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Ghrelin Prevents Malignant Arrhythmia and Early Left Ventricular Remodeling in Rats with Myocardial Infarction*

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ABSTRACT Objective: To investigate the effects of ghrelin on the cardiovascular system in rats with myocardial infarction (MI), such as preventing malignant arrhythmia, delaying left ventricular remodeling and decreasing mortality. **Methods:** Ghrelin (100 μg/kg sc, twice daily) or saline were administered for 2 weeks from the day of MI operation in Wistar rats. The effects of ghrelin on cardiac remodeling were evaluated by echocardiographic and hemodynamic. Serum insulin-like growth factor I (IGF-I), plasma concentrations of epinephrine, norepinephrine, and dopamine were measured by using enzyme immunoassay kit. Before and after ghrelin (100 μg/kg sc) was administered in conscious rats with MI, the autonomic nervous function was investigated by power spectral analysis obtained by a telemetry system. **Results:** Results showed that compared with that in the control group rats, the percent survival of ghrelin treated rats increased significantly ($P< 0.05$), the cardiac function enhanced remarkably, but the size of the infarct of the left ventricular wall did not significantly differ between MI + NS rats and MI + Ghrelin rats ($P> 0.05$). **Conclusions:** Ghrelin can increase the survival rate, improve cardiac arrythmias and alleviate left ventricular remodeling of myocardial infarction rats.

Key words: Ghrelin; Myocardial infarction; Left ventricular remodeling; Cardiac arrythmias
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Introduction

Myocardial infarction (MI) is one of the most common causes of death in the industrialized countries. In most cases, death occurs during the acute phase, i.e. the first 3-6 h after MI. The high mortality mainly results from malignant ventricular arrhythmia, which is strongly associated with an adverse and sustained increasing in cardiac sympathetic nerve activity (CSNA) [1]. Even for those who survive the immediate infarct, increased CSNA is also thought to contribute to left ventricular (LV) remodeling, which results in subsequent heart failure and mortality[2,3]. β-Adrenergic blockader, through the suppression of CSNA, has been shown to reduce the incidence of ventricular arrhythmia, attenuate the adverse ventricular remodeling, and decrease mortality after MI[4].

Ghrelin is a novel growth hormone (GH)-releasing peptide, originally isolated from the stomach, which has been identified as an endogenous ligand for the GH secretagogue receptor (GHS-R) [5]. GHS-R mRNA is detected in not only the hypothalamus and pituitary but also the heart and blood vessels , and much evidence for a cardiovascular function of ghrelin has been reported[6]. Previous studies revealed that chronic administration of ghrelin improved cardiac performance in rats with chronic heart failure, as indicated by increaseing in cardiac output and left ventricular (LV) fractional shortening [7] and that intravenous bolus infusion of human ghrelin significantly decreased mean arterial pressure in patients with chronic heart failure [8]. However, the precise mechanism of ghrelin actions remains unclear.

Therefore, in this study the rats with MI were randomly divided into two groups, ghrelin (100 μg/kg twice daily) or saline was administered subcutaneously for 2 weeks, the physiological indexes contrast with the sham-operated, we aimed to show, that administration of ghrelin after MI would be able to improve survival rate, attenuates development of cardiac cachexia and prevents early left ventricular remodeling.

1 Materials and Methods

1.1 Animals

The experiments used male Wistar rats (200-230 g, provided by Qingdao Institute of Marine Drug). The animals were housed in a temperature-controlled room (22-28 ℃) and exposed to light from 8:00 a.m. to 8:00 p.m. Standard laboratory chow pellets and tap water were available ad libitum. All of the animal experiments were approved and conducted according to guidelines for animal experimentation established by the Institutional Animal Care and Use Committee at Qingdao University.

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1.2 Model of MI

The rats were anesthetized with pentobarbital sodium (30 mg/kg ip). After a left thoracotomy, the left coronary artery was ligated 2 to 3 mm from its origin using a 6-0 Prolene suture. The chest was closed and the rats were allowed to recover. Sham-operated rats underwent the identical surgical procedure without coronary artery ligation.

