3, Fig. 2).

Table 3
levels of IL-10 and TNF-α

	Controls (n = 30)	non-LVH (n = 29)	LVH (n = 30)	F	P
IL-10(ng/ml)	6.82 ± 1.24	5.19 ± 1.05*	5.07 ± 0.85*	4.62	0.019
TNF-α(pg/ml)	7.11 ± 1.61	15.67 ± 7.62*	44.63 ± 17.96*#	21.78	< 0.001
* P < 0.05 vs. control, # P < 0.05 vs. non-LVH group					

Effects of Irbesartan on monocyte phenotype and inflammatory status in hypertensive patients with LVH

We stimulated the monocytes isolated from peripheral venous blood of hypertensive patients with LVH for 24 hours with Irbesartan (10^{-6} mol/L, 10^{-7} mol/L, 10^{-8} mol/L). Then we observed the morphology of monocytes (Fig. 3). We found that Irbesartan could upregulate the expression of CD163 and CD206 in monocytes of hypertensive patients with LVH in a concentration-dependent manner, of which the group of 10^{-6} mol/L was the most significant ($P < 0.01$) (Fig. 4). Irbesartan could also increase the expression of IL-10 and inhibit the expression of TNF-α in monocytes culture supernatant of hypertensive patients with LVH in a concentration-dependent manner, of which the group of 10^{-6} mol/L was the most significant ($P < 0.01$) (Table 4, Fig. 5).

Table 4
Effect of Irbesartan on the expressions of CD163, CD206, IL-10 and TNF-α in LVH patients

	Control	Irbesartan			F	P
		10^{-6}mol/L	10^{-7}mol/L	10^{-8}mol/L		
CD163(%)	68.69 ± 14.90	80.76 ± 18.61*	76.19 ± 10.25^{ab}	72.45 ± 8.27^{abc}	10.74	< 0.001
CD206(%)	12.42 ± 7.58	16.61 ± 8.69*	15.76 ± 6.83^{ab}	13.94 ± 5.17^{abc}	12.90	0.028
IL-10(ng/ml)	3.32 ± 0.90	5.42 ± 0.77*	4.51 ± 0.43^{ab}	3.64 ± 0.49^{abc}	11.63	< 0.001
TNF-α(pg/ml)	35.69 ± 4.79	25.93 ± 4.44*	27.37 ± 3.19^{ab}	30.04 ± 6.21^{abc}	4.81	0.011

* $P < 0.01$ vs. control, ^{a} $P < 0.05$ vs. control, ^{b} $P < 0.05$ vs. 10^{-6} mol/L group, ^{c} $P < 0.05$ vs. 10^{-7} mol/L group

Discussion

LVH is one of the most common target organ damages of hypertension It is the compensatory response of the heart to increased after-load, and also a risk factor of complications and prognosis deterioration. Currently, LVH is used as an independent risk factor for evaluation of cardiovascular diseases. LVH can lead to decreased blood flow reserve of coronary arteries and further myocardial ischemia. LVH also reduces left ventricular function, the cardiac contractile function of LVH patients is lower than that of normal people. Lack of energy supply of hypertrophic cardiomyocytes or metabolic disorders can aggravate the necrosis and fibrosis of cardiomyocytes. Then the whole cardiac contraction function and cardiac compliance would decrease, leading to the decompensation of cardiac function and heart failure [7]. LVH could also lead to alterations of cardiac cells and interstitial structures, causing electrophysiological abnormalities. In addition, the imbalance between coronary blood supply and myocardial area resulted from LVH could lead to cardiac ischemia and changes in the regulation of cardiac autonomic nerve function, which also leads to abnormal myocardial electrical activity and eventually arrhythmia [8]. Previous studies indicated that patients with hypertension showed that LVH reversal reduced overall cardiovascular event risk by 46%. Prevention and/or reversal of LVH can reduce the incidence and mortality of cardiovascular diseases and improve the prognosis of patients with hypertension [9, 10].

