



Interaction of Inflammatory Response and Sympathetic Nervous System in the Central Regulation of Chronic Heart Failure in Rats

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Conclusion: Inhibition of RAS levels in the central nervous system in rats with chronic heart failure can reduce the CHF of the sympathetic system and peripheral immune response to inflammation, improve heart function.

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I. INTRODUCTION

Immune inflammatory response and sympathetic nervous system activation plays an important role in the occurrence and development of chronic heart failure (CHF) [1,2], But its activation mechanism and the relationship between central and peripheral levels of activation are not clear. There is evidence to show that CHF central renin angiotensin angiotensin system (RAS) over enhancement, central Pro inflammatory cytokines (PIC) increased expression, and promote the activity of the sympathetic nervous system over enhancement, but the second not mediated CHF state week immune inflammatory reaction is uncertain [3, 4]. In this study, the CHF model of myocardial ischemia was made by ligation of the left anterior descending branch of the left coronary artery, and the central and peripheral

sympathetic activity and immune inflammatory response were observed at different time points after ligation. And through the intervention of the central level of RAS, to observe whether the coronary artery ligation in rats can reduce the level of immune inflammatory reaction and sympathetic nervous system activity, and improve the cardiac function. To provide new ideas and basis for the prevention and treatment of CHF.

II. MATERIALS AND METHODS

- a) **Animals and groups:** 36 rats of SPF grade male Sprague Dawley rats (Chinese Academy of Sciences Shanghai Laboratory Animal Center, weight of 280 to 320 g, were randomly divided into 3 groups: operation group (model), sham operation group (sham) and central intervention group (int), 12 rats in each group; central intervention group and operation group underwent coronary artery ligation surgery. In the sham group only thread ligation; central intervention group after operation via mini osmotic pumps to the bilateral lateral ventricle for 6 weeks to give AT1 receptor blocker losartan losartan 0.05ug/h. All rats were provided in the same environment and diet.
- b) Coronary artery anterior descending branch ligation experimental rats given ketamine (30 mg / kg) were anesthetized by intraperitoneal injection and adequate anesthesia endotracheal intubation mechanical ventilation (ALC - V8, Shanghai Alcott Biological Technology Co., Ltd.), open chest to expose the heart, with 6 / 0 fine needle through ligating coronary artery before descending of preparing the model of myocardial ischemia, ECG monitoring suggest that limb lead R wave amplitude increased, with I and AVL lead ST segment elevation prompt model was made successfully. Rats in sham operation group were only in the same area of the anterior descending branch of the heart coronary artery but not ligation.
- c) **Echocardiography detection:** The cardiac function of rats was detected by SEQUOIA ACUSON 512 ultrasonic diagnostic apparatus: The test items included left ventricular short axis systolic rate (FS), ejection fraction (EF), systolic left ventricular posterior wall thickness (LVPWs), left ventricular end

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diastolic diameter (LVEDD), and systolic left ventricular diameter (LVIDs).

- d) *Detection of sympathetic nerve activity Based on the level of sympathetic nerve activity:* A quick jugular vein injection of nerve blocking agent six hydrocarbon quaternary amine, to the average arterial pressure (MAP) decreased, MAP decreased the greater the higher the level of the basis of sympathetic nerve activity.
- e) The levels of catecholamine and inflammatory factors were detected by double antibody sandwich ELISA method, NE, E levels and TNF-, IL-1, IL-6 levels. All operations were carried out strictly in accordance with the instructions of the kit.
- f) Statistical methods using spss16 statistical software for statistical analysis, measurement data with mean

+ standard deviation ($\bar{X} \pm S$) to express data using single factor variance analysis, the groups were compared using t test, $P < 0.05$ said there was a statistically significant difference.

III. RESULTS

- a) Echocardiographic parameters. Compared with group Sham, LVPWs, LVIDd and LVIDs were significantly increased in group Model (P mean < 0.05); FS and EF were significantly lower (P mean < 0.05). Int group compared with LVPWs group Model, LVIDd and LVIDs were both decreased (P mean < 0.05); FS and EF increased (P mean < 0.05) (Table 1)

Table 1: Weeks after type M rat heart ultra parameters ($\bar{X} \pm S$, $n=12$)

Group	LVPWs(cm)	LVIDd(cm)	LVIDs(cm)	FS(%)	EF(%)
Sham	0.22±0.02 [#]	0.60±0.05 [#]	0.44±0.10 [#]	59.47±3.17 [#]	77.45±5.71 [#]
Model	0.33±0.03 [*]	0.89±0.10 [*]	0.78±0.12 [*]	21.45±2.11 [*]	40.20±3.76 [*]
Int	0.25±0.02 ^{*#}	0.68±0.04 ^{*#}	0.49±0.11 ^{*#}	37.78±3.42 ^{*#}	49.16±3.03 ^{*#}

Note: compared with Sham group, $*P < 0.05$; compared with Model group, $\#P < 0.05$.

