Am J Transl Res 2022;14(6):4097-4103
www.ajtr.org /ISSN:1943-8141/AJTR0143410

Original Article

Analysis of alterations of serum inflammatory cytokines and fibrosis makers in patients with essential hypertension and left ventricular hypertrophy and the risk factors

Xia Li, Xiaofan Guo, Ye Chang, Naijin Zhang, Yingxian Sun

Cardiovascular Medicine Department, First Affiliated Hospital of China Medical University, Shenyang 110001, Liaoning, China

Received April 9, 2022; Accepted May 20, 2022; Epub June 15, 2022; Published June 30, 2022

Abstract: Objective: This study mainly analyzed the alterations of serum inflammatory cytokines (ICs) and fibrosis makers in patients with essential hypertension (EH) and the risk factors (RFs). Methods: In this retrospective study, a total of 145 patients with EH admitted from January 2013 to January 2018 were selected as the research subjects, among which 89 patients without left ventricular hypertrophy (LVH) were included in the EH group and 56 patients with LVH were set as the LVH group. In addition, another 50 healthy subjects who underwent physical examination during the same period were selected as the healthy control (HC) group. The alterations of serum ICs such as interleukin (IL)-6, IL-10 and IL-18, and fibrosis makers like type III procollagen (PCIII), fibronectin (LN) and hyaluronic acid (HA) of the three groups were analyzed, and the RFs of LVH in EH patients were analyzed using the multivariate logistic model. Results: Statistically higher levels of IL-6, IL-18, PCIII, LN and HA with lower IL-10 levels were determined in the LVH group compared with the EH group. In comparison with the HC group, IL-6, IL-18, PCIII, LN and HA in the EH group were significantly higher, while IL-10 was significantly lower. On the other hand, BMI, LVMI, IL-6, IL-18, PCIII, LN, and HA were identified by multivariate logistic analysis to be the RFs affecting LVH in EH patients, while IL-10 was its protective factor. Conclusions: The above results suggest that serum ICs (except IL-10) and fibrosis markers are up-regulated abnormally in EH patients with LVH, and BMI, LVMI, IL-6, IL-10, IL-18, PCIII, LN, and HA are all independent predictors of LVH in EH patients.

Keywords: Hypertension, inflammatory cytokines, fibrosis, risk factors

Introduction

As a common chronic inflammatory condition and a prime reason for premature death and disability worldwide, essential hypertension (EH) leads to increased risk of cardio-cerebrovascular events such as myocardial infarction, atrial fibrillation, stroke and heart failure [1, 2]. As indicated by statistics, EH affects approximately 1 billion people around the world and causes 10 million deaths every year [3, 4]. Left ventricular hypertrophy (LVH) is an early pathological manifestation of EH and a common cause of EH-related targeted organ damage, mainly manifested as abnormal increase in myocardial fibrosis [5]. It is shown that 30% of EH patients may be complicated with LVH [6], among whom cognitive impairment, atherosclerosis and other adverse events frequently occur, which seriously threaten the prognosis of patients [7]. Therefore, revealing the clinical presentations of EH and its associated LVH, and exploring its related risk factors (RFs) from its pathological mechanism are of great value for the diagnosis, treatment and prevention of EH.

The pathological mechanism of EH is very complex, involving inflammatory reactions, hemodynamic disorders, the immune system and metabolic abnormalities [8]. Animal experiments also suggest that inflammatory responses mediate the nosogenesis of EH, in which many cell signal molecules play key roles and may

accelerate EH progression [9]. In addition, inflammation is also involved in the occurrence and progression of EH-related targeted organ damage, which is closely related to the pathological process of LVH [10]. Studies have shown that inflammatory cytokines (ICs) contribute to the malignant progression of cardiac fibrotic reprogramming and dysfunction by sharing macrophage-mediated responses and triggering cellular inflammatory cascades that promote the secretion of pro-fibrotic factors and activation of matrix metalloproteinases [11]. The novelty of this study is to analyze serum levels of ICs and fibrosis markers as well as the RFs in EH and EH combined with LVH (EH + LVH) patients, aiming to provide a new theoretical basis for clinical management of EH and EH + LVH.