1.3 Administration of ghrelin

From the day after the coronary ligation, the rats with MI were randomly divided into two groups: one to be administered with synthetic rat ghrelin (MI + ghrelin, n=50) and the other with saline (MI + NS, n=50) as vehicle. The sham-operated rats were administered with saline (SO + NS, n=30). Ghrelin (100 μg/kg twice daily, the dose of which was shown to improve LV function in rats with chronic heart failure [7]) or saline was administered subcutaneously for 2 weeks from the day after the operation.

1.4 Echocardiographic and hemodynamic studies

Echocardiographic studies were performed using an echocardiography system equipped with a 15-MHz phased-array transducer (SONOS 5500, Hewlett-Packard, Andover, MA) under anesthesia with pentobarbital sodium (30 mg/kg ip) 1 and 14 days after the experimental MI or sham operation. After the administration of ghrelin or saline for 2 weeks, hemodynamic studies were performed. After anesthesia,a polyethylene catheter (PE-50) was inserted into the aorta through the right carotid artery for the measurement of heart rate and mean arterial pressure, and the catheter was then advanced into the LV to measure LV pressure. These hemodynamic variables were measured with a pressure transducer connected to a physiological recorder (PowerLab system, AD Instruments, Mountain View, CA). After completion of hemodynamic measurements, blood sampling was performed, and the hearts were arrested by the injection of 30 mM potassium chloride through the carotid artery, excised, and weighed.

1.5 Hormone assays

Serum insulin-like growth factor I (IGF-I), plasma concentrations of epinephrine, norepinephrine, and dopamine were measured with an enzyme immunoassay kit (Active Rat IGF-I EIA, DSL, Webster, TX).

1.6 Acute effect of ghrelin on the cardiac sympathetic and parasympathetic nervous activity

After MI surgery operation for one week, the tip of the telemetry transmitter probe (TA11PA-C40, Data Science International, St. Paul, MN) was inserted into the femoral artery of the rats. Each rat cage was placed on a signal-receiving board (RLA1020, Data Science International) in the chamber. The pressure signal from conscious and unrestrained rats was continuously recorded by a pressure analyzing system (PowerLab system, AD Instruments). After we recorded the baseline for 0.5 h, ghrelin (100 μg/kg, the same as the one-shot dose of the antiremodeling study, n = 6) or saline (n = 6) was administered subcutaneously. The signals were recorded for 2.5 h thereafter. Acquisition of the pressure signal data was performed for 20 min before and every 1-h interval after the administration. The autonomic nervous function was investigated by a power spectral analysis of heart rate variability. The heart rate derived from pressure waves was used to generate a power spectral density curve by means of fast-Fourier transform. The range of the low-frequency (LF, 0.04-0.4 Hz) or high-frequency (HF, 0.4-1.5 Hz) component was chosen on the basis of our preliminary study.

1.7 Measurement of heart weight and infarct size

After the completion of each experiment, rats were euthanized via anesthetic overdose and the heart excised. The atria were removed and the right ventricle wall separated from the left ventricle and septum. Tissues were blotted and weighed and normalized to 100 g-body weight. The left ventricle was sectioned horizontally through the middle of the infarct area. The apical section of the left ventricle was fixed in 10% buffered formalin and subsequently embedded in paraffin. Sections of the infarcted area, 5 μm thick, were stained with Masons Trichrome stain, mounted for light microscopy examination, and photographed. The infarct size was determined by first measuring the entire endocardial circumference and then measuring the segment of the endocardial circumference that comprised the infarcted portion [9]. The infarct size was presented as a percentage of the total left ventricular wall.

1.8 Statistical analysis

All values are expressed as means ± SE. Differences among the groups were evaluated by one-way analysis of variance and two-way analysis of variance for repeated measurements, as appropriate. When a statistical difference was detected by analysis of variance, the Bonferroni method of adjusting for multiple pairwise comparisons was used. A value of $P < 0.05$ was considered statistically significant.

2 Results

2.1 Survival

38 rats of MI group died within 6 h after MI, compared with 7 of those sham-operated rats. 6 h after MI, 62 rats with MI were randomly divided into two groups (n=31). MI + ghrelin had a mortality of 25% within 2 weeks, compared with 40% of MI + NS rats (Fig. 1).

