Ketanserin improves cardiac performance after myocardial infarction in spontaneously hypertensive rats partially through restoration of baroreflex function

Jian-guang YU*, En-hui ZHANG*, Ai-jun LIU, Jian-guo LIU, Guo-jun CAI*, Ding-feng SU*

Department of Pharmacology, Second Military Medical University, Shanghai 200433, China

Aim: Baroreflex dysfunction is associated with a higher rate of sudden death after myocardial infarction (MI). Ketanserin enhances baroreflex function in rats. The present work was designed to examine whether ketanserin improves the post-MI cardiac function and to explore the possible mechanism involved.

Methods: Spontaneously hypertensive rats (SHR) were treated with ketanserin (0.3 mg·kg⁻¹·d⁻¹). Two weeks later, blood pressure and baroreflex function were measured, followed by a ligation of the left coronary artery. The expressions of vesicular acetylcholine transporter (VAChT) and α7 nicotinic acetylcholine receptor (α7-nAChR) in ischemic myocardium, angiogenesis, cardiac function, and left ventricular (LV) remodeling were evaluated subsequently.

Results: Ketanserin significantly improved baroreflex sensitivity (0.62±0.21 vs 0.34±0.12 ms/mmHg, P<0.01) and vagal tonic activity (heart rate changes in response to atropine, 54.8±16.2 vs 37.6±13.4 bpm, P<0.01) without affecting the blood pressure or basic heart rate in SHR. Treatment of SHR with ketanserin prominently improved cardiac function and alleviated LV remodeling, as reflected by increases in the ejection fraction, fractional shortening, and LV systolic pressure as well as decreases in LV internal diameter and LV relative weight. The capillary density, vascular endothelial growth factor expression, and blood flow in the ischemic myocardium were significantly higher in the ketanserin-treated group. In addition, ketanserin markedly increased the expression of VAChT and α7-nAChR in ischemic myocardium.

Conclusion: Ketanserin improved post-MI cardiac function and angiogenesis in ischemic myocardium. The findings provide a mechanistic basis for restoring baroreflex function using ketanserin in the treatment of MI.

Keywords: ketanserin; myocardial infarction; baroreflex; angiogenesis; α7-nAChR

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Introduction

Myocardial infarction (MI) is the leading cause of death in the world[1]. The classical risk factors for mortality after MI include depressed ventricular function[2], severe coronary atherosclerosis[3], and persistent complex ventricular arrhythmias[4]. With the increasing understanding of the importance of the autonomic nervous system, baroreflex deficiency has been identified as an independent risk factor for mortality after MI[5,6].

Baroreflex is the most important self-regulatory mechanism of the cardiovascular system. A series of studies by Schwartz and La Rovere demonstrated a close correlation of post-MI mortality with baroreflex sensitivity (BRS). The mortality increased dramatically to 40% in the patients with markedly depressed BRS, compared with 2.9% in the normal BRS patients[7]. These findings were repeatedly confirmed in their following studies[8,9]. It is well known that increasing BRS through physical exercise improves the prognosis of MI[10,11]. Although the pathological importance of impaired baroreflex function in high post-MI mortality has already been recognized, no effective long-term pharmacological intervention is available, which is the direct consequence of the lack of targeted drugs.

Ketanserin is a selective 5-hydroxytryptamine (5-HT₂A) antagonist with minor effects on α1 adrenergic receptors. Clinically, ketanserin is used as an antihypertensive drug. Previous studies in this laboratory indicated that the intragas-
tric administration of a small dose of ketanserin improves BRS without changing the blood pressure (BP) in hypertensive rats or rats with MI\[23\]. We also demonstrated that ketanserin produces organ protection after a long-term treatment in hypertensive rats\[13\]. We determined that the restoration of baroreflex function by ketanserin depends on central 5-HT\(_{2A}\) receptors\[14, 15\]. However, the effects of ketanserin on the long-term prognosis of MI, such as cardiac function, remain unclear.

