A NOVEL RAT MODEL OF CHRONIC HEART FAILURE FOLLOWING MYOCARDIAL INFARCTION


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SUMMARY

In this report, we describe an improved method for the establishment of reproducible congestive heart failure (CHF) in a rat model. The area of myocardial infarction (MI) after ligation of the left anterior descending (LAD) coronary artery was quantified. Histological changes, heart function detected by echocardiography and isolated Langendorff perfusion, and selected biochemical factors were monitored after ligation of the LAD. Contrary to previous beliefs, thoracotomy in the second intercostal space provided a much better visualization of and easier access to the LAD and significantly reduced the mortality rate. Surface electrocardiogram (ECG) showed that the S-T interval was arched raised upward immediately after ligation. Typical morphological and functional changes of CHF were observed after LAD ligation. Cardiomyocytes in the infarcted zone were depleted and denuded. Biochemical analysis and enzyme-linked immunosorbent assay (ELISA) showed that superoxide dismutase (SOD), glutathione peroxidase (GSH-Px) and nitric oxide (NO) levels were significantly lowered in rats with MI than in the normal and sham groups, whereas serum malondialdehyde (MDA), MB isoenzyme of creatine kinase (CK-MB), cardiac troponin (cTnT) and C-reactive protein (CRP) levels were elevated. After MI, N-terminal pro-brain natriuretic peptide (NT-proBNP) was increased but insulin-like growth factor I (IGF-I) and vascular endothelial growth factor (VEGF) in culture supernatant were lower than in the normal and sham groups. We present an improved model for maximal reproducibility of experimental CHF in rats which allows the study of molecular and physiological variables in relation to CHF.

Key words: Rat - Chronic heart failure - Myocardial infarct - Isolated Langendorff heart perfusion

INTRODUCTION

The use of laboratory rats as a model for cardiovascular research is common due to substantial anatomical, physiological and biochemical similarities between rats and humans, but also poses formidable challenges. The small size of the animals demands precise surgical skills, as well as specialized equipment for functional cardiovascular assessment. These are clear disadvantages when compared to larger experimental animals. However, the completed sequence of the rat genome has created tantalizing opportunities for the systematic study of specific gene functions in the field of cardiovascular pathophysiology and genetics, due to the need to use rats in cardiovascular research (1-4).

Congestive heart failure (CHF) is a condition in which the heart cannot supply the body's tissues with enough blood (5). The prevalence of CHF worldwide continues to increase and it is associated with high rates of morbidity and mortality, imposing enormous human, social and economic costs. Individuals with CHF usually develop symptoms gradually and they become increasingly less active and experience more frequent episodes of acute heart failure. CHF is a clinical syndrome that features a falling heart together with signs and symptoms arising from renal retention of salt and water, mediated by attendant neurohormonal activation, and prominently includes the renin-angiotensin-aldosterone system (6). In addition to this cardiorenal perspective, CHF is accompanied by systemic illness, the features of which include an altered redox state in a number of tissues and blood, an immunostimulatory state with proinflammatory cytokines and activated lymphocytes and monocytes, and a wasting of tissues that involves muscles and bones. However, the exact pathophysiology of CHF is not fully understood. A suitable animal model is therefore needed to study CHF. The rat model following myocardial infarction (MI) by ligation of the left anterior descending (LAD) coronary artery is frequently used as a CHF model but the required technical skills and relative lack of explanatory literature have restricted its use (7). In this study, we aim to introduce technical modifications to the conventional method of inducing CHF,
establishing a reproducible rat model for quantification and histo-
ological monitoring of experimental CHF.

MATERIALS AND METHODS

Animals

Adult male Sprague–Dawley rats weighing 180-240 g were used. The animals were maintained on a 12-h light/dark cycle receiving food and water ad libitum. The experimental protocols were approved by the Animal Ethics Research Committee of Guangdong General Hospital, Guangzhou, China.