- b) Sympathetic nerve activity level Compared with the sham operation group rats, the rats were subjected to left coronary anterior descending artery ligation of 6 weeks after baseline sympathetic nerve activity level increased significantly (22.17 + 3.25 Δ mmHg vs 47.74 5.28 + Δ mmHg, $P < 0.05$); int group compared with the model group decreased (35.08 + 2.75 delta mmHg vs 47.74 5.28 + Δ mmHg, $P < 0.05$).
- c) Ligation of left anterior descending coronary artery in rats after 3 days, 1 week, 2 weeks, 4 weeks, 6 weeks and plasma catecholamine, PIC levels were compared with the sham operated rats, coronary artery ligation rats plasma NE levels with time prolonged significantly increased, e non significant difference; coronary artery node ligation group plasma pic levels were also increased with time and increased significantly (Figure 1).

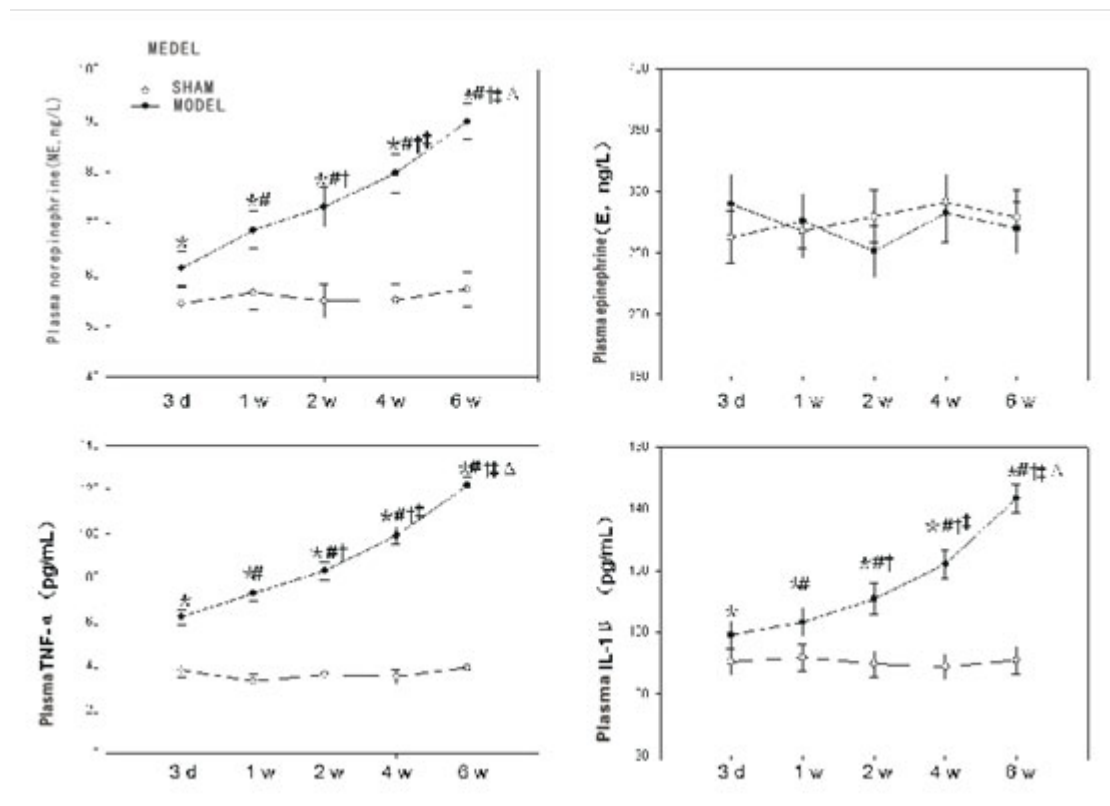


Fig. 1: Plasma catecholamine levels after operation. Compared with sham operated rats, the plasma NE level of the coronary artery ligation group was significantly higher than that of the E, while there was no significant difference between the two groups. Data to indicate. * at the same time with the sham operation group compared ($P < 0.05$). # and coronary artery ligation 3 D compared ($P < 0.05$). Compared to the 1 W † and coronary artery ligation ($P < 0.05$). Compared to the and coronary artery ligation in 2 w ($P < 0.05$). Compared to the Delta and coronary artery ligation for 4 W, $P < 0.05$.