The MI group rats may die of cardiac arrhythmias. To further clarify the mechanism of improved cardiac performance caused by ghrelin, the effects of ghrelin on plasma catecholamine concentrations were examined, which reflect sympathetic activation and spillover from nerve endings into circulation. Plasma norepinephrine concentration increased significantly in MI rats with the vehicle compared with that in the sham-operated rats. Importantly, ghrelin markedly decreased plasma concentration of norepinephrine to the same level as in the sham-operated group. Al-

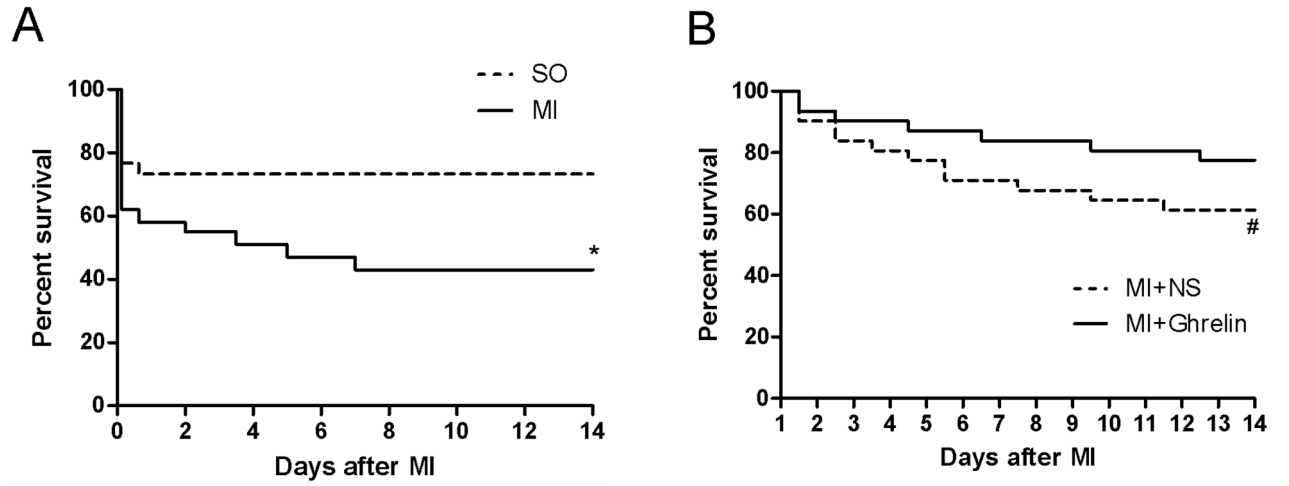

Fig. 1 Survival rate: A: the percent survival of sham-operated rats (SO) and MI rats (MI), *P < 0.05 vs. SO rats; B: the percent survival of MI rats treated with synthetic rat ghrelin (MI + Ghrelin) and treated saline (MI + NS) 6h after MI, #P < 0.05 vs. MI+NS.

though there were no significant differences of epinephrine and dopamine concentrations between the three groups, ghrelin tended to decrease these hormone levels. It was found that the IGF-1 of the two MI groups were significantly lower than that of the sham-operated group (Table 1).

Table 1 Effect of ghrelin on plasma concentrations of catecholamines

	Epinephrine (mg/ml)	Norepinephrine (mg/ml)	Dopamine (mg/ml)	IGF-1 (NG/ML)
SO + NS	0.13± 0.06	0.15± 0.02	0.07± 0.01	577.21± 23.65
MI + NS	0.63± 0.19	0.79± 0.19*	0.09± 0.02	473.85± 15.67*
MI + Ghrelin	0.48± 0.19	0.23± 0.08#	0.08± 0.01	500.19± 20.93#

Notes: *P < 0.05 vs. SO + NS, #P < 0.05 vs. MI + NS.

2.2 The effect of ghrelin on echocardiographic and hemodynamic parameters

Significant thinning of the anterior wall and hypertrophy of the posterior wall were observed in the two MI groups compared with the SO + NS group. There were no significant differences for these parameters between the vehicle and ghrelin groups even after treatment. Pretreatment, LV diastolic dimension was identical among the three groups, and LV fractional shortening was already smaller in MI rats with the vehicle than in sham-operated rats. In sham-operated rats, these parameters did not change after treatment. In MI rats with the vehicle, the LV enlargement and dysfunction deteriorated progressively during 2 weeks. Post treatment, LV diastolic dimension was significantly smaller in rats treated with ghrelin than that in rats treated with the vehicle. Furthermore, LV fractional shortening was significantly greater in rats treated with ghrelin than in rats treated with the vehicle.