Angiogenesis is critical for re-establishing the blood supply to the surviving myocardium after MI and, consequently, to the recovery of cardiac function\[16, 17\]. In our previous study, we demonstrated that baroreflex deficiency may hamper angiogenesis via \(a7\) nicotinic acetylcholine receptors (\(a7\)-nAChR) in a rat model of MI\[18\]. We speculated that restoring defective baroreflex function with ketanserin may improve cardiac function by enhancing angiogenesis after MI. A series of experiments on MI and angiogenesis were designed to test this hypothesis. The expression of vesicular acetylcholine transporter (VACHT) and \(a7\)-nAChR was also examined in the current study.

**Materials and methods**

**Animals**

Spontaneously hypertensive rats (SHR; 18-week-old) were bred in the Animal Center of the Second Military Medical University (Shanghai, China). The animals were housed at 22–25 °C under a 12/12 light schedule (on: 08:00), with free access to tap water and standard rat chow. The use and care of animals were in compliance with institutional guidelines for the health and care of experimental animals.

**Blood pressure and baroreflex sensitivity measurements**

Systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart period (HP) were continuously recorded as previously described\[19–21\]. Briefly, a polyethylene catheter for BP measurement was inserted into the lower abdominal aorta through the left femoral artery under anesthesia. Another catheter was placed in the left femoral vein for drug injection. Two days after the operation, the BP and BRS were determined while the rats were conscious. The rats received a bolus injection of phenylephrine. The dosage (typically at 5–10 \(\mu\)g/kg, iv) was adjusted to increase the SBP by 20–30 mmHg. The HP was plotted against the SBP for linear regression analysis; the slope of HP/SBP was used as an index for BRS (ms/mmHg).

**Preparation of myocardial infarction models**

Under ether inhalation anesthesia, the rat heart was exteriorized via the fourth intercostal space. The left anterior descending coronary artery was ligated. The heart was then placed back in its original position. After closing the incision, the animals were returned to their home cages. During the sham operation for MI, the silk suture around the left anterior descending coronary artery ligature was not ligated. The mortality after the coronary artery ligature was approximately 50% and typically occurred within 1 week of surgery\[22\].

**Immunohistochemical studies**

Two weeks after surgery, the capillaries in the rat heart were examined by immunohistochemistry using an anti-CD34 antibody. The animals were perfused with a 0.9% NaCl solution followed by a 4% paraformaldehyde in 0.1 mol/L phosphate buffer (pH 7.4). The heart was fixed in 4% paraformaldehyde for 24 h. Sections (5 \(\mu\)m) were cut transversely at 200-\(\mu\)m intervals into 5 slices from the ligation site to the apex. The sections were washed, dehydrated in a graded ethanol series, and embedded in paraffin. The capillary density was examined using an antibody against rat CD34 (R&D Systems, San Diego, CA, USA; 5 \(\mu\)g/mL). The myocytes were counterstained using eosin. The capillary density for each section was determined in ten randomly selected fields and is expressed as the number of capillaries/field (\(\times 400\))\[23–25\].

**Measurement of myocardial blood flow**

Blood flow to the myocardium was measured 1 month after the MI surgery. Briefly, sodium pertechnetate (\(^{99}\)Tc) solution (5 \(\mu\)Ci) was infused into the aortic root of the isolated hearts. The interventricular septum and ischemic area of the infarcted heart were cut from the left ventricle. Both sections were weighed, and the radioactivity in each fraction was measured using a gamma counter with a window of 140 keV. The radioactivity in the ischemic area was calculated as a percentage relative to that in the normal myocardium. The relative blood flow in the anterior wall of a normal left ventricle was 150% of that in the interventricular septum\[26, 27\].

**ELISA for vascular endothelial growth factor**

The amount of vascular endothelial growth factor (VEGF) in myocardium of rats (3 days after the MI surgery) was determined with ELISA (Raybiotech, Norcross, GA, USA).

