Effect of *Atractylodes macrocephala* extract on chronic heart failure in rats

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**Abstract**

**Purpose:** To investigate the effect of *Atractylodes macrocephala* extract (AME) on oxidative stress and hemodynamics in chronic congestive heart failure (CHF) rats.

**Methods:** After Sprague Dawley (SD) rats were successfully established into CHF, they were randomly divided into normal control group, negative control group, captopril group, as well as 1.4, 2.8 and 5.6 g/kg of AME groups, and treated with drugs for 4 weeks. Hemodynamic function, whole heart weight index, blood creatinine kinase (CK), superoxide dismutase (SOD), malondialdehyde (MDA), nitric oxide (NO), nitric oxide synthase (NOS) were measured.

**Results:** Compared with the normal control group, arterial systolic pressure (SBP) (83.12 ± 16.21 mmHg), diastolic pressure (DBP) (75.16 ± 20.18 mmHg), mean arterial pressure (MAP) (76.32 ± 13.43 mmHg), heart rate (HR) (353.25 ± 36.34 beats/min), left ventricular systolic peak (LVSP) (101.24 ± 16.13 mmHg), and left ventricular pressure change rate (dp/dt max) significantly decreased (p < 0.05), while left ventricular end diastolic pressure (LVEDP) (22.13 ± 1.57 mmHg), whole heart weight index (2.74 ± 0.16 mg/g), blood CK (0.93 ± 0.14 U/mL), MDA (19.13 ± 2.26 nmol/mL), NO (34.21 ± 3.16 umol/L), and NOS (42.13 ± 3.24 U/mL) increased significantly increased in the negative control group (p < 0.05).

High dose AME significantly improved hemodynamic function, lowered MDA (8.75 ± 2.09 nmol/mL) and NO (22.14 ± 3.27 umol/L) levels (p < 0.05), and also decreased CK (0.57 ± 0.31 U/mL) and NOS (24.24 ± 3.38 U/mL) in CHF rats (p < 0.05).

**Conclusion:** AME significantly improve adriamycin-induced chronic congestive heart failure in rats, which could be used for the therapeutic management of chronic congestive heart failure in future.

**Keywords:** *Atractylodes macrocephala*, Chronic heart failure, Hemodynamic function, Oxidative stress

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**INTRODUCTION**

Chronic heart failure (CHF) is a common, complex clinical syndrome that arises from structural or functional cardiac disorder, including changes in electrophysiology, contraction, and energy metabolism [1]. Heart failure (HF) is becoming a serious disease with an incidence approaching 1 percent of the population over 65 years of age in developed countries [2]. In China, it has been reported that the prevalence of HF in...
the adult population from ten provinces was 0.9 % [3]. The prognosis for CHF is poor and there are few therapeutic options. HF is even worse than many types of cancer [4]. Furthermore, it is an increased hospitalization burden, thus making it a global public health problem.

Therefore, it is necessary to seek novel effective drugs for HF. Traditional Chinese medicine has gained popularity in the treatment of complex multifactor diseases by targeting multiple pathways to improve therapeutic efficacy and reduces drug-related side effects and drug resistance. TCMs such as Shengmai [9], Sini decoction [10], Shuanglong formula [11], and Huangqi injection [12] have potential therapeutic effects on cardiovascular diseases.

*Atractylodes macrocephala* extract (AME) has the effects of promoting blood circulation and removing blood stasis, tonifying the blood and arresting bleeding, and alleviating pain [13,14]. However, the effect study of AME for treatment of cardiovascular diseases has not been reported yet. In this study, the effect of AME on chronic CHF was studied in adriamycin-induced CHF rats.

**EXPERIMENTAL**

**Preparation of AME**

The plant material *Atractylodes macrocephala* collected from Zhunyi City, Guizhou Province in China in October 2017. Taxonomic identification of the plant was performed by Professor LanWang of Hainan Medical University, China. A voucher specimen (no. PRLE 201710005) was deposited in the herbarium of College of Pharmacy, Hainan Medical University, China for future reference.

The herbal samples *Atractylodes macrocephala* were dried in an oven. AME was obtained by steeping the dried *Atractylodes macrocephala* in water at 60 °C. It was repeated for three times and each for one hour. Then it was putted in an oven and then freeze-dried. The yield was 66.67 %.