The parameters were examined by using echocardiography 1 day (Pre) and 2 weeks (Post) after MI. Significant thinning of anterior wall and hypertrophy of posterior wall were observed in 2 MI groups compared with the SO+NS. There were no significant differences of these parameters between vehicle and ghrelin groups even after treatment. In contrast, left ventricular (LV) end-diastolic dimension and LV fractional shortening were significantly improved in ghrelin-treated MI group compared with NS-treated MI group (Table 2).

Table 2 Echocardiographic parameters before and after ghrelin treatment in rats with experimental myocardial infarction

		Anterior wall thickness(mm)	Posterior wall thickness(mm)	LV diastolic dimension(mm)	LV fractional shortening(%)
SO + NS	pre	1.28± 0.32	1.29± 0.46	6.21± 1.13	36.22± 9.87
	post	1.32± 0.25	1.32± 0.38	6.82± 1.37	36.88± 7.32
MI + NS	pre	1.22± 0.17	1.32± 0.32	6.38± 1.89	16.46± 3.24*
	post	0.61± 0.22*	1.57± 0.25*	8.68± 1.87*	9.88± 2.71*
MI + ghrelin	pre	1.22± 0.36	1.31± 0.23	6.41± 1.33	15.93± 2.82*
	post	0.89± 0.17*	1.48± 0.22*	7.93± 2.12*#	18.97± 3.63*#

Notes: *P < 0.01 vs. SO + NS, #P < 0.01 vs. MI+NS.

The important thing is that heart rate increased in MI rats with the vehicle compared with sham-operated rats, but ghrelin significantly decreased heart rate to the same level as in the SO group. LV systolic pressure was lower in the MI groups with the vehicle and ghrelin than that in the SO group, but there was no difference in this parameter between the two MI groups. LV end-diastolic pressure was higher in MI rats with the vehicle than that in SO + NS rats. Ghrelin significantly decreased LV end-diastolic pressure. The peak rate of the rise and fall of LV pressure (dP/dt max/min) was lower in MI rats with the vehicle than in SO + NS rats. The MI-induced systolic and diastolic LV dysfunction was significantly improved by ghrelin (Table 3).

Table 3 Hemodynamic parameters

	Heart rate, beats/min	MAP, mmHg	LVSP, mmHg	LVEDP, mmHg	dP/dtmax (mm Hg/msec)	dP/dtmin (mm Hg/msec)
SO + NS	427.11± 7.22	122.95± 4.36	140.16± 4.23	7.79± 1.37	11.376 ± 0.94	-7.64 ± 0.83
MI + NS	449.78± 8.13*	108.28± 2.76*	121.46± 3.46*	21.89± 2.16*	7.4 1± 0.72*	-5.42 ± 0.51*
MI + Ghrelin	422.93± 9.49#	108.89± 3.73*	123.75± 3.76*	15.17± 2.38*#	9.43± 0.78*#	-5.81 ± 0.22*#

Notes: *P < 0.01 vs. SO + NS, #P < 0.01 vs. MI + NS.

2.3 Acute response of cardiac function variability to ghrelin

The acute effect of ghrelin on the heart rate variability was examined, which has been used to investigate the cardiac autonomic activity separately for the sympathetic and parasympathetic nerves in human and rats. In conscious rats, 7 days after MI, heart rate, the LF power, and the LF power-to-HF power ratio (LF/HF) were higher and mean arterial pressure was lower than that in sham-operated rats. On the other hand, there was no difference of the HF power between rats with MI and sham operation.

Acute administration of ghrelin significantly decreased heart rate in rats with MI, whereas ghrelin did not affect the heart rate in sham-operated rats. Ghrelin also tended to decrease mean arterial pressure in rats with and without MI. In conscious rats after MI, an acute administration of ghrelin decreased the LF power and tended to increase HF power obtained by a telemetry system. Therefore, ghrelin significantly decreased the LF/HF ratio in MI rats (Fig. 2). In sham-operated rats, ghrelin had no substantial effect on heart rate variability. Administration of saline (vehicle) instead of ghrelin did not affect the heart rate variability in rats with MI.