Hypertension is considered as a low inflammatory disease. Inflammatory response plays an important role in the occurrence and development of target organ damages in hypertension [11]. Monocyte/macrophage system is the main effector cell of innate immunity. It can be divided into two categories according to the activation mode and immune function. Interferon-γ (IFN-γ) induces macrophage M1 polarization (proinflammatory), which is called " classical activation type ". Interleukin-4

(IL-4) induces macrophage M2 polarization (anti-inflammatory), which is classified as " alternative activation type " [12]. The identification of macrophage subsets is based on the expression of specific extracellular and intracellular proteins. The markers of M1 macrophages include CD68, major histocompatibility complex-II (MHC-II), CD80, CD86, CC chemokine receptors, MCP-1, etc. on the cell surface. The markers of M2 macrophages include CD163, cx3c chemokine receptor 1 (CX3CR1), CD206, vascular endothelial growth factor (VEGF) and so on. TNF-α, IL-1β, IL-6, IL-12, IL-18, IL-23 and other proinflammatory factors were highly expressed in M1 type macrophages, while CD163, CD206, IL-10 and other anti-inflammatory factors were highly expressed in M2 type macrophages. Macrophages participate in the progression of hypertension and target organ damage. There are more pro-inflammatory monocytes in the circulation of hypertensive patients than those with normal blood pressure. Meanwhile, the levels of some pro-inflammatory cytokines increased in hypertensive patients [13–15]. Previous study found that the expression of CD163 and CD206 in SHR was decreased. After the activation of M2-type macrophages, the M1/M2 ratio was reduced, and the blood pressure of SHR gradually returned to normal [16]. It was proved that the level of TNF-α was positively correlated with the degree of LVH in hypertensive patients[17, 18]. Inhibiting the nuclear factor-κB (NF-κB) pathway could lead to the increase of IL-10, which represent M2-type macrophage. IL-10 may inhibit angiotensin via NF-κB pathway, thereby inhibit fibroblast proliferation and collagen synthesis, and eventually inhibiting myocardial interstitial fibrosis, indicating that IL-10 may have the effect of preventing and reversing hypertension LVH [19, 20]. In this study, the expression of CD163 and CD206 in peripheral blood monocytes and the concentrations of IL-10 and TNF-α in serum of the hypertensive patients were detected, and also the healthy participants. It was found that the expression of CD163 and CD206 and the concentration of IL-10 in LVH group were lower than those in healthy and non-LVH groups, while the concentration of TNF-α was significantly higher compared to the other two groups. The results indicated that inflammation was activated in hypertensive patients with LVH. The expression of pro-inflammatory factors increased and the expression of anti-inflammatory factors decreased, and monocytes in the blood were mainly pro-inflammatory M1-type in hypertensive patients with LVH. It suggested that the occurrence and development of LVH were related to the alterations of monocytes/macrophages phenotype and inflammatory status.

Irbesartan is a commonly used antihypertensive drug. Recent studies have shown that oral administration of Irbesartan can reverse hypertension LVH and reduce LVMI in addition to control blood pressure [21, 22]. Possible mechanisms include Irbesartan inhibits renin-angiotensin-aldosterone system (RAAS), reduces the level of AngII and blocks the binding of AngII to AT1R, so as to improve the metabolism of myocardial fibroblasts and reduce myocardial hypertrophy. In addition, Irbesartan can improve autonomic nerve function, maintain the balance of sympathetic and parasympathetic nerves, and reduce target organ damage caused by nerve dysfunction. Previous experiment proved that ARB could block NF-κB signaling pathway, inhibit the release of inflammatory cytokines, so that to prevent or ameliorate target organ damages of hypertension [23]. In this study, monocytes isolated from peripheral blood of hypertensive patients with LVH were stimulated by different concentrations of Irbesartan, the expression of CD163 and CD 206 in monocytes and the concentrations of IL-10 and TNF-α in the supernatant of the cells were determined. We found that Irbesartan could upregulate the expression of