Materials and methods

General data

A total of 145 patients with EH admitted from January 2013 to January 2018 were selected as the research participants, all of whom underwent echocardiography to determine the presence of LVH. LVH diagnostic criteria were [12]: a left ventricular mass index (LVMI) > 134 g/m^2 for males and > 110 g/m^2 for females; echocardiography showing a thickening of the left ventricular posterior wall or interventricular septal wall ≥ 12 mm; an S wave in lead V1 (SV1) + R wave in lead V5 (Rv5) ≥ 35 mm. Patients meeting any of the above criteria were confirmed with LVH, based on which, the 145 patients included were further grouped. Of them, EH patients without LVH were set as the EH group (n = 89), including 59 males and 30 females, with an average age of (54.19 ± 10.63) years. EH patients suffering from LVH were included in the LVH group (n = 56), including 29 males and 27 females, with a mean age of (54.68 ± 9.65) years. The age, sex and other general data of the two groups were comparable (P > 0.05). This retrospective study was conducted after approval by the Ethics Committee of the First Affiliated Hospital of China Medical University (2014-2-2), and all subjects signed the informed consent.

Inclusion and exclusion criteria

All the enrolled patients diagnosed with EH had complete medical records but no myocardial infarction in the past six months, no use of drugs with possible influences on the research results in the past six months and no blood system diseases.

Patients with severe cardiovascular diseases, malignant tumors, infectious diseases, heart surgery in the past month, or severe valvular diseases were excluded, as well as those with mental illness or communication disorders.

Inspection methods

From all subjects in the three groups, 5ml elbow venous blood was sampled on an empty stomach in the early morning and it was placed into procoagulant tubes and then transferred to new test tubes for 10 min of centrifugation (1500×g, 4°C). The serum was then collected and stored at -80°C until use. Serum levels of interleukin (IL)-6, IL-10, IL-18, type III procollagen (PCIII), fibronectin (LN) and hyaluronic acid (HA) were measured by an enzyme-linked immunosorbent assay (ELISA), and the operation process strictly followed the instructions of ELISA detection kits all supplied by Wuhan Fine Biotech. Finally, the concentration of each serum index was determined by a spectrophotometer (Zeping Bopscience and Technologies, Beijing, China, UV5Nano).

Statistical analysis

SPSS 22.0 was used for statistical analysis. Case number/percentage (n/%) and mean ± SEM were used to indicate categorical and quantitative data, respectively. The inter-group differences of categorical data were analyzed using the Chi-square test, and a continuous correction Chi-square test was used when the theoretical frequency was less than 5 in the Chi-square test. For quantitative data, the independent sample t-test was used for comparison between groups, and a one-way analysis of variance was used for comparison among multiple groups. The RFs of LVH in EH patients were determined using the multivariate logistic model. P < 0.05 was the significance level for all analyses.

Results

Analysis of general and pathological data of three groups of patients

The average age, residence, family history of LVH/EH, rates of smoking, alcoholism, triglycer-

Table 1. Analysis of general and pathological data of patients in two groups [n (%), mean ± SEM]

