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To Investigate the Pathogenesis and Inflammatory Response of Premature Ventricular Contractions Based on MAPK Signaling Pathway

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Abstract: **Objective:** To explore the involvement of MAPK signaling pathway in the pathogenesis of premature ventricular contractions (PVCs) and the regulation of inflammatory response. **Methods:** A total of 40 patients with PVCs admitted to Xi'an Hospital of Traditional Chinese Medicine from June 2021 to December 2021 were randomly selected as the observation group, and 40 healthy subjects during the same period were selected as the control group. Blood samples were collected intravenously, and the levels of MAPK, IL-1β, IL-6 and TNF-αin serum of the subjects were detected by enzyma-linked immunosorbent assay (ELISA). To analyze the relationship between MAPK signaling pathway and PVC and regulation of inflammatory response. **Results:** Compared with the control group, the levels of serum MAPK and inflammatory factors IL-1β, IL-6 and TNF-αin observation group were significantly increased ($P<0.05$), and the expression of MAPK signaling pathway was highly positively correlated with the levels of inflammatory factors IL-1β, IL-6 and TNF-αin observation group. **Conclusion:** The pathogenesis of PVCs may be related to MAPK signaling pathway and inflammatory response. PVCs may promote the release of IL-1β, IL-6 and TNF-α by activating MAPK signaling pathway, up-regulating MAPK expression, and inducing inflammatory response.

1. Introduction

Premature ventricular contractions (PVCS), referred to as premature ventricular contraction caused by premature depolarization of ectopic rhythm points of ventricular muscles below his bundle and its branches, are one of the common arrhythmias in clinical practice. It can be seen in normal healthy people and patients with various heart diseases, and its incidence is positively correlated with age. The incidence of 24 h or 48 h holter can be as high as 40%-75% [1]. A study has shown that ventricular premature beat load is an independent influencing factor of cardiac dysfunction [2]. More studies have confirmed that frequent ventricular premature contractions may promote hemodynamic changes and increase myocardial oxygen consumption by improving the excitatory activity of

sympathetic nerves and vagus nerves, increasing ventricular perfusion, reducing cardiac systolic efficiency and other mechanisms, thereby damaging cardiac structure and affecting cardiac diastolic and systolic functions. It can lead to secondary cardiomyopathy, even malignant arrhythmia, sudden cardiac death, heart failure and other serious heart diseases [3-5].

Premature ventricular contractions are often induced by poor lifestyle or organic heart disease, the latter caused by coronary heart disease is particularly common, and its onset is closely related to myocardial ischemia and hypoxia.

A study of cytokines and premature ventricular contractions-induced cardiomyopathy (PIC) showed that several proinflammatory factors in the serum of patients with PIC, for example, interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) were significantly increased. In the presence of this inflammatory response, peripheral monocytes are activated to produce a large number of inflammatory mediators, which may contribute to the development of PIC [6]. Therefore, the study on the changes of serum inflammatory factors in patients with premature ventricular contractions is helpful to early predict the possible adverse consequences of premature ventricular contractions, so as to help judge the severity and prognosis of patients.

Mitogen-activated protein kinase (MAPK) signaling pathway plays an important regulatory role in a variety of cardiomyocyte injury and inflammation [7]. A large number of experimental studies have shown that inhibiting or blocking MAPK signaling pathway can reduce myocardial oxygen consumption, improve myocardial ischemia and injury, and inhibit myocardial fibrosis [8-10]. It also exhibits anti-inflammatory, anti-apoptotic and antioxidant activities to a certain extent [11]. Studying the expression of serum MAPK signaling pathway in patients with ventricular premature contractions is conducive to verifying the regulatory role of MAPK signaling pathway in the pathogenesis of ventricular premature contractions, and observing the related changes of MAPK and inflammatory factors is helpful to understand the regulatory role of this pathway in the inflammatory response of patients.

Therefore, this study aimed to analyze the involvement and expression mechanism of MAPK signaling pathway in the pathogenesis of ventricular premature contraction, and to analyze the role of MAPK signaling pathway in regulating inflammatory response by observing the levels of serum inflammatory factors interleukin-1β (IL-1β), interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α). To provide experimental data reference for clinical research on the related physiological and pathological mechanisms and treatment ideas of premature ventricular contractions.