**Western blot analysis**

VACHT and \(a7\)-nAChR expression was examined 1 week after MI surgery. Tissue membrane proteins were extracted using Mem-PER Eukaryotic Membrane Protein Extraction Reagent Kit (Thermo Fisher Scientific, Rockford, IL, USA). Equivalent amounts of protein (50 \(\mu\)g) were subjected to SDS-PAGE and then transferred to a polyvinylidene fluoride membrane. After blocking with 5% BSA at room temperature for 2 h, the membrane was incubated with specific primary antibodies (Sigma-Aldrich, St. Louis, MO, USA) against VACHT (1:1000) or \(a7\)-nAChR (1:3000) at 4°C overnight. After incubation with a peroxidase-conjugated secondary antibody (Sigma-Aldrich, St Louis, MO, USA; 1:50000) for 1 h, enhanced chemiluminescence was performed (Thermo Fisher Scientific, Rockford, IL, USA). The blots were stripped and re-probed with an antibody against β-actin (1:40000)\[28–30\].

**Echocardiography**

Echocardiographic evaluation was performed by a double-blinded observer. Rats were anaesthetized (50 mg/kg ketamine, ip), and images were captured using an animal-specific echocardiographic system (17.5-MHz transducer; Vevo770.
High Resolution Imaging System, Visual Sonics, Toronto, Canada) to obtain measurements of cardiac function, including ejection fraction (EF), fractional shortening (FS), stroke volume (SV), cardiac output (CO), and left ventricular (LV) end diastolic and systolic volume (LVEDV and LVESV, respectively), as well as morphometric parameters, including interventricular septal thickness in end diastole and systole (IVSTd and IVSTs, respectively), LV diastolic and systolic internal diameter (LVIDd and LVIDs, respectively), and LV diastolic and systolic posterior wall thickness (LVPWTD and LVPWTS, respectively), as described in detail elsewhere[23]. An EF≤45% was set as the standard for a successful MI operation.

Hemodynamic and morphological assessments
The rats were weighed and anesthetized using sodium pentobarbital (50 mg/kg, ip). A polyethylene catheter connected to a pressure transducer, which was equipped with a polygraph, was inserted into the right carotid artery and then advanced into the left ventricle cavity. The stable ventricular pressure was recorded for 10 min. The mean heart rate (HR), LV systolic pressure (LVSP), LV end diastolic pressure (LVEDP), and maximal rate of pressure development (+dp/dt) and decline (−dp/dt) during the last 5 min were analyzed. After hemodynamic evaluation, the heart was rapidly removed and washed in ice-cold saline. Excess tissue and vasculature was trimmed, and the heart weight (HW) was determined. The left ventricle was dissected from the other chambers and weighed, and the heart and LV relative weight was calculated as the ratio of the HW and LV weight (LVW) to body weight (BW), which are respectively presented as HW/BW and LVW/BW[22].

Protocol
Effects of ketanserin on angiogenesis and cardiac function
Spontaneously hypertensive rats received ketanserin (Janssen Pharmaceutica, Beerse, Belgium; 0.3 mg·kg⁻¹·d⁻¹, delivered in food) or regular rat chow throughout the entire experiment. Two weeks later, coronary artery ligation was performed. The capillary density, regional blood flow, and expression of VEGF were examined in the ischemic area of the myocardium (n=8 in each group). Echocardiology was performed 3 months after MI operation for a separate group of rats. Ten rats were included in each group as MI models, as were another ten sham-operated SHR without ketanserin treatment. Hemodynamic and morphological assessments were performed after a 2-d recovery period.

Effects of ketanserin on cardiac vagal activity and expression of vesicular acetylcholine transporter and α7 nicotinic acetylcholine receptor
The systolic blood pressure, DBP, HR, BRS, and cardiac vagal tone (HR increase in response to atropine 0.03 mg/kg, iv) were evaluated in conscious SHR 2 weeks after the beginning of ketanserin treatment (n=20 in each group). After a 2-d recovery period, the coronary artery was ligated. The expression of VACHT and α7-nAChR within the ischemic area of the myocardium was examined at 1 week after the MI surgery (n=6 in each group). The experimental protocol was illustrated in Figure 1. The time points at which the differences between the groups were the most remarkable were determined according to previous studies to perform different detections.