CD163 and CD206 in monocytes of hypertensive patients with LVH in a concentration-dependent manner, of which the group of 10^{-6} mol/L was the most significant. Irbesartan could also increase the expression of IL-10 and inhibit the expression of TNF-α in monocytes culture supernatant of hypertensive patients with LVH in a concentration-dependent manner, of which the group of 10^{-6} mol/L was the most significant. These results indicated that Irbesartan could change monocyte phenotype and inflammatory status in hypertensive patients with LVH. The possible mechanisms include the antioxidant effect of Irbesartan. The physicochemical stimulation of monocytes/macrophages by Irbesartan with different concentrations leads to autophagy of monocytes/macrophages, and then the functional status of monocytes/macrophages is changed. Finally, the inflammatory factors released from monocytes/macrophages were changed [24, 25]. The specific mechanism remains to be further explored. In this study, through the in vitro experiments, it was verified for the first time that Irbesartan could change the monocyte phenotype and inflammatory status of hypertensive patients with LVH. Meanwhile, Irbesartan could control blood pressure and reverse LVH by way of immune inflammation regulation, providing a new direction for hypertensive target organ damage protection. However, there were still several defects in this study, such as the sample size was relatively small, which would easily lead to statistical bias and experimental deviation. And further clinical studies were needed to confirmed the result of the in vitro studies.

Conclusion

In conclusion, inflammation was activated in hypertensive patients with LVH, the monocyte phenotype was mainly pro-inflammatory. The expression of pro-inflammatory factors in serum increased while the expression of anti-inflammatory factors decreased. Irbesartan could alter monocyte phenotype and inflammatory status in hypertensive patients with LVH, which may be a new mechanism of Irbesartan to reverse LVH.

List Of Abbreviations

left ventricular hypertrophy (LVH)

tumor necrosis factor-α (TNF-α)

interleukin-1β (IL-1β)

interleukin-6 (IL-6)

monocyte chemoattractant protein-1 (MCP-1)

Angiotensin II (Ang II)

Angiotensin type 1 receptor (AT1R)

Angiotensin receptor antagonists (ARB)

left ventricular mass index (LVMI)

blood pressure (BP)

systolic blood pressure (SBP)

diastolic blood pressure (DBP)

body mass index (BMI)

total cholesterol (TC)

triglyceride (TG)

high density lipoprotein cholesterol (HDL-C)

low density lipoprotein cholesterol (LDL-C)

homocysteine (Hcy)

high sensitivity creative protein (hs-CRP)

β-2 microglobulin (β-2MG)

left ventricular end diastolic diameter (LVEDd)

interventricular septal diastolic thickness (IVSTd)

left ventricular posterior wall diastolic thickness (LVPWTd)

left ventricular mass (LV mass)

left ventricular mass index (LVMI)

body surface area (BSA)

analysis of Variance (ANOVA)

interferon-γ (IFN-γ)

interleukin-4 (IL-4)

major histocompatibility complex-II (MHC-II)

cx3c chemokine receptor 1 (CX3CR1)

vascular endothelial growth factor (VEGF)

nuclear factor-κB (NF-κB)

renin-angiotensin-aldosterone system (RAAS)

Declarations

Ethics approval and Consent to participate:

The study protocols were approved by the Ethical Committee of the Second Affiliated Hospital of Dalian Medical University. Each patient signed the informed consent to participate in this study.

Consent for publication:

Informed consent for publication was obtained from all participants.

Availability of data and material:

All relevant data are available from the corresponding author on reasonable request.

Competing interests:

The authors declare that they have no conflict of interest.

Funding:

Not applicable.

Authors' contributions:

YD designed the experiment and contributed significantly to analysis and manuscript preparation. JZ performed the experiment and wrote the manuscript. LY performed the experiment and the data analyses.