2. Data and methods

2.1. General data

A total of 40 patients who met the diagnosis of premature ventricular contractions in Xi 'an Hospital of Traditional Chinese Medicine from June 2021 to December 2021 were randomly selected as the observation group, and 40 healthy people in the same period were selected as the control group. There were 17 males and 23 females in the observation group. The average age was (47.70±12.84) years (range, 13-72 years). There were 19 males and 21 females in the control group. The average age was (44.10±12.94) years (range, 22-69 years). There was no significant difference in clinical data between the two groups ($P > 0.05$), which was comparable. The study was in accordance with the ethical standards for human experimentation and approved by the ethics Committee of Xi'an Hospital of Traditional Chinese Medicine. All subjects signed the informed consent voluntarily.

The inclusion criteria of the observation group were as follows: (1) Electrocardiogram: ① QRS wave group occurred in advance, the duration was usually more than 0.12 seconds, broad deformity, the direction of ST segment and T wave was opposite to the direction of the main QRS wave; (2)

Constant pairing interval; (3) Complete compensatory interval after ventricular presystole. (2) Lown classification of ventricular premature contractions on 24-hour holter: Grade 0: no ventricular prephase contraction; Grade 1: sporadic, single form of ventricular prephase contraction < 30 / hour; Grade 2: frequent, single form of ventricular prephase contraction ≥30 times/hour; Grade 3: frequent, multiform ventricular prephase contraction; Class 4A: consecutive paired preventricular contractions; Grade 4B: ≥3 consecutive preventricular contractions; Level 5: R-on-T. Any item in (1) and (2) can be diagnosed [12]. Exclusion criteria :(1) persons with mental disorders; (2) pregnant or breastfeeding women, allergic constitution and allergic to a variety of drugs; (3) Patients with ventricular arrhythmia caused by digitalis poisoning, electrolyte disturbance and acid-base imbalance; (4) Patients with hepatic or renal insufficiency or critically ill or multiple organ failure complicated with ventricular arrhythmia; (5) Marked bradycardia (including sick sinus syndrome and atrioventricular block above degree II); (6) supraventricular premature contractions with differential conduction and intermittent ventricular preexcitation.

2.2. Experimental Methods

5 mL of fasting elbow venous blood was collected, centrifuged at 3000 R /min for 10 min, and the supernatant was taken and stored in a refrigerator at -20℃. The serum levels of MAPK, IL-1β, IL-6 and TNF-α were detected by enzyme-linked immunosorbent assay (ELISA). All the kits were purchased from Xi 'an Lanrui Biotechnology Co., LTD., and the microplate reader was used for detection. The experiment was carried out in strict accordance with the kit instructions and instrument operation guide.

2.3. Statistical Methods

Chi-square test was used for counting data, t-test was used for measurement data, and independent sample t-test was used for comparison between groups. Linear regression model was used to analyze the relationship between MAPK and inflammatory factors. 0.05 was considered statistically significant.

3. Result

3.1. Comparison of serum MAPK levels between the two groups

The serum MAPK level in the observation group was significantly higher than that in the control group, and the difference was statistically significant (P < 0.05), as shown in Table 1.

Table 1: Comparison of serum MAPK levels between the two groups ($\bar{x} \pm s$)

Groups	n	MAPK(pg/mL)
observation group	40	88.85±19.12
control group	40	72.29±19.85
t value		3.799
P value		＜0.001

3.2. Comparison of serum inflammatory factors IL-1β, IL-6 and TNF-α levels between the two groups

The levels of serum inflammatory factors IL-1β, IL-6 and TNF-α in the observation group were significantly higher than those in the control group, and the differences were statistically significant

(P < 0.05), as shown in Table 2.

Table 2: Comparison of serum inflammatory factors IL-1β, IL-6 and TNF-α levels between the two groups ($\bar{x} \pm s$)

Groups	n	IL-1β(pg/mL)	IL-6(pg/mL)	TNF-α(pg/mL)
observation group	40	74.49±16.48	41.38±8.50	59.21±8.89
control group	40	66.69±12.19	34.73±8.34	53.11±10.18
t value		2.405	3.533	2.857
P value		0.019	0.001	0.005

3.3. Correlation analysis of serum MAPK expression and inflammatory factors in patients with premature ventricular contraction

Serum MAPK expression in patients with ventricular premature contractions was highly positively correlated with the levels of inflammatory factors IL-1β, IL-6 and TNF-α (P < 0.05), as shown in Table 3.