LAD coronary artery ligation

The rats were anesthetized by i.m. injection of 4 mg/kg diazepam and 2 mg/kg ketamine. The animals were placed in a supine position with their paws taped on a board before intubation and ventilation, as previously described, using a small animal ventilator (T/KR-200C type; Tei Apparatus, Jiangxi, China) hooked up to an oxygen concentrator apparatus that provided 94-96% oxygen. The ventilator was set at positive end-expiratory pressure mode of ventilation with a stroke pressure of 0.01 Pa and at 80 strokes/min. Passive thoracotony proceeded laterally on the upper border of the third rib to avoid damaging the intercostal nerves and vessels on the lower border of the second rib. Hooked microretractors were then used to separate the second and third ribs enough to gain adequate exposure of the operating region while preserving rib integrity. With minimal manipulation of the fat pad surrounding the heart, and delicately dissected cardiac pericardium, the LAD component of the left coronary artery could easily be visualized. A 7/0 Prolene suture (Ethicon, Johnson & Johnson, Brussels, Belgium) was then passed under the LAD at 2-3 mm distal to the left atrial appendage, immediately after bifurcation of the major left coronary artery. During surgery, care was taken to avoid contact with the lungs. The chest wall was closed with one or two interrupted stitches using a 3/0 silk suture (Ethicon). The left rectus thoracis, serratus anterior and the left pectoral major muscles were then returned to their original position and the skin closed with 3/0 Prolene continuous sutures. The rats were gen-
tly disconnectioned from the ventilator and spontaneous breathing resumed almost immediately. The entire procedure usually took about 15-20 min. During recovery from the anesthesia, the rats were kept in a humidified 30 °C incubator.

Surface electrocardiogram

On the day of the experiment, electrodes for obtaining the electrocardiogram (ECG) were implanted s.c. in a standard lead II configuration (right arm, left leg and right leg) under light ketamine anesthesia. ECG signals were band-pass filtered, amplified, digitized (500 Hz/animal) and stored using a customized PC-based data acquisition system (Mathworks Inc., Natick, MA, USA) with a 12-bit analog-to-digital converter (National Instruments Co., Austin, TX, USA). In order to obtain stable ECG recordings in unrestrained animals, the rats were lightly sedated with a single dose of diazepam (12 mg/kg i.p.) 15-20 min before the beginning of the experiment. ECG recordings from diazepam-treated animals were of high qual-
ity and measures of heart rate were consistent at an interval of 5 min.

Echocardiography

Cardiac function was measured before the operation and then 1, 2, 4, 6 and 8 weeks after the operation with echocardiography by a single observer blind to the experiment. The rats (n = 6 per group per time point) were anesthetized with ketamine and left parasternal images were taken in the right lateral decubitus position with a 13-MHz trans-
ducer (Acuson, Mountain View, CA, USA). The hearts were first imaged two-dimensionally in long-axis views at the level of the greatest left ventricle (LV) diameter. The systolic and diastolic LV areas were measured at the same time. This view was used to position the M-mode cursor perpendicular to the LV anterior and posterior walls. As a measure of LV function, the shortening fraction was calculated from M-mode recordings. Dimensions were measured between the anterior wall and the posterior wall from the short-axis view at the level of papillary muscles. The LV dimension was measured at the LV end-diastolic dimension (LVEDD) and at the LV end-systolic dimension (LVESD). The dimensions were calculated from the average measurements of three selected beats. The LV percent fractional shortening (FS%) was calculated as (LVEDD-LVESD/LVEDD × 100 (%). Interventricular septum diastole (IVs), Interventricular septum systole (IVs), ejection fraction (EF), mitral valve diastolic blood flow rate (MV), LV internal diameter at end-diastole (LVIDd), LV internal diameter at end-systole (LVIDs), end-diastolic volume (EDV) and end-
systolic volume (ESV) were also measured. For each measurement, in a blinded fashion, three consecutive cardiac cycles were traced and averaged by an experienced examiner.

Isolated Langendorff heart perfusion

Cardiac function of rats was evaluated with isolated Langendorff heart perfusion (n = 6 per group; these same rats were subsequent-
ly used for morphological and histological studies), as previously described (8). Hearts were rapidly excised and cooled in ice-cold Krebs–Henseleit solution (mM/L: NaCl 125, KCl 4.7, NaHCO3 20, NaH2PO4 0.43, MgCl2 1.0, CaCl2 1.3 and d-glucose 9.1; pH 7.4) until contractions stopped and prepared for Langendorff perfusion. Continuously carbogen-gassed (95% O2/5% CO2) Krebs–Henseleit solution at 37 °C was perfused immediately after cannulation of the aorta at a constant perfusion pressure of 80 mmHg. After measurement, the heart was then fixed at a ventricular pressure of 30 mmHg with 10% phosphate-buffered formalin solution for 48 h. For base-
line measurements, cardiac performances were determined by examining both systolic and diastolic function using the isolated perfused heart preparation (Langendorf). Systolic function was assessed from the mean LV pressure (LVp), mean LV systolic pres-
sure (LVSP), LV developed pressure (LVDP), mean maximum rate of left intraventricular pressure change (+dp/dtmax) and mean maximal physiological velocity (+Vp). Diastolic function was assessed from the LV end-diastolic pressure (LVEDP) and maximum rate of left intra-
ventricular pressure change (−dp/dtmax). Coronary flux (CF) was also determined.