Acknowledgements:

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Figures

Figure1

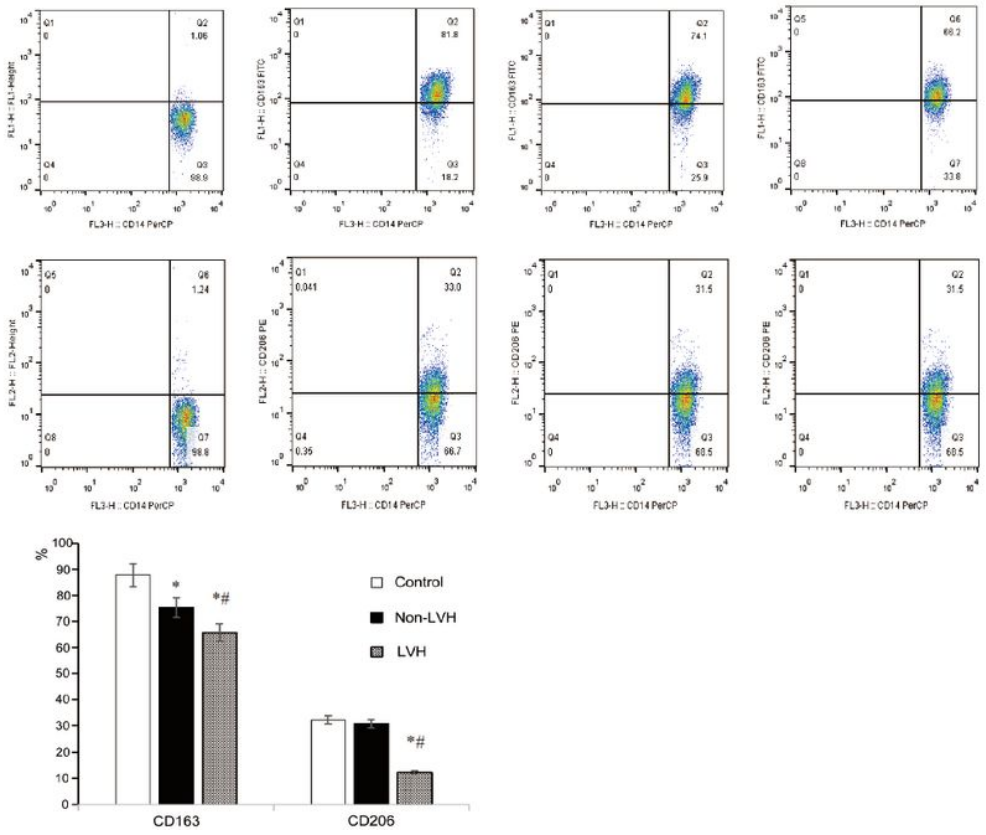

Figure 1

Expressions of CD163 and CD206 in monocytes detected by flow cytometry. CD163 and CD206 expression in monocytes of LVH group was lower than non-LVH and control groups (P<0.05). CD163 in non-LVH group was lower than control group (P<0.05). * P<0.05 vs. control, # P<0.05 vs. non-LVH.