Table 3: Correlation between serum MAPK expression and inflammatory factors in patients with ventricular premature contraction

Factor	Linear Model	r	r2	P value
MAPK and IL-1β	Y=1.078X+8.537	0.929	0.863	<0.001
MAPK and IL-6	Y=2.126X+0.875	0.945	0.893	<0.001
MAPK and TNF-α	Y=2.028X-31.234	0.942	0.888	<0.001

4. Discussion

Premature ventricular contractions (PVCS) are one of the common arrhythmias in clinical practice,with varying degrees of symptoms and severity. Many domestic and foreign studies have pointed out that frequent premature ventricular contractions can lead to cardiomyocyte injury, cardiac structural changes, cardiac dysfunction, and increase the risk of cardiomyopathy, heart failure, and even sudden cardiac death [13]. In myocardial injury, endothelial cells are more likely to be injured, and the damage of vascular endothelial function will promote the secretion of inflammatory factors by endothelial cells. Appropriate inflammatory response will help to eliminate apoptotic cells and promote the recovery of ischemic myocardium. However, when the elimination of inflammatory reaction is delayed or excessive, inflammatory cell infiltration will be triggered, which will further accelerate myocardial cell injury, induce myocardial cell apoptosis, and lead to myocardial necrosis [14]. Apoptotic cardiomyocytes release proinflammatory cytokines, including IL-1β, IL-6, TNF-α, etc., which may expand ischemic injury of normal cardiomyocytes [15].

In recent years, MAPK has been proved to be an important signaling pathway in ventricular myocytes, which can regulate cardiomyocyte fibrosis, participate in a variety of inflammatory reactions, and activate REDOX stress and proinflammatory cytokines, including IL-1β, etc [16]. Some anti-inflammatory immune modulators can reduce inflammatory infiltration, inhibit myocardial lymphocyte infiltration and regulate body immunity through MAPK signaling pathway [17]. A network pharmacological study showed that drugs may play a therapeutic role in premature ventricular contractions by acting on MAPK signaling pathway [18]. Therefore, MAPK signaling pathway may be involved in the expression and regulation of inflammatory response in the pathogenesis of PVCS.

The results of this study showed that the serum MAPK level in patients with PVCS was

significantly higher than that in the control group, which verified the involvement and regulation of MAPK signaling pathway in the pathogenesis of PVCS. Compared with the control group, the levels of serum inflammatory factors IL-1β, IL-6 and TNF-α in the patients were significantly increased, indicating that the onset of premature ventricular contractions activated the infiltration of inflammatory cells through some mechanisms and triggered the inflammatory response. In addition, serum MAPK expression in patients with PVCS is highly positively correlated with the levels of inflammatory factors IL-1β, IL-6 and TNF-α, suggesting that the inflammatory response in patients with PVCS may be related to the involvement and regulation of MAPK signaling pathway. It is concluded that ventricular premature contractions can lead to ischemia and hypoxia injury of cardiomyocytes and impaired function of vascular endothelial cells, thereby activating intracellular MAPK signaling pathway, upregulation of MAPK expression, promoting the release of inflammatory factors IL-1β, IL-6 and TNF-α, and inducing inflammatory response.

To sum up, the serum MAPK signaling pathways associated with the onset of patients with ventricular premature beat, ventricular premature beat all the levels of inflammatory markers in serum increased that it has obvious inflammation in the body, and MAPK signal pathways and the inflammation factor showed high correlation, prompt MAPK signaling pathway may be involved in regulating the body's inflammatory response caused by ventricular premature beat. However, this study only showed the correlation between patients with PVCS and MAPK signaling pathway and inflammatory changes, without in-depth exploration of the specific mechanism, which needs to be further studied in the future.

References

[1] Cao Kejiang, Chen Keping, Chen Minglong, et al.2020 Chinese Expert Consensus on Ventricular arrhythmia (Upgraded version of 2016 Consensus) [J]. Chinese Journal of Cardiac Pacing and Electrophysiology, 2020, 03: 189-253.

[2] Zhang Yixue, Chen Moshui.Research progress on the relationship between premature ventricular contractions and cardiac dysfunction [J]. Guangdong Medical Journal, 2014, 35(05): 791-793.