Factor	HC group (n = 50)	EH group (n = 89)	LVH group (n = 56)	P
Average age (years)	53.60 ± 7.56	54.19 ± 10.63	54.68 ± 9.65	0.848
Sex				0.095
Male	25 (50.00)	59 (66.29)	29 (51.79)	
Female	25 (50.00)	30 (33.71)	27 (48.21)	
BMI (kg/m^2)	23.74 ± 3.02	24.70 ± 3.87	27.29 ± 3.17$^{*,\#}$	< 0.001
SBP (mmHg)	111.30 ± 18.91	159.78 ± 24.51*	165.55 ± 21.30*	< 0.001
DBP (mmHg)	78.34 ± 9.24	97.78 ± 14.09*	99.13 ± 12.26*	< 0.001
Residence				0.131
Urban	32 (64.00)	68 (76.40)	45 (80.36)	
Rural	18 (36.00)	21 (23.60)	11 (19.64)	
Family history of LVH				0.448
Yes	11 (22.00)	20 (22.47)	8 (14.29)	
No	39 (78.00)	69 (77.53)	48 (85.71)	
Family history of EH				0.146
Yes	3 (6.00)	15 (16.85)	10 (17.86)	
No	47 (94.00)	74 (83.15)	46 (82.14)	
Smoking				0.740
Yes	29 (58.00)	52 (58.43)	36 (64.29)	
No	21 (42.00)	37 (41.57)	20 (35.71)	
Alcoholism				0.060
Yes	23 (46.00)	59 (66.29)	31 (55.36)	
No	27 (54.00)	30 (33.71)	25 (44.64)	
Total cholesterol (mmol/l)	4.06 ± 0.37	4.46 ± 0.42*	4.54 ± 0.30*	< 0.001
Triglyceride (mmol/l)	1.28 ± 0.33	1.32 ± 0.39	1.39 ± 0.33	0.274
LVEF (%)	64.00 ± 6.48	65.82 ± 7.41	65.91 ± 9.72	0.363
LVMI (g/m^2)	84.18 ± 8.48	95.39 ± 12.71*	130.71 ± 7.83$^{*,\#}$	< 0.001

Note: *P < 0.05 compared with the HC group; $^{\#}$P < 0.05 compared with the EH group. BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; LVH, left ventricular hypertrophy; EH, essential hypertension; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index.

ide levels, and left ventricular ejection fraction (LVEF) were not significantly different among the three groups (P > 0.05), but there were significant differences in body mass index (BMI), systolic/diastolic blood pressure (SBP/DBP), total cholesterol, and LVMI (P < 0.05). The comparison results between the EH group and LVH group showed that the two groups were only significantly different in BMI and LVMI (P < 0.05) **Table 1**.

Comparison of serum ICs among the three groups of patients

We measured serum ICs in EH and EH + LVH patients as well as healthy controls with an ELISA. IL-6, IL-10, and IL-18 levels were found to be (20.80 ± 2.78) pg/ml, (5.93 ± 1.52) ng/ml, and (46.18 ± 8.38) pg/ml in the EH group and (29.60 ± 2.75) pg/ml, (4.40 ± 0.96) ng/ml, and (60.26 ± 4.61) pg/ml in the LVH group, respectively. Similarly, the levels of IL-6, IL-10, and IL-18 in the HC group were (14.40 ± 2.29) pg/mL, (11.48 ± 2.21) ng/mL, and (21.14 ± 3.86) pg/mL, respectively. By comparison, we found that IL-6 and IL-18 were statistically higher while IL-10 was lower in the LVH group compared with the EH group (P < 0.05). In comparison with the HC group, the levels of IL-6 and IL-18 were higher in the EH group and the IL-10 level was lower, with statistical significance (P < 0.05) **Figure 1**.

Comparison of serum fibrosis makers among the three groups of patients

We compared and analyzed serum fibrosis makers of the three groups, and found that