Statistical analysis
The data are expressed as the mean±SD. For experiments involving two groups, the data were analyzed using an unpaired Student’s t-test. For experiments involving more than two groups, the data were analyzed using ANOVA followed by Dunnett’s t-test. All P-values are two-tailed. P<0.05 was considered statistically significant. Analyses were performed using SPSS 18.0 software (SPSS Inc, Chicago, IL, USA).

Results
Effects of ketanserin on cardiac vagal activity
Ketanserin (0.3 mg·kg⁻¹·d⁻¹ delivered in food) significantly improved BRS (0.62±0.21 vs 0.34±0.12 ms/mmHg in controls, n=20, P<0.01) without affecting the SBP, DBP, or HR. The cardiac vagal tone, expressed as the increase in HR elicited by atropine 0.03 mg/kg iv, was significantly increased by ketanserin (54.8±16.2 vs 37.6±13.4 bpm in controls, n=20, P<0.01).

Effects of ketanserin on cardiac function after myocardial infarction
MI rats displayed a larger LV cavity and worse contractile function compared with sham-operated rats, which was improved by ketanserin (Figure 2). Long-term treatment with ketanserin alleviated MI-induced cardiac dysfunction, as reflected by increases in EF (+16.5%, P<0.05) and FS (+53.0%, P<0.01) and decreases in LVEDV (-11.7%, P<0.01) and LVESV (-17.9%, P<0.01). MI-induced LV remodeling was also reduced by ketanserin, as reflected by decreases in LVIDd (P<0.01),
LVIDs \( (P<0.01) \), and LVPWTd \( (P<0.05) \), Table 1).

Effects of ketanserin on hemodynamic and morphological analysis after myocardial infarction
Hemodynamic data were obtained 3 months after MI to assess cardiac function. Myocardial infarction induced prominent cardiac dysfunction, as reflected by an increase in LVEDP and decreases in LVSP and \( \pm dP/dt \). These changes were significantly reduced by ketanserin (Table 2). After ketanserin treatment, the HW and LVV as well as HW/BW and LVV/BW were significantly lower than those in the MI group (Table 3).

Effects of ketanserin on angiogenesis after myocardial infarction
The capillary density in the ischemic area was significantly higher in rats treated with ketanserin in comparison with control rats \( (29.6\pm7.56 < 21.1\pm6.83 \text{ capillaries/field}, P<0.05, \text{Figures 3A and 3B}) \). Blood flow to the ischemic area was also significantly increased by ketanserin \( (+32.8\%, P<0.05, \text{Figure 3C}) \). Ketanserin treatment significantly increased VEGF expression in the ischemic myocardium \( (+22.6\%, P<0.01, \text{Figure 3D}) \).

Table 1. Echocardiographic data at 3 months after myocardial infarction. Values are mean±SD. \( n=10 \) in each group. \( ^aP<0.05, ^bP<0.01 \) vs Sham MI. \( ^cP<0.05, ^dP<0.01 \) vs MI.

|                | Sham MI | MI | KET+MI |
|----------------|---------|----|--------|
| IVSTd (mm)     | 1.09±0.14 | 1.17±0.12 | 1.15±0.13 |
| IVSTS (mm)     | 2.10±0.14 | 1.99±0.16 | 2.08±0.14 |
| LVIDd (mm)     | 7.28±0.48 | 10.93±0.43 \( ^c \) | 8.90±0.49 \( ^r \) |
| LVIDs (mm)     | 4.29±0.26 | 9.28±0.30 \( ^c \) | 6.85±0.55 \( ^r \) |
| LVPWTd (mm)    | 1.48±0.13 | 1.63±0.17 \( ^n \) | 1.49±0.13 \( ^n \) |
| LVPWTS (mm)    | 2.50±0.16 | 2.50±0.15 | 2.49±0.16 |
| LVEDV (μL)     | 563±35 | 691±49 \( ^c \) | 610±48 \( ^c \) |
| LVESV (μL)     | 164±42 | 481±36 \( ^c \) | 395±43 \( ^c \) |
| SV (μL)        | 399±48 | 210±39 \( ^n \) | 215±30 \( ^n \) |
| CO (mL/min)    | 140±13 | 74±11 \( ^c \) | 76±9 \( ^c \) |
| EF (%)         | 70.9±7.3 | 30.3±4.5 \( ^c \) | 35.3±4.3 \( ^c \) |
| FS (%)         | 40.9±3.0 | 15.1±1.4 \( ^c \) | 23.1±2.8 \( ^c \) |