figure 2

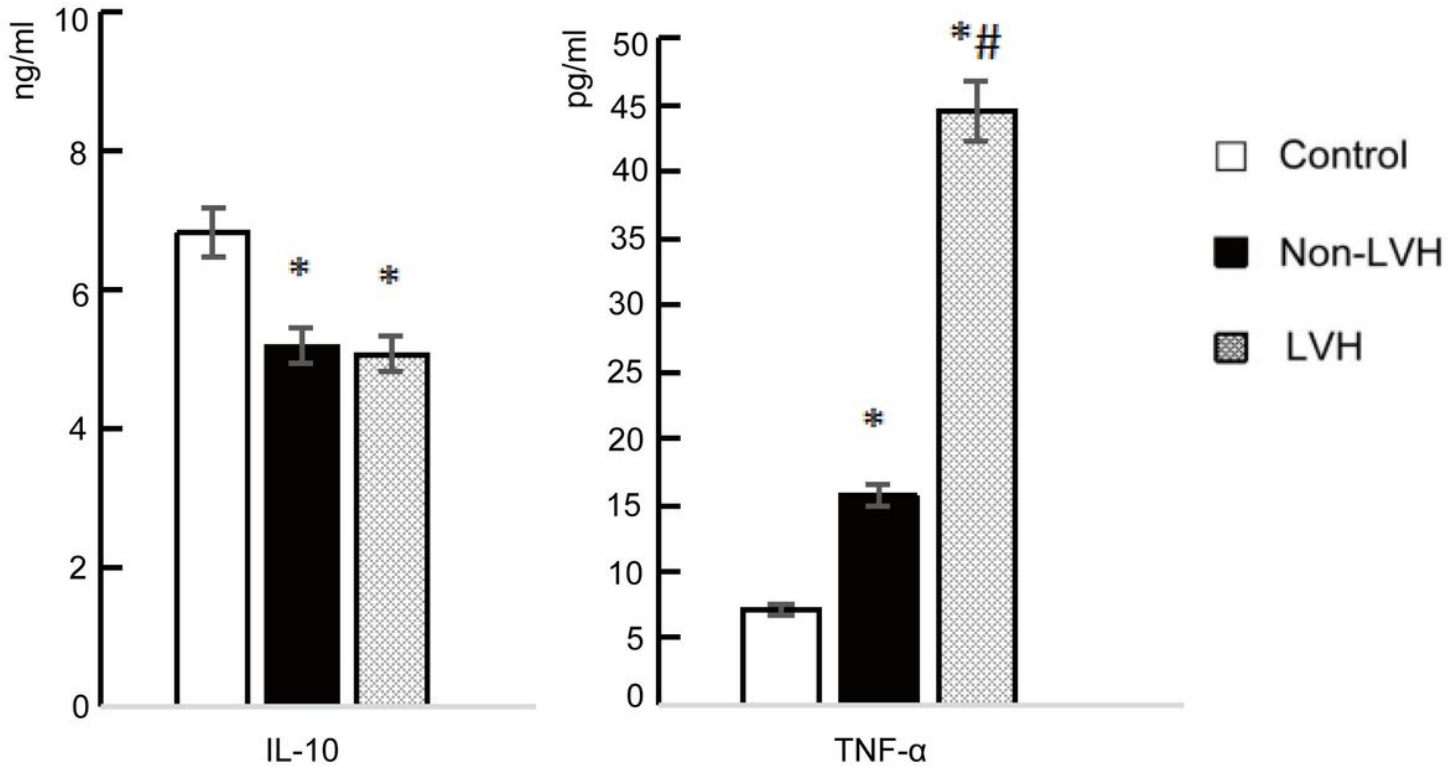

Figure 2

Levels of IL-10 and TNF-α. IL-10 of LVH and non-LVH groups were lower than control (P<0.05). TNF-α of LVH group was significantly higher than non-LVH and control groups, and non-LVH group was higher than control (P<0.05). * P<0.05 vs. control, # P<0.05 vs. non-LVH.