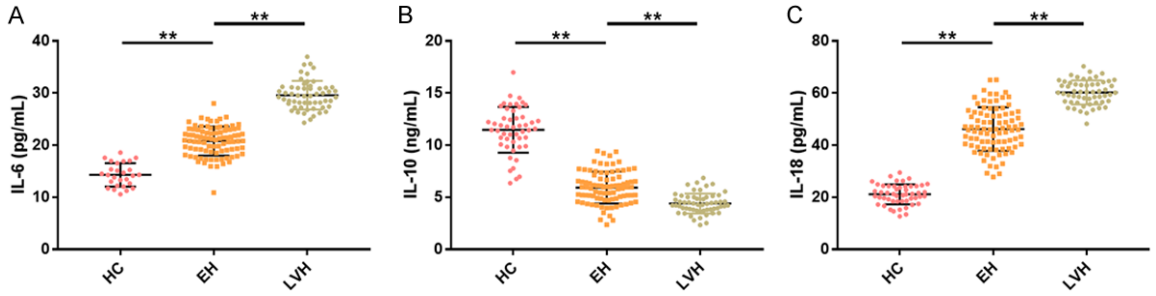

Figure 1. Comparison of serum inflammatory cytokines between EH and EH + LVH patients. A. IL-6 levels in the three groups. B. IL-10 levels in the three groups. C. IL-18 levels in the three groups. Note: **P < 0.01. IL-6, interleukin-6; IL-10, interleukin-10; IL-18, interleukin-18.

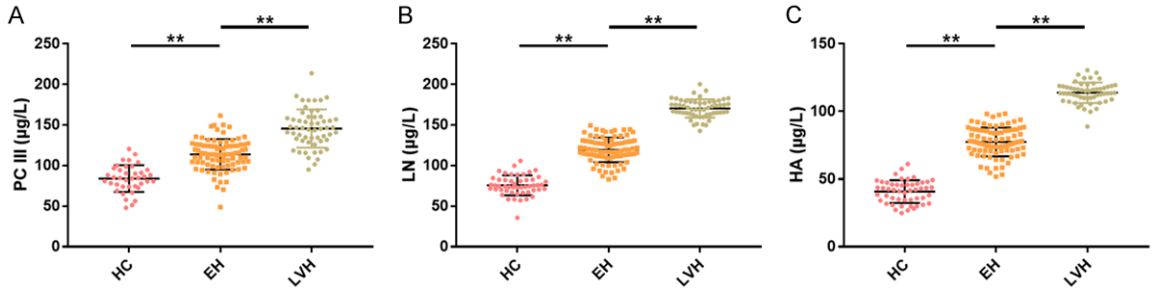

Figure 2. Comparison of serum fibrosis makers between EH and EH + LVH patients. A. PCIII levels in the three groups. B. LN levels in the three groups. C. HA levels in the three groups. Note: **P < 0.01. PCIII, type III procollagen; LN, fibronectin; HA, hyaluronic acid.

Table 2. Logistic multivariate regression assignment

Factor	Variable	Assignment
BMI	X1	Continuous variable
LVMI	X2	Continuous variable
IL-6	X3	Continuous variable
IL-10	X4	Continuous variable
IL-18	X5	Continuous variable
PCIII	X6	Continuous variable
LN	X7	Continuous variable
HA	X8	Continuous variable

Note: BMI, body mass index; LVMI, left ventricular mass index; IL-6, interleukin-6; IL-10, interleukin-10; IL-18, interleukin-18; PCIII, type III procollagen; LN, fibronectin; HA, hyaluronic acid.

PCIII, LN and HA levels were (113.79 ± 18.79) pg/ml, (119.43 ± 15.12) ng/ml and (77.56 ± 10.56) pg/ml in the EH group, (145.69 ± 23.50) pg/ml, (170.43 ± 11.24) ng/ml and (113.88 ± 7.57) pg/ml in the LVH group, and (14.40 ± 2.29) pg/mL, (11.48 ± 2.21) ng/mL, and (21.14 ± 3.86) pg/mL in the HC group, respectively. PCIII, LN and HA levels were the highest in the LVH group and the lowest in the HC group, with those of the EH group in between, with statistical significance among the three groups (P < 0.05) **Figure 2**.