MI, myocardial infarction; KET, ketanserin; IVSTd and IVSTS, interventricular septal thickness in end diastole and systole, respectively; LVIDd and LVIDs, left ventricular diastolic and systolic internal diameter, respectively; LVPWTd and LVPWTS, left ventricular diastolic and systolic posterior wall thickness, respectively; LVEDV and LVESV, left ventricular end diastolic and systolic volume, respectively; SV, stroke volume; CO, cardiac output; EF, ejection fraction; FS, fractional shortening.

Table 2. Hemodynamic data at 3 months after myocardial infarction. Values are mean±SD. \( n=10 \) in each group. \( ^aP<0.01 \) vs Sham MI. \( ^bP<0.05, ^cP<0.01 \) vs MI.

|                | Sham MI | MI | KET+MI |
|----------------|---------|----|--------|
| HR (bpm)       | 352±20 | 355±19 | 354±20 |
| LVSP (mmHg)    | 159±8.4 | 105±22 \( ^c \) | 137±13 \( ^c \) |
| LVEDP (mmHg)   | -2.65±1.74 | 23.0±9.22 \( ^c \) | 11.8±8.80 \( ^c \) |
| +dp/dt (mmHg/s) | 7.886±1.177 | 3530±820 \( ^d \) | 5436±841 \( ^d \) |
| -dp/dt (mmHg/s) | 7.189±958 | 3102±734 \( ^d \) | 5309±846 \( ^d \) |

MI, myocardial infarction; KET, ketanserin; HR, heart rate; LVSP and LVEDP, left ventricular end systolic and diastolic pressure, respectively; +dp/dt and -dp/dt, maximal rate of pressure development and decline, respectively.

Table 3. Morphological data at 3 months after myocardial infarction. Values are mean±SD. \( ^aP<0.01 \) vs Sham MI. \( ^bP<0.01 \) vs MI. \( n=10 \) in each group.

|                | Sham MI | MI | KET+MI |
|----------------|---------|----|--------|
| BW (g)         | 209±13 | 204±10 | 203±12 |
| HW (mg)        | 745±58 | 864±49 \( ^c \) | 781±59 \( ^c \) |
| LW (mg)        | 517±30 | 630±56 \( ^c \) | 538±58 \( ^c \) |
| HW/BW (mg/g)   | 3.57±0.32 | 4.24±0.24 \( ^c \) | 3.85±0.29 \( ^c \) |
| LVW/BW (mg/g)  | 2.48±0.11 | 3.09±0.24 \( ^c \) | 2.66±0.30 \( ^c \) |

MI, myocardial infarction; KET, ketanserin; BW, body weight; HW, heart weight; LVW, left ventricular weight.

Discussion
Impaired BRS was repeatedly demonstrated to be associated with a poor prognosis in MI patients and in dogs with coronary artery ligation. Consistent with these studies, we observed a higher mortality after MI in rats with lower BRS \( (P<0.01, \text{Figure 4A}) \). The expression of \( \alpha_7 \)-nAChR in ischemic myocardium was also enhanced by ketanserin \( (+151.6\%, P<0.01, \text{Figure 4B}) \).
receptors on platelets. In this study, we demonstrated that ketanserin or those that were not treated (data not shown). Classicaly, ketanserin promotes platelet inhibition to prevent occlusive arterial thrombus formation and inhibits the activation of cardiac fibroblasts to alleviate cardiac remodeling by decreasing BP and avoid side effects. In our previous studies, we demonstrated that ketanserin at a small dose could effectively restore baroreflex function independent of decreasing BP and avoid side effects [12–15]. In this study, ketanserin (0.3 mg·kg⁻¹·d⁻¹) was proven to enhance BRS but not to change the BP and HR of SHR; therefore, we can infer that ketanserin enhances cardiac function through the restoration of baroreflex function.