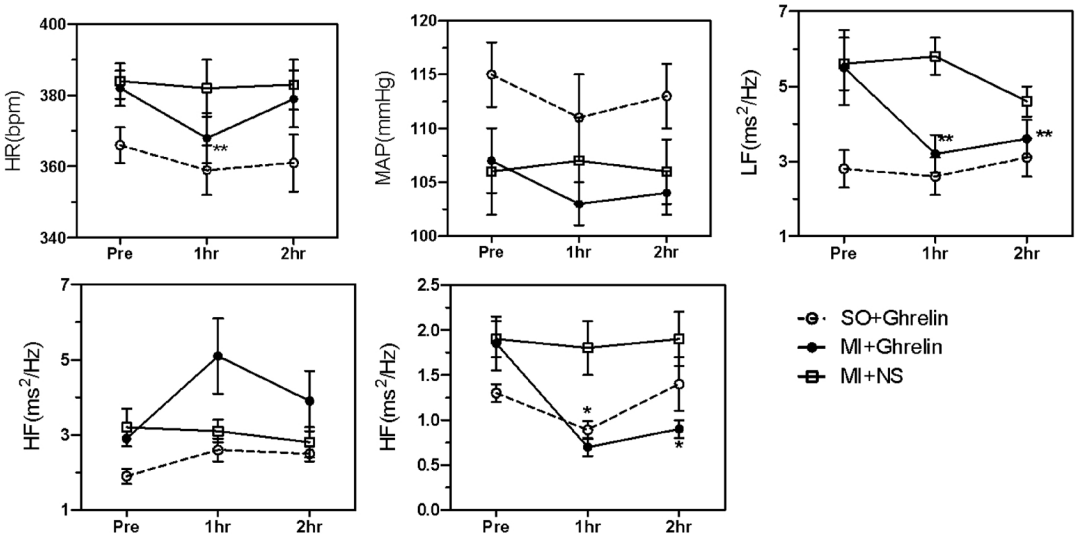

Fig. 2 Effect of ghrelin on heart rate (HR) variability

Notes: *P < 0.05, **P < 0.01 vs. SO + Ghrelin.

2.4 Heart weight and infarct size

The heart weight of MI + NS rats had significantly increased by approximately 26.23% in the 2 weeks period after an acute MI (P < 0.01), compared with that in the SO + NS rats, reflecting the structural changes (e.g. hypertrophy) associated with ventricular remodeling (Table 4). In MI + Ghrelin rats, the magnitude of cardiac hypertrophy, although still significant (P <0.05), was attenuated compared with that of MI+NS rats. The size of the infarct of the left ventricular wall did not significantly differ between MI+NS rats and MI + Ghrelin rats (Table 4).

3 Discussion

In the present study, LV enlargement induced by MI was significantly attenuated by ghrelin treatment. Moreover, there was a substantial decrease in LV end-diastolic pressure, and there were increases in dP/dtmax/min in ghrelin-treated MI rats compared with saline-treated MI rats. It have been previously reported that

Table 4 Heart weight and infarct size

	Heart weight per 100g (mg)	Infarct size
SO + NS	279.79 ± 8.81	-
MI + NS	352.76 ± 16.32**	37.91± 4.43%
MI + Ghrelin	311.73 ± 8.51*#	35.67± 3.28%

Notes: *P < 0.05, **P < 0.01 vs. SO+NS, #P < 0.01 vs. MI+NS.