Analysis of RFs influencing LVH in EH patients

BMI, LVMI, IL-6, IL-10, IL-18, PCIII, LN, and HA factors with differences between the EH group and LVH group were included in the analysis and used as dependent variables to assign values, while whether it affects EH + LVH was used as the dependent variable for multivariate analysis using the Logistic regression model. The results identified that BMI (P = 0.023), LVMI (P = 0.004), IL-6 (P = 0.029), IL-10 (P = 0.002), IL-18 (P = 0.037), PCIII (P = 0.010), LN (P = 0.008), and HA (P = 0.006) independently affected the occurrence of LVH in EH patients **Tables 2** and **3**.

Discussion

The clinical manifestation of EH is an increased systemic arterial blood pressure, accompanied by functional or organic damage to the heart,

Table 3. Multivariate analysis of factors influencing LVH in EH patients

Factor	β	S.E	Wald	P	OR	95% CI
BMI	1.736	0.954	3.453	0.023	2.341	1.365-3.847
LVMI	2.451	0.872	4.798	0.004	4.574	3.258-7.792
IL-6	0.887	0.711	6.651	0.029	3.058	2.245-5.473
IL-10	-2.254	0.894	7.146	0.002	0.674	0.301-0.845
IL-18	0.893	0.750	6.654	0.037	3.159	2.257-5.389
PCIII	0.125	0.287	6.750	0.010	3.047	1.947-5.247
LN	0.456	0.168	7.225	0.008	1.573	1.130-2.196
HA	0.789	0.303	7.032	0.006	2.212	1.233-3.978

Note: BMI, body mass index; LVMI, left ventricular mass index; IL-6, interleukin-6; IL-10, interleukin-10; IL-18, interleukin-18; PCIII, type III procollagen; LN, fibronectin; HA, hyaluronic acid.

brain, kidney and other organs [13]. At present, preventing and alleviating LVH has become the long-term treatment goal of EH [14]. Previous studies have also shown that LVH regression in EH patients can reduce the risk of overall cardiovascular events by 46% and improve patient prognosis [15]. This research confirms that inflammatory reactions and fibrosis are present in EH patients with LVH, which are independent RFs for EH + LVH.

Inflammation is involved in the key responses during EH-related myocardial remodeling [16]. IL-6 and IL-18 are highly expressed in M1 macrophages as pro-ICs, while IL-10 is overexpressed in M2 macrophages as an anti-IC [17]. The phenotypic conversion of macrophages not only modulates the inflammatory micro-environment but is closely related to left ventricular remodeling in EH [18]. IL-6 also acts as an indicator of systemic endothelial inflammation, which may promote the process of myocardial cell stiffness, hypertrophy and interstitial fibrosis by mediating the cross-linking between microvessels and cardiomyocyte compartments [19]. Meléndez et al. [20] pointed out that IL-6 may accelerate the pathological deterioration of EH by promoting processes such as myocardial fibrosis, concentric hypertrophy and diastolic dysfunction in rats. IL-18 is also a pro-hypertrophic IC, and the up-regulation of it and IL-6 is a typical hallmark of cardiac involvement [21]. As to IL-10, it participates in the chronic activation of the sympathetic nervous system, thus regulating cardiac hypertrophy and fibrosis [22]. In this study, IL-6 and IL-18 levels showed a significant increasing trend in HC, EH, and LVH groups, while IL-10 showed an obvious decreasing trend in these three groups. Findings from the research of Shi et al. [23], revealed that the higher the disease severity of patients with pregnancy induced hypertension syndrome, the higher the IL-6 level, which was similar to our findings. Su et al. [24] reported that IL-6 can act as a pro-inflammatory mediator to enhance vascular cell inflammation in EH lesions, showing significantly higher expression in EH patients compared with healthy controls, and notably elevated expression in EH patients with complications versus EH patients, which supports our findings. IL-10, as an immunoregulatory cytokine is protective of the vasculature, which may exert a protective mechanism against EH by activating cellular cascades [25]. In the study of Serinkan et al. [26] the level of IL-10 in the EH group was significantly lower than that in the HC group, which was consistent with our research results. De et al. [27] confirmed that IL-18 plays a promoting role in the pathological development of EH, mainly by participating in the activation of inflammasomes and cell pyroptosis to induce EH lesions.