Histological analysis

To harvest the hearts for histological analysis, the rat hearts were set overnight in 10% formalin, paraffin-embedded and cut into 2-
mm thick sections. They were mounted on normal glass slides and stained with hematoxylin and eosin as described in the man-

Methods Find Exp Clin Pharmacol. 2009, 30(6)
manufacturer's specifications (Sigma, St. Louis, MO, USA). The area of Ml at different times after coronary artery ligation was quantified by a micrograph analytical system (Micro-Cosmos MVnt, Zhuhai Scientific Technology Ltd Co., Zhuhai, China). The expression of macrophage migration inhibitory factor (MIF) was detected by an immunohistological method. Tissue sections were stained with the rabbit antibody against MIF (Santa Cruz Biotech, Santa Cruz, CA, USA), followed by donkey antirabbit antibody. 3,3'-Diaminobenzidine (DAB) was used to produce brown staining as positive expression.

ELISA

We measured the concentrations of N-terminal pro-brain natriuretic peptide (NT-proBNP), insulin-like growth factor I (IGF-I) and vascular endothelial growth factor (VEGF) in the culture supernatant with rat NT-proBNP, rat IGF-I and rat VEGF ELISA kits, respectively (R&D Systems, Minneapolis, MN, USA), according to the manufacturer's instructions.

Biochemical analysis

Venous blood was collected into evacuated tubes without anticoagulant and allowed to clot at room temperature. Sera were separated and processed immediately after blood centrifugation (1000 g for 15 min at 10 °C). Nitric oxide (NO), malondialdehyde (MDA), total superoxide dismutase (SOD) activity and glutathione peroxidase (GSH-Px) activity were measured by an automatic biochemistry analyzer. MB isoenzyme of creatine kinase (CK-MB), tumor necrosis factor-α (TNF-α), MIF, C-reactive protein (CRP) and cardiac troponin (cTnI) concentrations were measured on a Beckman TLX-100 automatic analyzer.

Statistical analysis

The data are expressed as means ± SD. Variables in multiple groups were compared using repeated-measures ANOVA followed by the Tukey-Kramer multiple-comparison test. Differences from control were accepted as statistically significant at P < 0.05.

RESULTS

Modification of LAD ligation procedure

The conventional thoracotomy in the third intercostal space was replaced with thoracotomy in the second intercostal space. The advantages of this procedure were twofold: it provided a much better visualization of and easier access to the LAD and significantly reduced the mortality rate from about >50% to <10% over a 4-week period. Rats undergoing the conventional procedure exhibited obvious pain and distress. Using the modified procedure, rats resumed their normal patterns of feeding, drinking and mobility with no obvious pain or distress within 4-6 h after recovering from the anesthesia.

Morphology of the heart

One week after the operation, the rat hearts appeared bigger than before and showed obvious pallor in the infarcted region. Cardiac dilatation could be seen at week 2. After ligation, infarct size was enlarged severely from week 1 to week 8 (Table I). It showed prominent cardiac dilatation, thinning of the LV wall with or without aneurysm. The myocardium was attenuated and the ventricular chamber was enlarged gradually, especially at weeks 6 and 8 (Fig. 1).

Surface ECG

R-R interval was measured as an index of cardiac rate and S-T interval was measured as an index of MI. Surface ECG showed that the S-T interval was arched raised upward immediately after ligation (Fig. 2).

ECG

After MI, the heart rate of rats increased and IVs/d, IVs, EF, FS and MV were all gradually reduced, especially from week 4 to week 8, compared with the control and sham groups (P < 0.01; Table II). Moreover, LVDD, LVDS, EDV and ESV were increased stepwise, especially from week 4 to week 8 (P < 0.01), compared with the control and sham groups (Fig. 3).

Langendorff study

During the Langendorff study, CF, LVDP, LVS, +dp/dt_{max} and −dp/dt_{max} were similar in the control and sham groups but decreased in the operation group, especially after 4 weeks (P < 0.05; Table III).