**Animals**

SD male rats, weighing 180 ± 20 g, were purchased from the Experimental Animal Center of Hainan Province (Certificate no. SYXX 2008-0001). Each rat was raised in single cage, at the environment temperature of 20 ± 2 °C, and humidity 55 - 65 %. They were free access to food and water. The rat experiment was approved by the Animal Care and Use Committee of Central South University Xiangya School of Medicine Affiliated Haikou Hospital (approval ref no. 20081029) and carried out in compliance with the guidelines of Directive 2010/63/EU on the handling of animals used for scientific purposes [15].

**Preparation of chronic heart failure rats and treatment**

Sixty SD rats were divided into normal control, negative control, captopril, and 1.4, 2.8 and 5.6 g/kg AME groups. There were 10 rats in each group. Normal control rats were treated with intraperitoneal injection of 0.2 mL saline. Other rats were administered intraperitoneal injection of adriamycin hydrochloride (2 mg/kg) once a week. It was repeated 6 times. Six weeks later, 2 rats were randomly selected from the survived rats with heart failure for detection of the cardiac function. Administration of drugs lasted from the 7th week after CHF was established. The rats in normal control and negative control groups were intragastrically administered 2 mL saline, once a day; rats of the AME group were administrated intragastrically with AME. The dosage was 1.4, 2.8 or 5.6 g/kg, respectively, once a day. The rats in the captopril group were administrated with captopril, (80 mg/kg), once each day. The administration lasted for 4 weeks.

**Determination of cardiac function and hemodynamics**

Twenty four hours after the last intragastrical administration, the rats were anesthetized by intraperitoneal injection of 20 % urethane solution and were fixed on a table in a spinal position. The right common carotid artery was separated with a ventricular canula (cardiac catheter 1 mm in diameter), which was connected with the Biopac multichannel physiological sign collection and processing system via a pressure transducer; SBP, DBP, MAP, HR were recorded. The cardiac catheter was slowly pushed, and at the same time the pressure oscilloscope was observed. After stabilization for 3 min, the LVSP, LVEDP, + dp/dt max and - dp/dt max were recorded. For the hemodynamic indices, 5 sections were respectively taken for calculation of the mean.
value. Then, 10 mL blood was taken from the abdominal aorta, 5 mL added to 200 mL EDTA; 5 mL (without anti-coagulant) was centrifuged at 3000 rpm for 15 min. The plasma and serum samples were kept at -20 °C for other index assay.

**Determination of heart weight index (heart weight/weight)**

After hemodynamic assessment and blood sampling, the heart was rapidly detached from the rat body and the blood stain washed with saline with the water on it absorbed with a filter paper. The whole heart was weighed, and the whole heart weight index was calculated. Whole heart weight index = whole heart weight (mg)/body weight (g).

**Biochemical tests**

CK, MDA, SOD, NO and NOS in plasma and serum were determined according to the manufacturer’s instruction of ELISA kits (Shenzhen Xin Bo Sheng Biological Technology Co., Ltd., Shenzhen, China).

**Statistical analysis**

All tests were analyzed using Statistical Product and Service Solutions (SPSS) 16.0 software (SPSS Inc, Illinois, Chicago, USA). Data are expressed as mean ± standard error of mean (SEM) and were analyzed by one-way analysis of variance (ANOVA) followed by Dunnett’s t-test. A value of \( p < 0.05 \) was considered statistically significant.

**RESULTS**

**Effect of AME on whole heart weight index**

The heart weight index (HWI) in the negative control group was higher than that in the normal control group (\( p < 0.05 \)), indicating that there are myocardial hypertrophy or stasis of blood in the negative control group. Compared with model group, HWI was not significantly changed in the captopril and AME treatment groups (Table 1).

**Effect of AME on hemodynamic parameters**

Compared with the normal control group, SBP, DBP, MAP, HR, LVSP, \( \frac{dp}{dt_{max}} \) were significantly decreased (\( p < 0.05 \)), and LVEDP was significantly increased in the model group (\( p < 0.01 \)). AME significantly improved vasomotoricity and the left ventricular function of the rats with CHF (\( p < 0.05 \)); while captopril did not have significant effects on vasomotoricity and the left ventricular function of the rats with CHF (Table 2 and Table 3).