[3] Guo Jihong. Discussion on the pathogenesis of premature ventricular cardiomyopathy [J]. Journal of Clinical Electrocardiology, 2015, 24(03): 215-226.

[4] Yang Li, Guo Lijun, Wang Lixin. Effects of frequent right ventricular outflow tract premature contractions on left ventricular diastolic function in young people [J]. Chinese Journal of Cardiology, 2021, 03: 219-223.

[5] Gopinathannair R, Etheridge SP, Marchlinski FE,et al. Arrhythmia-Induced Cardiomyopathies: Mechanisms, Recognition, and Management. [J]. Journal of the American College of Cardiology. 2015; 66(15): 1714-1728.

[6] Ghadrdoost B, Aboutaleb N, Nikougoftar Zarif M, et al. Association between cytokines and two circulating micro-RNAs and development of premature ventricular contractions-induced cardiomyopathy. [J]. Iranian journal of basic medical sciences. 2019; 22(10): 1125-1131.

[7] Zheng Enchanting, Wang Fuwen.The role of p38MAPK in myocardial injury [J]. Food and Medicine, 2015, 01: 59-63.

[8] Yang Fei, Huang Hui, Wang Fang, et al. The protective effect of Asiaticoside on myocardial ischemia-reperfusion injury in rats and the influence of MAPK pathway [J]. Chinese Journal of Hospital Pharmacy, 2021, 15: 1514-1518.

[9] Hirschhäuser Christine, Lissoni Alessio, Görge Philipp Maximilian, et al. Connexin 43 phosphorylation by casein kinase 1 is essential for the cardioprotection by ischemic preconditioning. [J]. Basic research in cardiology, 2021, 116(1) : 21-21.

[10] Zhang Sijie, Wu Yaqiong, Li Xingtao. Protective effect of p38MAPK inhibitor combined with coenzyme Q10 on rat cardiomyocytes under oxidative stress [J]. Journal of Zhengzhou University (Medical Science), 2019, 05: 699-703.

[11] Ekta Mutneja, Vipin K. Verma, Salma Malik, et al. Erdosteine salvages cardiac necrosis: Novel effect through modulation of MAPK and Nrf-2/HO-1 pathway [J]. Journal of Biochemical and Molecular Toxicology, 2020, 34(12): e22590-e22590.

[12] Standardization project group of Clinical Application Guidelines for the Treatment of Dominant Diseases by proprietary Chinese Medicines. Clinical application guideline of Chinese patent medicine in the treatment of premature ventricular contractions (2020) [J]. Chinese Journal of Integrated Traditional and Western Medicine, 2021, 06: 646-651.

[13] Huang Yongqi, Tian Longhai, Yang Long. Ventricular presystolic cardiomyopathy [J]. Progress in Cardiology, 2022, 43(04): 348-351.

[14] Zhang Jiehan, Li Hongrong. The role of microvascular endothelial cell dysfunction in cardiac arrhythmias [J]. Journal of Difficult Diseases, 2021, 20(12): 1273-1276+1281.
[15] Lu Bin, Liu Xiao, Tan Wangxiao, et al. Role of inflammatory cascade in the development of myocardial infarction and drug therapy [J]. Journal of Tianjin University of Traditional Chinese Medicine, 2021, 04: 424-430.
[16] Daniel N Meijles, Joshua J Cull, Thomais Markou , et al. Redox Regulation of Cardiac ASK1 (Apoptosis Signal-Regulating Kinase 1) Controls p38-MAPK (Mitogen-Activated Protein Kinase) and Orchestrates Cardiac Remodeling to Hypertension [J]. Hypertension (Dallas, Tex.: 1979), 2020, 76(4), 1208-1218.
[17] Sun Lin. IL-37 alleviates cardiomyocyte apoptosis in viral myocarditis by inhibiting P38 MAPK signaling pathway [D]. Shandong university, 2021.
[18] Qian Wei, Hu Yuanhui, Hao Zhiye, et al. Study on the efficacy and network pharmacology of Zhizigui decoction Hedanzhi Xiaoyao Sanhua Decoction in the treatment of 97 patients with ventricular prephase contraction of coronary heart disease [J]. Anhui medicine, 2021, 07: 1459-1463+1486-1487.