Histological features of ischemia in the rat model and relation to specific time points

When evaluating the histological features of the infarcted myocardium at several time points, it was noted that all the experimental infarcts at a given time point exhibited similar features. The histological studies indicated that cardiomyocytes were depelet and deranged. After infarction, cardiac myocytes were decreased and substituted by collagen fibers and inflammatory cells from week 1 to week 8 (Fig. 4). Immunohistochemistry demonstrated that MIF was not expressed in the control group but was highly expressed in the infarcted group, especially at 2 weeks after ligation (Fig. 5).

Biochemical analysis and ELISA

The MDA level following MI at week 4 was significantly higher than in the normal and sham groups (P < 0.01). SOD, GSH-Px and NO

| Table I. Infarct size of rats at different time points. |
|-------------|-------------|-------------|-------------|-------------|-------------|-------------|
| Group       | Normal      | Sham        | MI (week 1) | MI (week 2) | MI (week 4) | MI (week 6) |
| MI area (%) | 0           | 0           | 7.94 ± 1.7* | 22.8 ± 1.5* | 36.13 ± 3.2* | 46.21 ± 2.3* |

Data are mean ± SD of 6 rats. MI, myocardial infarction. *P < 0.01 vs. normal group.

Figure 1. Anatomical observation in the rat model of heart failure. The upper line shows the whole hearts and the lower line shows a cross-section of the left ventricle before (control) or after ligation at different times. Black bars denote a length of 1 cm.

Figure 2. Electrocardiogram (ECG) of rats before ligation (A) and after ligation (B & C).

Table II. In vivo heart functional parameters of rats by echocardiographic (ECG) detection.

<table>
<thead>
<tr>
<th>Heart function</th>
<th>Normal group (n = 10)</th>
<th>Sham group (n = 10)</th>
<th>MI (week 1) (n = 10)</th>
<th>MI (week 2) (n = 10)</th>
<th>MI (week 4) (n = 8)</th>
<th>MI (week 6) (n = 6)</th>
<th>MI (week 8) (n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVIDd (cm)</td>
<td>0.423 ± 0.05</td>
<td>0.429 ± 0.04</td>
<td>0.584 ± 0.11*</td>
<td>0.553 ± 0.09*</td>
<td>0.593 ± 0.12*</td>
<td>0.658 ± 0.05*</td>
<td>0.553 ± 0.04*</td>
</tr>
<tr>
<td>LVIDs (cm)</td>
<td>0.237 ± 0.03</td>
<td>0.241 ± 0.05</td>
<td>0.376 ± 0.09**</td>
<td>0.375 ± 0.08**</td>
<td>0.420 ± 0.11**</td>
<td>0.580 ± 0.04**</td>
<td>0.575 ± 0.04**</td>
</tr>
<tr>
<td>EDV (cm)</td>
<td>0.192 ± 0.0562</td>
<td>0.242 ± 0.057</td>
<td>0.465 ± 0.25**</td>
<td>0.364 ± 0.11**</td>
<td>0.586 ± 0.30**</td>
<td>0.792 ± 0.26**</td>
<td>0.757 ± 0.30**</td>
</tr>
<tr>
<td>EF%</td>
<td>80.32 ± 2.72</td>
<td>81.39 ± 4.76</td>
<td>67.20 ± 7.55**</td>
<td>58.26 ± 4.73**</td>
<td>52.90 ± 2.17**</td>
<td>51.12 ± 3.32**</td>
<td>45.97 ± 3.74**</td>
</tr>
<tr>
<td>ESV (cm)</td>
<td>0.041 ± 0.02</td>
<td>0.079 ± 0.04</td>
<td>0.119 ± 0.09*</td>
<td>0.120 ± 0.06*</td>
<td>0.263 ± 0.14*</td>
<td>0.41 ± 0.17*</td>
<td>0.428 ± 0.22*</td>
</tr>
<tr>
<td>FS%</td>
<td>43.38 ± 2.75</td>
<td>43.23 ± 5.55</td>
<td>37.54 ± 3.37**</td>
<td>31.57 ± 5.05**</td>
<td>25.03 ± 1.97**</td>
<td>24.14 ± 1.94**</td>
<td>22.60 ± 4.75**</td>
</tr>
</tbody>
</table>

Data are mean ± SD. MI, myocardial infarction; LVIDd, left ventricular internal diameter at end-diastole; LVIDs, left ventricular internal diameter at end-systole; EDV, end-diastolic volume; EF, ejection fraction; ESV, end-systolic volume; FS%, percent fractional shortening. *P < 0.05, **P < 0.01, compared with sham group.
Figure 3. Echocardiography of rat hearts. A: sham group; B: ligation after 4 weeks.