figure 3

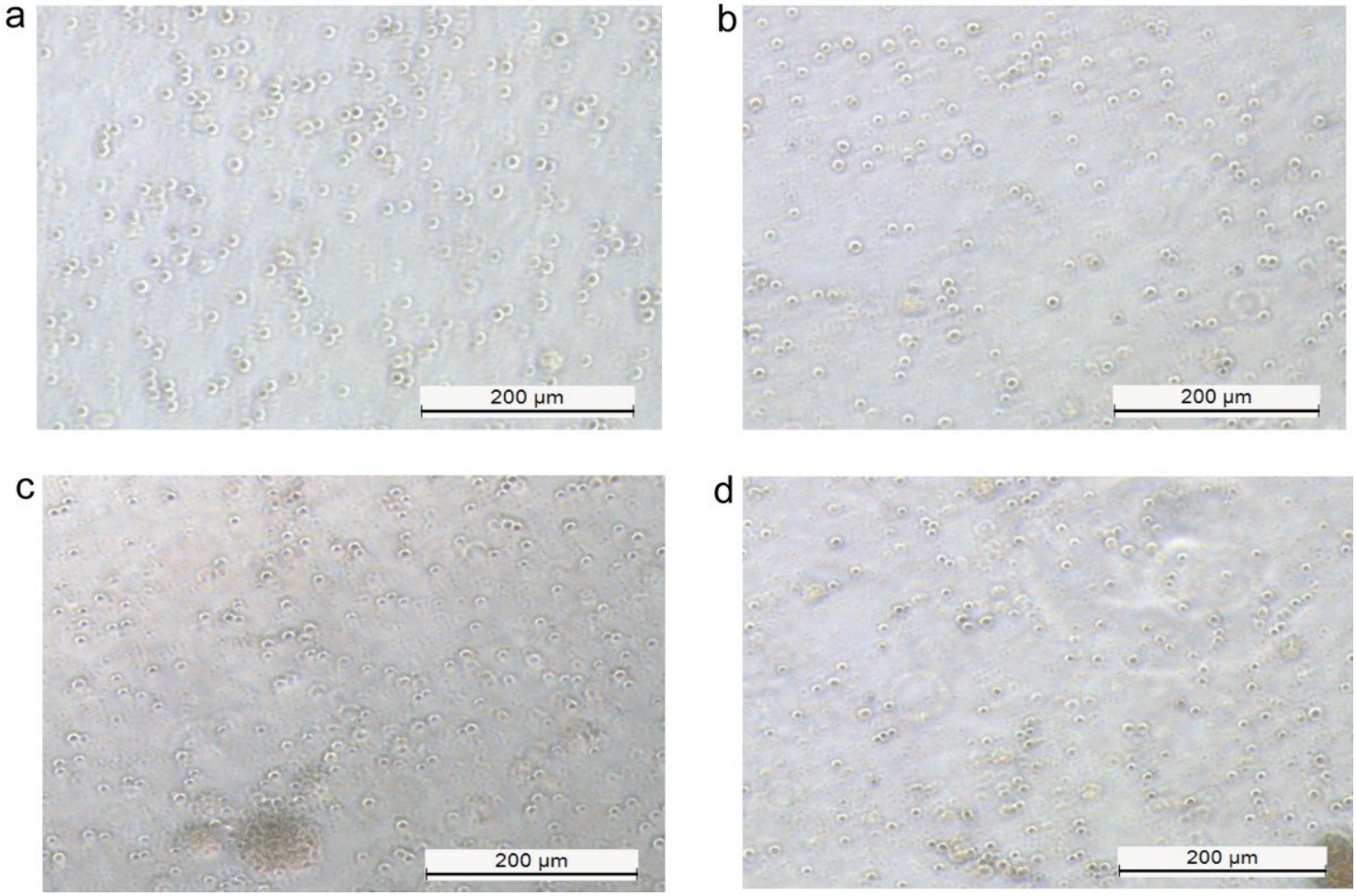

Figure 3

Morphology of monocytes stimulated by different concentrations of Irbesartan. (a) Control (blank). (b-d) Irbesartan stimulation groups (10-6, 10-7, 10-8 mol/ L, respectively).