d) Ligation of left anterior descending coronary artery in rats after 3 days, 1 week, 2 weeks, 4 weeks, 6 weeks central pic levels were compared with the sham operated rats, coronary artery ligation group rat paraventricular nucleus (PVN) and rostral ventrolateral medulla Department (RVLM) in TNF alpha, IL-1 beta level from 3 days to 6 weeks were significantly increased, but between each time point without significant difference. (Figure 2)

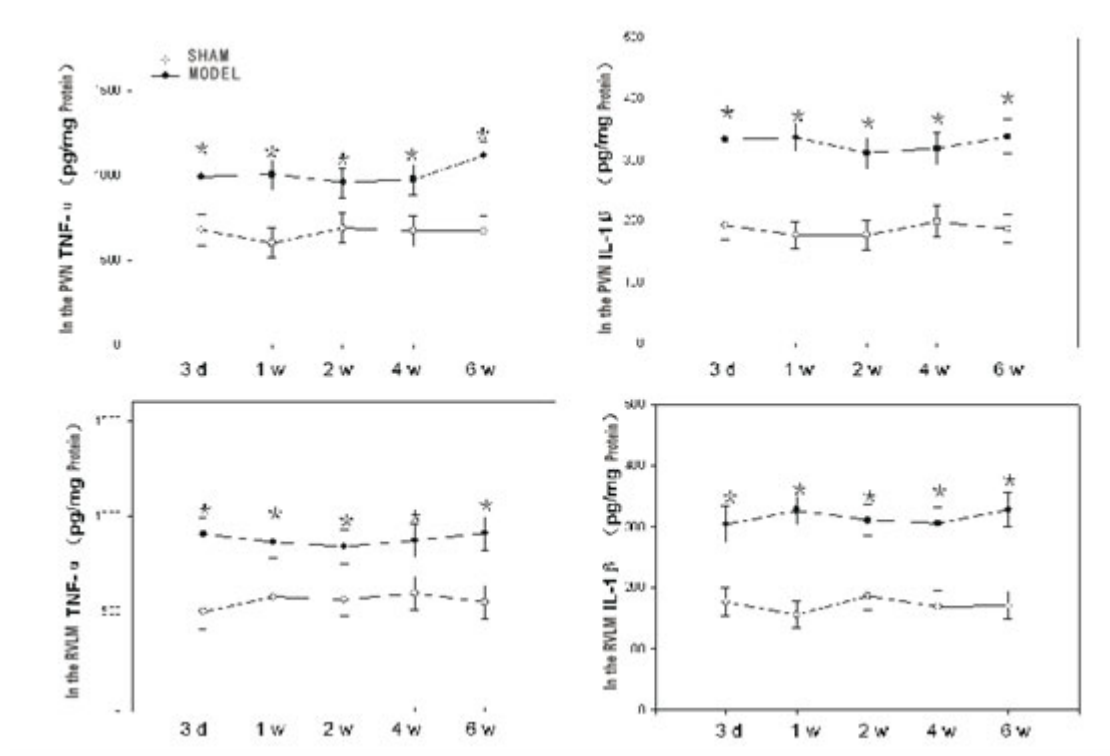


Figure 2: PVN and TNF-α in RVLM and IL-1β after operation. Compared with sham operated rats, 3 D, 1 W, 2 W, 4 W, 6 W, RVLM, PVN, TNF-α, and the levels of and IL-1β in the coronary artery ligation group were significantly higher than that in sham operated rats. Data to indicate. * compared with sham operated group at the same time point, P<0.05.

e) The effect of RAS intervention on the level of immune response and sympathetic nervous system activity in the peripheral level of the central nervous system. Compared with group Sham, the levels of TNF-α, IL-1β and NE in group Model were significantly increased (P mean <0.05), and E had no significant change (P>0.05). The levels of Int group compared with TNF-α group Model, IL-1β and NE were all decreased (P mean <0.05), and E had no significant change (P>0.05). (Table 2).