Table III. In vitro heart functional parameter of rats by Langendorff study.

<table>
<thead>
<tr>
<th>Heart function</th>
<th>Normal group (n = 10)</th>
<th>Sham group (n = 10)</th>
<th>MI (week 1) (n = 10)</th>
<th>MI (week 2) (n = 10)</th>
<th>MI (week 4) (n = 10)</th>
<th>MI (week 6) (n = 6)</th>
<th>MI (week 8) (n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CF (mL/min)</td>
<td>10.06 ± 0.35</td>
<td>9.83 ± 0.81</td>
<td>8.68 ± 1.02*</td>
<td>6.70 ± 0.44**</td>
<td>5.23 ± 0.53**</td>
<td>6.07 ± 0.38**</td>
<td>6.70 ± 0.76**</td>
</tr>
<tr>
<td>LVSP (mmHg)</td>
<td>92.68 ± 6.25</td>
<td>92.52 ± 6.46</td>
<td>63.38 ± 7.43**</td>
<td>57.21 ± 5.56**</td>
<td>59.04 ± 11.26**</td>
<td>62.89 ± 9.69**</td>
<td>56.82 ± 10.49**</td>
</tr>
<tr>
<td>LVDP (mmHg)</td>
<td>5.89 ± 1.69</td>
<td>6.27 ± 1.71</td>
<td>10.82 ± 2.67**</td>
<td>12.96 ± 5.99**</td>
<td>27.19 ± 3.36**</td>
<td>28.60 ± 4.83**</td>
<td>33.42 ± 3.10**</td>
</tr>
<tr>
<td>+dp/dt_max</td>
<td>5509.37 ± 704.95</td>
<td>4897.26 ± 840.8</td>
<td>3763.33 ± 412.88**</td>
<td>2821.61 ± 579.59**</td>
<td>2156.76 ± 364.40**</td>
<td>1969.62 ± 732.39**</td>
<td>1506.92 ± 533.19**</td>
</tr>
<tr>
<td>-dp/dt_max</td>
<td>3258.45 ± 641.69</td>
<td>315.92 ± 226.73</td>
<td>2311.98 ± 527.9**</td>
<td>1605.69 ± 440.95**</td>
<td>1251.89 ± 224.00**</td>
<td>1136.44 ± 499.37**</td>
<td>841.02 ± 333.3**</td>
</tr>
<tr>
<td>V_max</td>
<td>97.71 ± 19.2</td>
<td>88.09 ± 12.76</td>
<td>61.40 ± 9.32**</td>
<td>50.69 ± 7.64**</td>
<td>46.21 ± 4.48**</td>
<td>54.42 ± 9.70**</td>
<td>47.31 ± 5.68**</td>
</tr>
</tbody>
</table>

Data are mean ± SD. MI, myocardial infarction; CF, coronary flux; LVSP, left ventricular systolic pressure; LVDP, left ventricular end-diastolic pressure; +dp/dt_max, mean maximum rate of left intraventricular pressure change; -dp/dt_max, maximum rate of left intraventricular pressure change; V_max, mean maximal physiological velocity. *P < 0.05, **P < 0.01 vs. sham group.

Figure 4. Hematoxylin and eosin staining of rat myocardium under microscope (× 400). N, normal control; MI-1-8, post-infarction at weeks 1, 2, 4, 6 and 8 after ligation.

Figure 5. Immunohistochemistry of macrophage migration inhibitory factor (MIF) in left ventricular muscle tissue at 2 weeks after ligation. A and C: sham control group; B and D: ligation group after 2 weeks.
levels were significantly lower in the MI groups than those in the normal and sham groups (P < 0.01). Plasma MIF was significantly increased 1 week after ligation and achieved a peak at week 2, declining to baseline levels after week 4. Plasma TNF-α was also significantly elevated after week 2 and gradually increased to peak value at week 8. CK-MB, cTnT and CRP levels were elevated at week 1 after MI, but decreased thereafter. However, after ligation, CK-MB and CRP levels were always higher than in the normal and sham groups from weeks 1 to 8 (P < 0.01). NT-proBNP was gradually increased after MI, especially from week 4 (P < 0.001). In the operated rats, IGF-I and VEGF were lower than in the normal and sham groups (Table IV).