figure 4

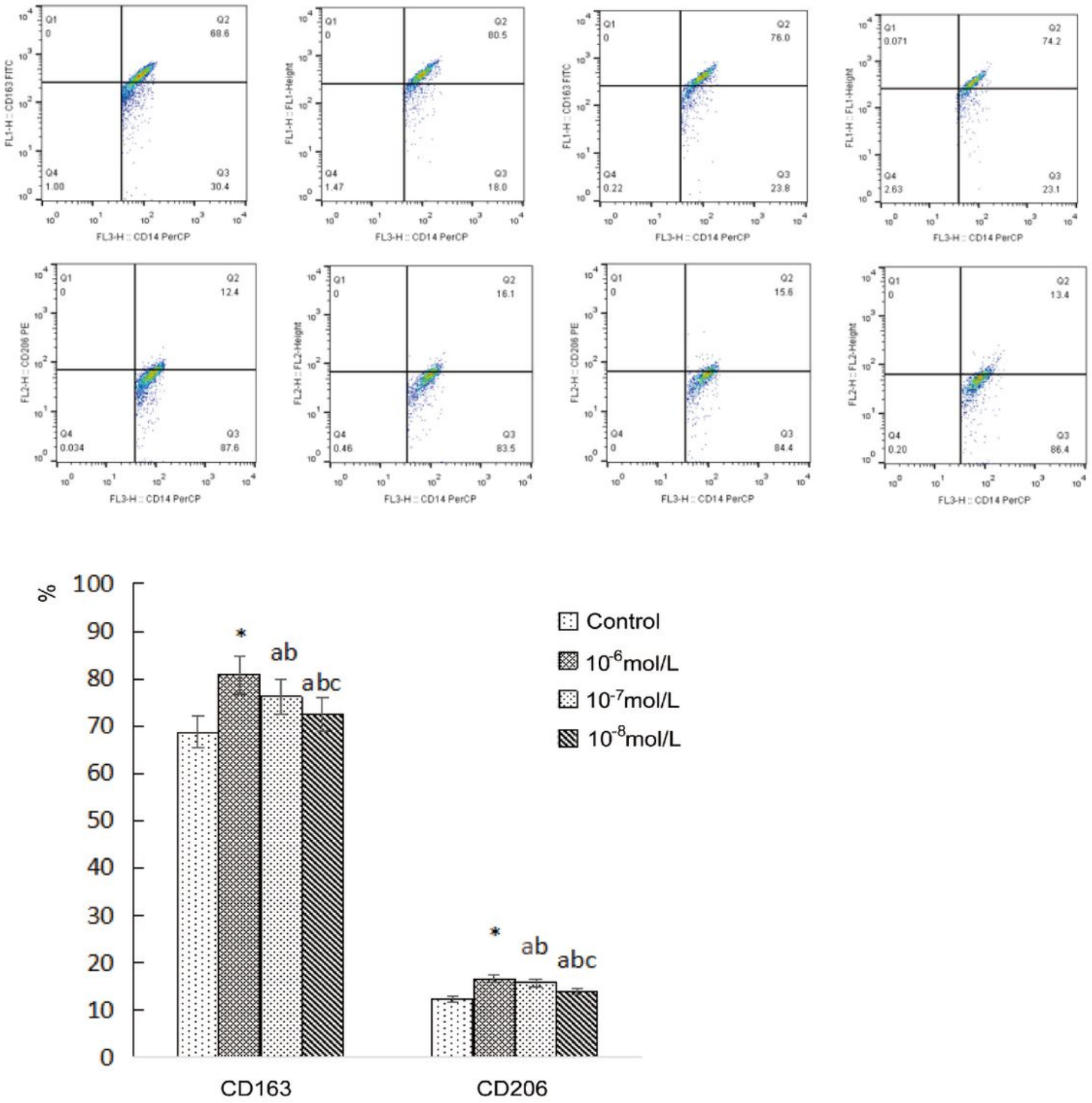

Figure 4

The expressions of CD163 and CD206 in LVH patients affected by different concentrations of Irbesartan. Irbesartan could up-regulate the expression of CD163 and CD206 in a concentration-dependent manner, of which the 10-6 mol/L group was the most significant (P<0.01). * P<0.01 vs. control, a P<0.05 vs. control, b P<0.05 vs. 10-6 mol/L group, c P<0.05 vs. 10-7 mol/L group.