The sympathetic and parasympathetic nervous systems are the two parallel arms of baroreflex. Generally speaking, baroreflex vascular control is mainly mediated by sympathetic nerves, and cardiac control is mainly mediated by parasympathetic nerves. BRS, which is used in patients as well as in animals, determines the baroreflex cardiac control, and the parasympathetic component is estimated to be approximately 78% [33]. Vagal activities can be classified as phasic (or reflex) activity and tonic activity, which can be evaluated, respectively, by BRS and HR changes in response to atropine [34]. Acetylcholine, the endogenous transmitter of the vagus nerve, and α7-nAChR, a nicotinic acetylcholine receptor, have recently become research hotspots. Both acetylcholine and α7-nAChR can be locally synthesized in organs without vagal innervation [35]. In our previous studies, we demonstrated that baroreflex dysfunction exhibited a decrease not only in BRS but also in vagal tonic activity, acetylcholine expression and α7-nAChR expression. In this study, ketanserin enhanced both BRS (+82.4%) and tonic vagal activity (+45.7%). In addition, ketanserin increased endogenous acetylcholine, which is reflected by the expression of VACHT and α7-nAChR in ischemic myocardium in SHR.

Long-term prognosis after MI is influenced by re-establishing the blood supply to the myocardium, which in turn is partly dependent on angiogenesis. In addition to impaired baroreflex function, SHR exhibits poor cardiac function [36] and high mortality [37] after MI and impaired angiogenesis in the setting of tissue ischemia compared with Wistar-Kyoto rats [38, 39]. The results from the current study demonstrated that in SHR with MI, ketanserin increased VEGF expression (+22.6%), capillary density (+40.2%), and especially regional blood flow (+32.8%), which represented functional neovascularization transporting blood to ischemic myocardium. Recently, it was reported that α7-nAChR was up-regulated during hypoxia-induced proliferation of subconfluent endothelial cells [40] and that angiogenesis was attenuated in α7-nAChR knockout mice [18]. Therefore, we infer that ketanserin may restore baroreflex function, especially vagal activity, to improve cardiac function and alleviate LV remodeling after MI by promoting angiogenesis via α7-nAChR.

In our previous study, we discovered that baroreflex function did not affect infarct size but did affect the angiogenesis of heart in rats. To test the possibility that the improvement of cardiac function induced by ketanserin may be mediated by actions other than BRS, we examined the effects of ketanserin on the infarct size in this research. However, no significant difference was discovered between rats treated with ketanserin or those that were not treated (data not shown). Classicaly, ketanserin promotes platelet inhibition to prevent occlusive arterial thrombus formation and inhibits the activation of cardiac fibroblasts to alleviate cardiac remodeling by antagonizing 5-HT₂A receptors on platelets [41, 42]. These actions may also contribute to the beneficial effects of ketanserin in the prognosis of MI.

In conclusion, our results indicate that ketanserin enhances...
post-MI cardiac function and angiogenesis in ischemic myocardium. These findings support the restoration of baroreflex function using ketanserin as a clinically useful strategy in the long-term treatment of MI to improve the prognosis.

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Author contribution
Ding-feng SU and Guo-jun CAI designed the study and experiments; Jian-guang YU, En-hui ZHANG, and Ai-jun LIU performed the experiments; Jian-guo LIU contributed new analytical tools and reagents; Jian-guang YU and En-hui ZHANG analyzed the data; Jian-guang YU, Ding-feng SU, and Guo-jun CAI wrote the paper.

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