DISCUSSION

We report here a reliable, quantifiable and reproducible CHF model in a common experimental rat strain, including surgical, anatomical and pathological characteristics. We demonstrate that thoracotomy in the second intercostal space and ligation of the LAD at 1-2 mm from the left atrium resulted in a similar loss of microperfusion in the LV and a highly reproducible area and extent of the infarct. Its accurate quantification may allow future comparison between pre- and postischemic treatments. This animal model did not require an incision in the trachea and the achievement ratio was above 95%.

A major advantage of this model is the ability to study the morphological and molecular changes of heart failure at different time points. In this study we demonstrated that the histological phenotype of the ischemic changes can be monitored and show considerable consistency. We describe histological changes similar to those identified previously in humans, highlighting the adequacy of this model to correlate pathophysiological and histological appearance with molecular processes.

The time for formation of CHF in animals following acute MI varied considerably in previous reports (9, 10). We evaluated the development of heart failure by small-animal echocardiography, Langendorff study and histopathology. Our results demonstrate that CHF began at week 4 after acute MI. The mechanism by which MI causes heart failure has not yet been completely identified. We studied the development of heart failure by detecting some related factors such as MIF, TNF-α, NT-proBNP, CK-MB, CRP, rat IGF-I and rat VEGF. CRP is involved in the nonspecific acute phase response to inflammation and tissue damage, including acute MI and ischemia–reperfusion injury. Recently, it was reported that the CRP response not only reflects tissue damage, but may also contribute significantly to the severity of ischemic myocardial injury (11). Both elevated MIF and TNF-α reflect the inflammatory damage in the heart. NT-proBNP is a new diagnostic criteria for CHF (12, 13). Brain natriuretic peptide (BNP) is promising diagnostic and prognostic markers for a variety of cardiovascular diseases, particularly heart failure due to systolic dysfunction (14). The predominant stimulus for BNP release is myocyte stretch and the major site of production is the LV. BNP is synthesized by cleavage of a precursor protein, pro-brain natriuretic peptide (proBNP), into the 32-amino-acid active hormone BNP and the biologically inactive 76-amino-acid peptide NT-proBNP. Measuring NT-proBNP has analytical advantages over BNP because of greater stability. Furthermore, NT-proBNP plasma levels are higher compared with BNP levels due to a longer half-life of the former. Indeed, recent studies have shown that NT-proBNP can be used as a diagnostic marker for heart failure due to systolic dysfunction and a prognostic marker for mortality and cardiac mor-