figure 5

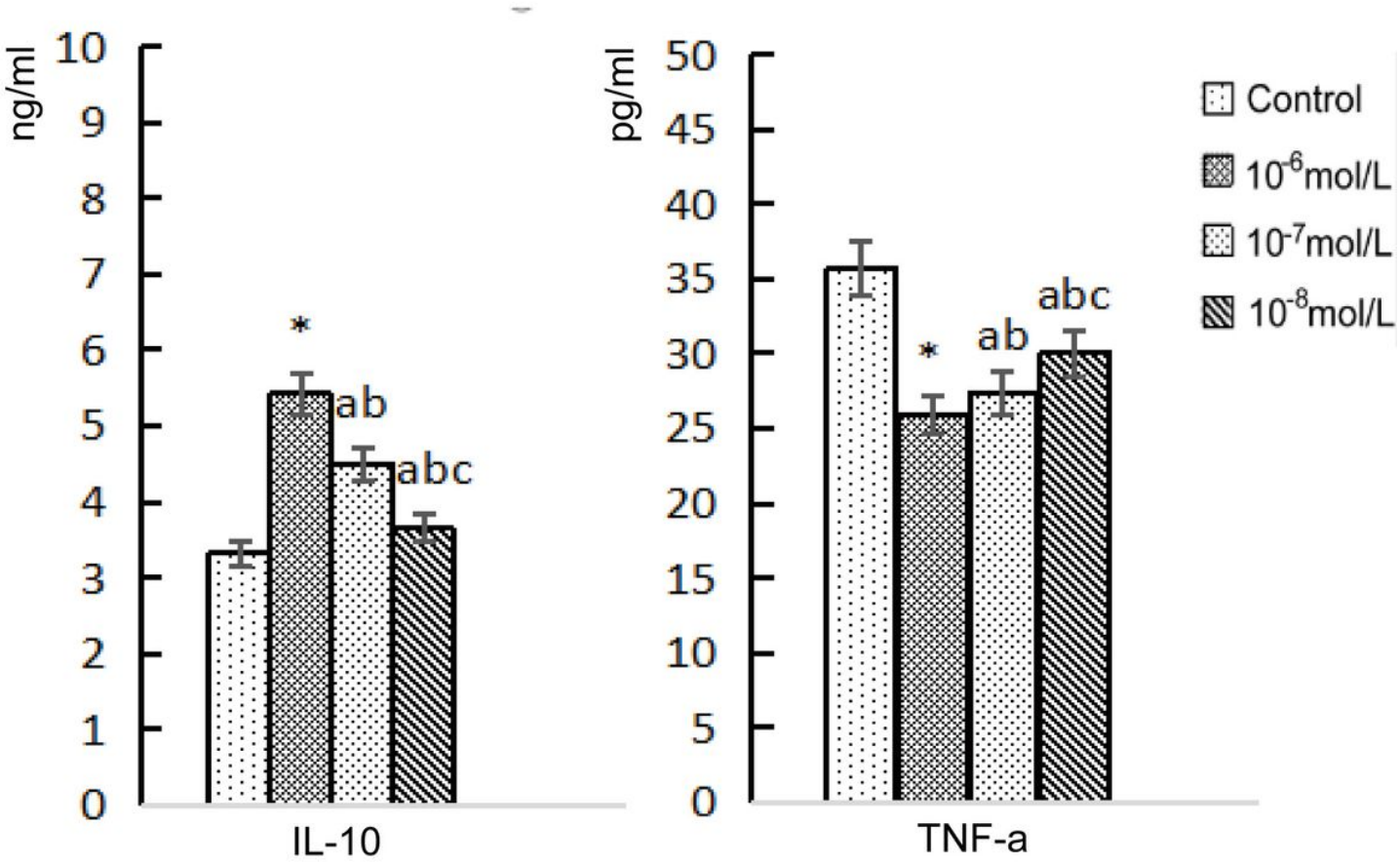

Figure 5

The expressions of IL-10 and TNF-α in LVH patients affected by different concentrations of Irbesartan. Irbesartan could up-regulate the expression of IL-10 and inhibit the expression of TNF-α in a concentration-dependent manner, of which the group of 10-6 mol/L was the most significant (P<0.01). * P<0.01 vs. control, a P<0.05 vs. control, b P<0.05 vs. 10-6 mol/L group, c P<0.05 vs. 10-7 mol/L group.