PCIII, LN and HA are typical serum fibrosis makers and important components of the myocardial extracellular matrix (ECM), while excessive accumulation of the ECM is the main manifestation of cardiac fibrosis [28, 29]. In this study, PCIII, LN and HA were the highest in the LVH group, followed in descending order by the EH group, and the HC group, with statistical significance among the three groups. It suggests that there was significant cardiac fibrosis in EH patients compared with healthy controls, and the cardiac fibrosis in EH patients complicated by LVH was more prominent than that in EH patients. Li et al. [30] proposed in their study that the levels of PCIII, LN and HA in the rat liver fibrosis model decreased significantly after receiving anti-fibrotic drug therapy, suggesting that the three indexes may be positively correlated with the severity of fibrosis. Finally, we conducted a multivariate analysis on factors influencing LVH in EH patients, and identified that BMI, LVMI, IL-6, IL-10, IL-18, PCIII, LN and HA are independent RFs for EH complicated with LVH. Kianu et al. [31] reported an obviously positive connection between LVH in EH patients and BMI, and the role of BMI as a key

influencing factor of left ventricular mass in EH patients of African descent. Fu et al. [5] pointed out that elevated LVMI independently affected LVH in elderly EH patients, which is consistent with our research results. Moreover, ÖZzbïçer et al. [32] reported that IL-18 was independently related to LVMI in EH patients, suggesting that it may be a potential therapeutic target for EH patients with LVH.

Still, there are some limitations in this study that require further consideration. First, the sample size of this study was small, making it difficult to conduct a more detailed subgroup analysis. Second, this is a single-center retrospective study, which may result in potential problems such as selection bias and confounding factors. Finally, the detailed pathological mechanism of EH complicated with LVH needs further study and disclosure by laboratory experiments.

To sum up, EH patients complicated by LVH show more significant serum inflammation and fibrosis levels than EH patients, and BMI, LVMI, IL-6, IL-10, IL-18, PCIII, LN and HA are significantly related to the risk of LVH in EH patients, which provides a means for the prediction and monitoring of LVH in patients with EH.

Acknowledgements

This work was supported by the National Key Research and Development Program of China (Grant #2017YFC1307600) and the Science and Technology Program of Liaoning Province, China (Grant #2020JH1/10300002).

Disclosure of conflict of interest

None.

Address correspondence to: Yingxian Sun, Cardiovascular Medicine Department, First Affiliated Hospital of China Medical University, Nanjing North Street 155, Heping District, Shenyang 110001, Liaoning, China. Tel: +86-024-961200; E-mail: yxsundr@yeah.net

References

[1] Yan WF, Gao Y, Zhang Y, Guo YK, Wang J, Jiang L, Li Y and Yang ZG. Impact of type 2 diabetes mellitus on left ventricular diastolic function in patients with essential hypertension: evaluation by volume-time curve of cardiac magnetic resonance. Cardiovasc Diabetol 2021; 20: 73.

[2] Huang M, Long L, Deng M, Yu Z, Qu H, Tan L, Peng Y and Fu C. Effectiveness and safety of Yufeng Ningxin for the treatment of essential hypertension: a protocol for systematic review and meta-analysis. Medicine (Baltimore) 2021; 100: e24858.

[3] Yu J, Wei Y, Jing Y and Gao Y. Effect of acupuncture on essential hypertension: a protocol for systematic review and meta-analysis. Medicine (Baltimore) 2021; 100: e25572.

[4] GBD 2017 Risk Factor Collaborators. Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet 2018; 392: 1923-1994.

[5] Fu J, Lin F, Pan Z and Wu C. Correlations of circulating miR-26b level with left ventricular hypertrophy and cardiac function in elderly patients with hypertension. Pak J Med Sci 2021; 37: 966-971.