<table>
<thead>
<tr>
<th>Group</th>
<th>Dose (g/kg)</th>
<th>HWI (mg/g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>—</td>
<td>2.19±0.25</td>
</tr>
<tr>
<td>Negative control</td>
<td>—</td>
<td>2.85±0.19</td>
</tr>
<tr>
<td>Captopril</td>
<td>0.08</td>
<td>2.40±0.22</td>
</tr>
<tr>
<td>AME-L</td>
<td>1.4</td>
<td>2.64±0.31</td>
</tr>
<tr>
<td>AME-M</td>
<td>2.8</td>
<td>2.58±0.28</td>
</tr>
<tr>
<td>AME-H</td>
<td>5.6</td>
<td>2.52±0.24</td>
</tr>
</tbody>
</table>

Compared with model group, \( p < 0.05, p < 0.01 \). AME-L: 1.4 g/kg of AME, AME-M: 2.8 g/kg of AME, AME-H: 5.6 g/kg of AME

**Effect of AME on blood CK, SOD, MDA, NO and NOS**

Compared with the normal control group, CK and NOS activities, MDA and NO levels were significantly increased (\( p < 0.01 \)), and SOD activity was significantly decreased in the model group (\( p < 0.01 \)). Compared with the model group, blood CK activity, MDA and NO levels were significantly decreased in the captopril group (\( p < 0.01 \), and MDA and NO levels, NOS activity significantly decreased in the AME group (\( p < 0.01 \), Table 4).

**Table 1: Heart index of CHF rats (n = 10)**

<table>
<thead>
<tr>
<th>Group</th>
<th>Dose (g/kg)</th>
<th>SBP (mmHg)</th>
<th>DBP (mmHg)</th>
<th>MAP (mmHg)</th>
<th>HR (beats/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>—</td>
<td>116.23±12.31</td>
<td>109.24±15.26</td>
<td>102.16±15.35</td>
<td>456.14±30.36</td>
</tr>
<tr>
<td>Negative control</td>
<td>—</td>
<td>83.12±16.21</td>
<td>75.16±20.18</td>
<td>76.32±13.43</td>
<td>353.25±36.34</td>
</tr>
<tr>
<td>Captopril</td>
<td>0.08</td>
<td>108.18±22.37</td>
<td>94.23±34.31</td>
<td>96.24±23.16</td>
<td>407.21±45.23</td>
</tr>
<tr>
<td>AME-L</td>
<td>1.4</td>
<td>96.25±17.24</td>
<td>82.25±27.35</td>
<td>82.12±16.27</td>
<td>375.21±32.11</td>
</tr>
<tr>
<td>AME-M</td>
<td>2.8</td>
<td>103.16±16.22</td>
<td>96.24±18.34</td>
<td>98.21±13.17</td>
<td>387.33±30.54</td>
</tr>
<tr>
<td>AME-H</td>
<td>5.6</td>
<td>119.38±11.42</td>
<td>102.12±17.25</td>
<td>109.26±12.51</td>
<td>413.42±37.31</td>
</tr>
</tbody>
</table>

Compared with model group, \( p < 0.05, p < 0.01 \). AME-L: 1.4 g/kg of AME, AME-M: 2.8 g/kg of AME, AME-H: 5.6 g/kg of AME

**Table 2: Hemodynamic indices of CHF rats (n = 10)**
 Toxicity, thus promoting tissue injury. The findings of this study indicate that AME significantly decreased blood MDA and NO levels, and CK and NOS activities but not blood SOD activity. Therefore, it is considered that the improvement of oxidative stress state by AME in CHF rats is not carried out by SOD.

**DISCUSSION**

Hemodynamic parameters are important markers which reflect cardiac functions. AME strengthened the diastolic and contractile functions of the artery and left ventricle, and significantly improved the left ventricular function with no change of heart rate.

Oxidative stress is one key factor for heart failure [16]. In heart failure, a large number of active oxygen families and nitric oxide are produced. In physiological state, the organism has an anti-oxidation system, for example SOD can clear away superoxide anions in time, and reduce lipid peroxidation. In physiological state, NO has the function of dilating blood vessels. However, NO does not only induce the production of free radicals, but also mediates serious neurotoxicity and cytotoxicity, thus promoting tissue injury. Synthesis of NO needs the participation of NOS [17]. AME significantly decreased blood MDA and NO levels, and CK and NOS activities but not blood SOD activity. Therefore, it is considered that the improvement of oxidative stress state by AME in CHF rats is not carried out by SOD.

**CONCLUSION**

The findings of this study indicate that AME improves chronic congestive heart failure in CHF rats, and this is probably linked to the alleviation of oxidative stress and improvement in left ventricular function. Thus, AME has the potential to be developed as an alternative medicine for treating chronic heart failure.

**DECLARATIONS**

**Conflict of interest**

No conflict of interest is associated with this work.

**Contribution of authors**

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Lu Shi-juan designed all the experiment and revised the paper. Huang Kang, Zhong Jiang-hua, Wu Miao, Zhang Wei, Li Qiang and Xiang Qun performed the experiment, and Zhou Yi-lei and Wang Liu wrote the paper.

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REFERENCES