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Normal group (n = 10)</th>
<th>Sham group (n = 10)</th>
<th>MI (week 1) (n = 10)</th>
<th>MI (week 2) (n = 10)</th>
<th>MI (week 4) (n = 8)</th>
<th>MI (week 6) (n = 6)</th>
<th>MI (week 8) (n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDA (nmol/mL)</td>
<td>2.85 ± 0.65</td>
<td>2.72 ± 0.54</td>
<td>2.80 ± 1.36</td>
<td>5.76 ± 1.84**</td>
<td>3.95 ± 1.72</td>
<td>4.40 ± 1.74</td>
<td>3.22 ± 1.55</td>
</tr>
<tr>
<td>SOD (μmol/L)</td>
<td>161.33 ± 3.11</td>
<td>159.03 ± 2.34</td>
<td>157.41 ± 3.57</td>
<td>156.05 ± 3.95**</td>
<td>155.01 ± 2.88**</td>
<td>151.45 ± 3.68**</td>
<td>148.77 ± 2.54**</td>
</tr>
<tr>
<td>GSH-Px (U/L)</td>
<td>385.53 ± 26.62</td>
<td>354.52 ± 31.33</td>
<td>364.42 ± 42.96**</td>
<td>364.28 ± 26.82**</td>
<td>301.92 ± 33.76</td>
<td>327.18 ± 42.56**</td>
<td>291.72 ± 55.92**</td>
</tr>
<tr>
<td>NO (μmol/L)</td>
<td>130.72 ± 36.39</td>
<td>123.82 ± 26.86</td>
<td>104.72 ± 3.95</td>
<td>96.60 ± 17.4**</td>
<td>94.29 ± 6.10**</td>
<td>57.25 ± 11.6**</td>
<td>50.70 ± 13.96**</td>
</tr>
<tr>
<td>CK-MB (U/L)</td>
<td>542.25 ± 128.85</td>
<td>445.49 ± 286.15</td>
<td>350.43 ± 955.11**</td>
<td>2570.71 ± 798.79**</td>
<td>2794.84 ± 991.04**</td>
<td>1387.33 ± 872.99**</td>
<td>1239.55 ± 763.46**</td>
</tr>
<tr>
<td>CRP (nmol/L)</td>
<td>2.69 ± 1.66</td>
<td>2.74 ± 0.83</td>
<td>9.51 ± 2.95**</td>
<td>4.61 ± 1.65**</td>
<td>5.33 ± 3.22**</td>
<td>4.50 ± 1.06**</td>
<td>5.34 ± 1.74**</td>
</tr>
<tr>
<td>cTnI (ng/mL)</td>
<td>148.14 ± 11.19</td>
<td>3.78 ± 2.87</td>
<td>12.91 ± 6.32**</td>
<td>4.51 ± 2.39</td>
<td>3.08 ± 1.26</td>
<td>0.68 ± 0.59</td>
<td>1.38 ± 1.15</td>
</tr>
<tr>
<td>NT-proBNP (pg/mL)</td>
<td>55.65 ± 13.73</td>
<td>75.52 ± 7.20</td>
<td>180.25 ± 6.20*</td>
<td>167.69 ± 47.88**</td>
<td>216.59 ± 276.08**</td>
<td>215.73 ± 231.06**</td>
<td>211.27 ± 313.75**</td>
</tr>
<tr>
<td>IGF-I (pg/mL)</td>
<td>4356.32 ± 255.83</td>
<td>3780.35 ± 366.86</td>
<td>3115.69 ± 286.93**</td>
<td>2960.32 ± 311.51**</td>
<td>2756.17 ± 120.67**</td>
<td>3226.89 ± 411.54**</td>
<td>314.87 ± 423.75**</td>
</tr>
<tr>
<td>VEGF (pg/mL)</td>
<td>510.71 ± 7.17</td>
<td>45.49 ± 28.15</td>
<td>30.91 ± 3.09**</td>
<td>33.44 ± 2.68**</td>
<td>27.77 ± 3.28**</td>
<td>25.84 ± 1.75**</td>
<td>24.98 ± 3.10**</td>
</tr>
<tr>
<td>MIF (pg/mL)</td>
<td>274.56 ± 5.62</td>
<td>28.27 ± 8.77</td>
<td>39.75 ± 6.52</td>
<td>43.20 ± 10.11**</td>
<td>31.68 ± 5.99</td>
<td>31.71 ± 6.38</td>
<td>33.68 ± 7.29</td>
</tr>
<tr>
<td>TNF-α (pg/mL)</td>
<td>16.52 ± 8.91</td>
<td>17.88 ± 5.89</td>
<td>20.25 ± 5.27</td>
<td>29.77 ± 8.22</td>
<td>32.20 ± 13.39*</td>
<td>32.02 ± 15.68</td>
<td>53.20 ± 7.12**</td>
</tr>
</tbody>
</table>

Data are mean ± SD. MDA, malondialdehyde; SOD, superoxide dismutase; GSH-Px, glutathione peroxidase; NO, nitric oxide; CK-MB, MB isoform of creatine kinase; CRP, C-reactive protein; cTnI, cardiac troponin; NT-proBNP, N-terminal pro-brain natriuretic peptide; IGF-I, insulin-like growth factor I; VEGF, vascular endothelial growth factor; MIF, macrophage migration inhibitory factor; TNF-α, tumor necrosis factor-α. *P < 0.05, **P < 0.01 vs. sham group.
bidity (15, 16). Furthermore, our results demonstrate that NT-proBNP was increased after MI, especially from week 4 to week 8, along with LV remodeling, cavity enlargement and heart function deceleration.

In conclusion, our study describes an improved rat model of CHF following myocardial infarction with reproducibility that can be fully monitored.

ACKNOWLEDGMENTS

This work was supported by the National Science Foundation of China (Nos. 30772412, 30772620, and 30672077), the Team Program of Guangdong Provincial Science Foundation (Nos. 050105 and 825108004000001) and the National Key Basic Research Program (973P) of China (No. 2006CB503806).

DISCLOSURE

The authors state no conflicts of interest.

REFERENCES


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