[6] Cuspidi C, Sala C, Negri F, Mancia G and Morganti A; Italian Society of Hypertension. Prevalence of left-ventricular hypertrophy in hypertension: an updated review of echocardiographic studies. J Hum Hypertens 2012; 26: 343-349.

[7] Zhang J, Yang L and Ding Y. Effects of irbesartan on phenotypic alterations in monocytes and the inflammatory status of hypertensive patients with left ventricular hypertrophy. BMC Cardiovasc Disord 2021; 21: 194.

[8] Formanowicz D, Rybarczyk A, Radom M and Formanowicz P. A role of inflammation and immunity in essential hypertension-modeled and analyzed using petri nets. Int J Mol Sci 2020; 21: 3348.

[9] Gordon JH, LaMonte MJ, Zhao J, Genco RJ, Cimato TR, Hovey KM, Andrews CA and Wactawski-Wende J. The association between serum inflammatory biomarkers and incident hypertension among postmenopausal women in the Buffalo OsteoPerio Study. J Hum Hypertens 2021; 35: 791-799.

[10] Xiao L and Harrison DG. Inflammation in hypertension. Can J Cardiol 2020; 36: 635-647.

[11] Loi H, Kramar S, Laborde C, Marsal D, Pizzinat N, Cussac D, Roncalli J, Boal F, Tronchere H, Oleshchuk O, Korda M and Kunduzova O. Metformin attenuates postinfarction myocardial fibrosis and inflammation in mice. Int J Mol Sci 2021; 22: 9393.

[12] Sueta D, Yamamoto E, Usuku H, Suzuki S, Nakamura T, Matsui K, Akasaka T, Shiosakai K, Sugimoto K and Tsujita K; ESES-LVH Study Investigators. Rationale and design of the efficacy and safety of esaxerenone in hyperten-