subcutaneous administration of ghrelin improves LV dysfunction and attenuates the development of LV remodeling in rats with chronic heart failure [7]. In the study, ghrelin apparently stimulates the GH/IGF-I axis, which could induce myocardial growth, and therefore, the beneficial effects of ghrelin could be mediated by the activation of the GH/IGF-I pathway [1]. In the present study, serum IGF-I concentration did not increase in MI rats treated with ghrelin, and there was no difference of heart weight between MI rats with and without ghrelin. The discrepancy between the present study and the previous study using same daily dose of ghrelin might be due to the different study period (acute phase and chronic phase) after MI. In the early phase of MI, serum IGF-I levels were shown to decrease , which is compatible with our results that serum IGF-I concentration was lower in the two MI groups than in the sham-operated group [11]. The neurohumoral changes following MI, which include elevated interleukin-1 and tumor necrosis factor-α or reduced IGF-binding proteins, might contribute to the sustained decrease in IGF-I[12]. The suppressive effects of these factors on IGF-I might be stronger than the stimulatory effect of exogenous ghrelin on the GH/IGF-I axis. Furthermore, several previous studies suggested that ghrelin has cardioprotective and vasodilatory effects not mediated by GH, because the synthetic GHS-R ligand hexarelin prevented cardiac damage after ischemia-reperfusion even in hypophysectomized rats[13], and vasodilatory effects of ghrelin were not affected by GH release inhibitors [14]. Taken together, we suggest that ghrelin has beneficial effects on early cardiac remodeling and dysfunction after acute MI through a GH/IGF-I-independent mechanism.

The main novel findings of the present study are that a continuous administration of ghrelin improved LV dysfunction and attenuated early cardiac remodeling after acute MI. The beneficial effects of ghrelin were accompanied by the suppression of MI-induced increase of heart rate and plasma norepinephrine concentration. In addition, in conscious rats after MI, an acute administration of ghrelin decreased the cardiac sympathetic nerve activity, which was examined by heart rate variability using a telemetry system. Taken together, the cardioprotective effects of ghrelin could be mediated by the suppression of cardiac sympathetic nerve activity.

In the present study, it had shown for the first time that, in conscious rats after MI, an acute administration of ghrelin decreased the activated LF and LF/HF ratio, reflecting sympathetic activity. In contrast, in sham-operated rats, the LF, LF/HF ratio, and heart rate were substantially not affected by ghrelin administration. Thus ghrelin may have stronger effect on the activated sympathetic nervous system than on the nonactivated system. This hypothesis is supported by the preliminary study that, in sham-operated rats, ghrelin had no significant effects on the body weight, heart weight, and serum IGF-I concentration. Since a previous study reported that higher LF and total power were associated with the subsequent LV dilatation in patients with first MI [15], the suppressive effect of ghrelin on the sympathetic activity could lead to the attenuated LV remodeling in rats with MI.

A therapeutic role for the peptide hormone ghrelin has been proposed in patients suffering from end-stage heart failure and cardiac cachexia [16]. Ghrelin has been shown to increase appetite and body weight, and it is thought to have beneficial effects on cardiac function. The increase in food intake is thought to be independent of the GHS-receptor [17]. While Nagaya et al.[7] have shown weight and cardiac effects on rat ghrelin, they have not assessed the body composition changes of treatment.

In conclusion, the present study demonstrated that subcutaneous administration of ghrelin improved LV dysfunction and attenuated early cardiac remodeling after MI. These beneficial effects of ghrelin might be mediated by the suppression of cardiac sympathetic nerve activity. At the same time, ghrelin also can attenuate development of cardiac cachexia, increase survival rate. These data suggest the potential usefulness of ghrelin as a new therapeutic agent after MI.

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Ghrelin 对心肌梗死大鼠恶性心律失常和早期左室重构的影响 *

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摘要 目的：本文主要研究 ghrelin 对心肌梗死大鼠恶性心律失常和早期左室重构的影响。**方法：**心肌梗死大鼠模型每天两次注射 ghrelin(100 μg/kg)或生理盐水。通过超声心动图评估大鼠的心脏重量并且观察大鼠的血流动力学。使用酶免疫分析法测定血清胰岛素生长因子 I(IGF-1)、血浆肾上腺素、去甲肾上腺素和多巴胺的浓度。注射药物前后分析大鼠的神经功能。**结果：**与对照组相比，ghrelin 治疗的心肌梗死模型大鼠生存率显著增加(P< 0.05)，心脏功能增强，但心肌梗死面积差异不大 (P> 0.05)。**结论：** Ghrelin 能够提高心肌梗死模型大鼠的生存率、缓解心肌梗死大鼠心率失常、改善心肌梗死大鼠左心室重构。

关键词：Ghrelin；心肌梗死；左心室重构；心律失常
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