Table 2: Comparison of parameters of peripheral immune inflammatory response and sympathetic nervous system activity in rats after 6 weeks ($\bar{X} \pm S$, n=12)

Group	TNF-α (pg/ml)	IL-1β (pg/ml)	NE (ng/l)	E (ng/l)
Sham	36.27±3.04 [#]	87.60±5.05 [#]	52.37±4.62 [#]	259.96±13.17
Model	118.47±3.79 [*]	140.27±5.17 [*]	92.27±8.1 [*]	268.62±12.31
Int	61.22±4.02 ^{*#}	103.63±4.74 ^{*#}	64.44±5.71 ^{*#}	262.32±13.12

Note: compared with Sham group, *P<0.05; compared with Model group, #P<0.05.

f) Effect of RAS intervention on central immune response to central immune system. Compared with the sham group, model group PVN and RVLM of TNF-α and IL-1β levels were significantly increased (P < 0.05); int group PVN and RVLM of TNF-α and IL-1β level compared with model group PVN and RVLM of TNF-α and IL-1β levels decreased (P <0.05). (Table 3).

Table 3: Comparison of parameters of central immune system in rats after 6 weeks ($\bar{X} \pm S$, n=12)

Group	TNF-α (pg/mgprotein)		IL-1β (pg/mgprotein)	
	PVN	RVLM	PVN	RVLM
Sham	734.22±42.04 [#]	484.82±32.37 [#]	189.66±22.02 [#]	174.47±20.05 [#]
Model	1018.47±105.79 [*]	881.73±62.45 [*]	369.97±25.82 [*]	304.04±24.47 [*]
Int	821.04±41.02 ^{*#}	618.54±35.57 ^{*#}	263.24±24.04 ^{*#}	231.15±15.48 ^{*#}

IV. DISCUSSION

Chronic heart failure (CHF) is a serious hazard to human health, but the treatment effect is not good enough. Urgent need to explore the mechanism of CHF disease progression in order to find a more effective treatment. There is an interaction between sympathetic nervous system and immune system activation in the CHF state. In the past, most of the researches are based on the activation of sympathetic nervous system and immune system, which is an effective method for the treatment of CHF. Less research about the interaction between sympathetic nervous system and immune system in CHF, especially the change of the peripheral activity of a certain factor. Studies have shown that CHF myocardial ischemia and infarction by autonomic nerve afferent signals reach the central, thereby inducing central pic increased generation [5, 8], and central pic and ROS[2; 7]; mutual effect of 8] and RAS[9] system in control of sympathetic activity, inhibition of central pic can reduce the CHF of the sympathetic nervous system excitability [6,7]. However, it is not clear whether CHF and RAS in the PIC state of cardiovascular central nuclei, such as the nucleus of the hypothalamus (PVN) and the rostral medulla (RVLM), mediate the inflammatory response. In this study, the CHF model of myocardial ischemia was made by ligation of the left anterior descending branch of the left coronary artery, and the central and peripheral sympathetic activity and immune inflammatory response were observed at different time points after ligation. Compared with the sham operated rats, coronary artery ligation rats plasma NE levels with time prolonged significantly increased, e non significant difference was found; coronary artery ligation rats plasma pic levels also with time prolonged increased significantly; coronary artery ligation group rat paraventricular nucleus (PVN), Yin cord rostral ventrolateral (RVLM) TNF alpha and IL-1 beta level from 3 days to 6 weeks were significantly increased, but between each time point without significant difference. Further, we use via mini osmotic pumps to the bilateral lateral ventricle for 6 weeks to give AT1 receptor blocker losartan intervention central RAS, observe whether it can reduce the coronary artery ligated rats the level of peripheral inflammatory reaction and the activity of the sympathetic nervous system, improve heart function; Results suggest that heart failure rat sympathetic nerve activity level was significantly enhanced and peripheral plasma TNF alpha, IL-1 beta and NE levels were significantly increased ($P < 0.05$), and given the AT1 receptor blockade losartan via mini osmotic pumps to the bilateral lateral ventricle administration intervention RAS in central nervous system after the excessive proliferation of strong sympathetic nerve activity level decreased significantly and peripheral TNF alpha, IL-1 beta and NE levels were decreased ($P < 0.05$). That

heart failure rat central RAS inhibition can reduce the peripheral excessive inflammatory reaction and the activity of the sympathetic nervous system, also found that the intervention after cardiac function was significantly improved, and the model group were significant differences ($P < 0.05$), suggesting that the cardiac function as with inhibition of Ras in central nervous system, thereby reducing the CHF when the excitement of the sympathetic system and outer peripheral immune inflammation. This study is expected to explain the mechanism of the interaction between the sympathetic nervous system and the immune system, and provide a new idea and basis for the prevention and treatment of CHF. In addition, this study on heart failure rats given AT1 receptor blockade losartan via mini osmotic pumps to the bilateral lateral ventricle administration intervention central Ras levels found the pivot pic levels were also significantly decreased, the interaction between the two and peripheral inflammation, sympathetic nerve activity regulation of network access and the specific mechanism still need further study.

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