sive patients with left ventricular hypertrophy (ESES-LVH) study - protocol for a multicenter, open-label, exploratory interventional study. Circ Rep 2022; 4: 99-104.
[13] Fang G, Qi J, Huang L and Zhao X. LncRNA MRAK048635_P1 is critical for vascular smooth muscle cell function and phenotypic switching in essential hypertension. Biosci Rep 2019; 39: BSR20182229.
[14] Fagard RH, Celis H, Thijs L and Wouters S. Regression of left ventricular mass by antihypertensive treatment: a meta-analysis of randomized comparative studies. Hypertension 2009; 54: 1084-1091.
[15] Pierdomenico SD and Cuccurullo F. Risk reduction after regression of echocardiographic left ventricular hypertrophy in hypertension: a meta-analysis. Am J Hypertens 2010; 23: 876-881.
[16] Huang J, Liu Y, Chen JX, Lu XY, Zhu WJ, Qin L, Xun ZX, Zheng QY, Li EM, Sun N, Xu C and Chen HY. Harmine is an effective therapeutic small molecule for the treatment of cardiac hypertrophy. Acta Pharmacol Sin 2022; 43: 50-63.
[17] Wang J, Ding Q, Yang Q, Fan H, Yu G, Liu F, Bello BK, Zhang X, Zhang T, Dong J, Liu G and Zhao P. Vibrio alginolyticus triggers inflammatory response in mouse peritoneal macrophages via activation of NLRP3 inflammasome. Front Cell Infect Microbiol 2021; 11: 769777.
[18] Yu FF, Yang GH, Chen SB, Niu XL, Cai W, Tao YY, Wang XJ, Li M, Li YM and Zhao JH. Pseudolaric acid B attenuates high salt intake-induced hypertensive left ventricular remodeling by modulating monocyte/macrophage phenotypes. Med Sci Monit 2021; 27: e932404.
[19] Mocan M, Mocan Hognogi LD, Anton FP, Chiorescu RM, Goidescu CM, Stoia MA and Farcas AD. Biomarkers of inflammation in left ventricular diastolic dysfunction. Dis Markers 2019; 2019: 7583690.
[20] Melendez GC, McLarty JL, Levick SP, Du Y, Janicki JS and Brower GL. Interleukin 6 mediates myocardial fibrosis, concentric hypertrophy, and diastolic dysfunction in rats. Hypertension 2010; 56: 225-231.
[21] Tsuruda T, Higashi Y, Gi T and Nakao S. Pericardial effusion in the course of Fabry disease cardiomyopathy: a case report. Eur Heart J Case Rep 2021; 5: ytab407.
[22] Levick SP, Murray DB, Janicki JS and Brower GL. Sympathetic nervous system modulation of inflammation and remodeling in the hypertensive heart. Hypertension 2010; 55: 270-276.
[23] Shi F, Yu A and Yuan L. Clinical significance of detection of coagulation indexes, immune factors and inflammatory factors in patients with pregnancy-induced hypertension syndrome in China. Iran J Public Health 2019; 48: 681-687.
[24] Su Z, Tian S and Liang W. Circulating CTRP1 levels are increased and associated with the STOD in essential hypertension in Chinese patients. Cardiovasc Ther 2019; 2019: 4183781.
[25] Miguez JSG, Dela Justina V, Bressan AFM, Marchi PGF, Honorio-Franca AC, Carneiro FS, Clinton Webb R, Tostes RC, Giachini FR and Lima VV. O-Glycosylation with O-linked beta-N-acetylglucosamine increases vascular contraction: Possible modulatory role on Interleukin-10 signaling pathway. Life Sci 2018; 209: 78-84.
[26] Serinkan Cinemre FB, Cinemre H, Bahtiyar N, Kahyaoglu B, Agac MT, Shundo H, Sevinc L and Aydemir B. Apelin, Omentin-1, and Vaspin in patients with essential hypertension: association of adipokines with trace elements, inflammatory cytokines, and oxidative damage markers. Ir J Med Sci 2021; 190: 97-106.
[27] De Miguel C, Pelegrin P, Baroja-Mazo A and Cuevas S. Emerging role of the inflammasome and pyroptosis in hypertension. Int J Mol Sci 2021; 22:1064.
[28] Zhou Z, Xu L, Wang R, Varga-Szemes A, Durden JA, Joseph Schoepf U, Sun Z and Fan Z. Quantification of doxorubicin-induced interstitial myocardial fibrosis in a beagle model using equilibrium contrast-enhanced computed tomography: a comparative study with cardiac magnetic resonance T1-mapping. Int J Cardiol 2019; 281: 150-155.
[29] Ibarrola J, Garaikoetxea M, Garcia-Pena A, Matilla L, Jover E, Bonnard B, Cuesta M, Fernandez-Celis A, Jaisser F and Lopez-Andres N. Beneficial effects of mineralocorticoid receptor antagonism on myocardial fibrosis in an experimental model of the myxomatous degeneration of the mitral valve. Int J Mol Sci 2020; 21: 5372.
[30] Li C, Meng M, Guo M, Wang M, Ju A and Wang C. The polysaccharides from Grifola frondosa attenuate CCl4-induced hepatic fibrosis in rats via the TGF-beta/Smad signaling pathway. RSC Adv 2019; 9: 33684-33692.
[31] Kianu Phanzu B, Nkodila Natuhoyila A, Kintoki Vita E, M'Buyamba Kabangu JR and Longo-Mbenza B. Association between insulin resistance and left ventricular hypertrophy in asymptomatic, Black, sub-Saharan African, hypertensive patients: a case-control study. BMC Cardiovasc Disord 2021; 21: 1.
[32] S OZ and Ulucam ZM. Association between interleukin-18 level and left ventricular mass index in hypertensive patients. Korean Circ J 2017; 47: 238-244.