Chronic administration of angiotensin-(1-7) attenuates pressure-overload left ventricular hypertrophy and fibrosis in rats

WANG Li-jun, HE Jian-gui, MA Hong*, CAI Yi-ming, LIAO Xin-xue, ZENG Wu-tao, LIU Jun, WANG Li-chun
Department of Cardiology, First Affiliated Hospital of Sun Yat-sen University, Guangzhou 510080, China

Abstract: Background To test the hypothesis that chronic administration of angiotensin-(1-7) [Ang-(1-7)] attenuates cardiac hypertrophy in rats in vivo. Methods Coarctation of the suprarenal abdominal aorta was performed in 41 8-week-old male Sprague Dawley rats. Twenty-four hours after the operation, osmotic minipumps were surgically implanted subcutaneously in the rats, which were randomly divided into 3 groups, including a sham-operation group (n=15) receiving infusion with normal saline, a suprarenal aortic coarctation group (n=12), and a suprarenal aortic coarctation group (n=14) with Ang-(1-7) treatment at the dose of 25 μg·kg⁻¹·h⁻¹. Four weeks later, the systolic and diastolic blood pressures were measured and the left ventricular mass index (LVMI, mg/g) was calculated from the ratio of left ventricular weight to body weight. The concentrations of Ang II in the plasma and myocardium were measured by radioimmunoassay, and myocardial interstitial collagen volume fraction (ICVF) was determined by quantitative morphometry of the sections with Picrosirius red staining using an automated image analyzer. Results Suprarenal abdominal aortic coarctation induced a significant increase in carotid artery systolic and diastolic blood pressure, heart weight, LVMI, ICVF, and the concentration of Ang II in the myocardium (P<0.01). Chronic administration of Ang-(1-7) attenuated the increase in heart weight, LVMI, ICVF and left ventricular diastolic end pressure (LVEDP) caused by suprarenal abdominal aortic coarctation (P<0.05). Ang-(1-7) also increased the formerly decreased maximum left ventricular pressure reduction rate (-dP/dt max) (P<0.05), but had no effect on blood pressure and the concentration of Ang II in the myocardium. No difference was noted in plasma concentration of Ang II between the 3 groups. Conclusions Ang-(1-7) attenuates cardiac hypertrophy and fibrosis and preserved the impaired left ventricular function induced by left ventricular pressure-overload in rats. These effects are not associated with the changes in the concentrations of Ang II in the left ventricular myocardium and plasma. Key words: angiotensin-(1-7); left ventricular; hypertrophy; fibrosis; suprarenal aortic coarctation

Left ventricular (LV) hypertrophy, a dynamic response of the heart to work load alterations and damages, is a major risk factor for the incidence of adverse cardiovascular events in the setting of hypertension and other cardiovascular diseases. The ventricular hypertrophy consists of myocyte hypertrophy and reactive myocardial fibrosis that extends from the perivascular space into the intramuscular interstitium. Excessive myocyte hypertrophy and disproportionate myocardial fibrosis are the major determinants of increased myocardial stiffness and impaired pumping capacity in patients with chronic hypertension.

It has been well established that activation of the rennin-angiotensin system (RAS) plays a detrimental role in the progression of ventricular hypertrophy. Drugs like ACE inhibitors (ACEIs) and angiotensin AT1 receptor blockers (ARBs) are able to reverse the progression of ventricular hypertrophy in patients with hypertension and reduce the infarct size in animal models of myocardial ischemia-reperfusion injury, suggesting that the deleterious actions of angiotensin II (Ang II) are mediated via the angiotensin AT1 receptor. Recent studies suggest that the beneficial effect of ACEIs and ARBs on cardiovascular diseases may be partially attributed to the elevation of plasma level of angiotensin-(1-7) [Ang-(1-7)], an important biologically active component of the RAS.

Ang-(1-7) is produced primarily by the enzymatic breakdown of either angiotensin I (Ang I) or the vasoconstrictor Ang II. Ang-(1-7) is formed directly from Ang I by multiple endopeptidases including neprilysin (NEP 24.11, EC 3.4.24.11), prolyl oligopeptidase (POP) and thimet oligopeptidase (TOP). Ang-(1-7) is also produced by the metabolism of Ang II at the C-terminus by carboxypeptidases. Recent studies suggest that angiotensin-converting enzyme 2 (ACE2) is the primary enzyme catalyzing this reaction. ACE2 can generate Ang-(1-7) from Ang II or less efficiently through hydrolysis of Ang I to Ang-(1-9) with subsequent Ang-(1-7) formation. ACE2 has a distinct substrate specificity and its activity is not inhibited by ACEIs. While Ang-(1-7) is synthesized...
by the action of ACE2, the heptapeptide is degraded into Ang-(1-5) by ACE [12].

Accumulating evidence suggests that Ang-(1-7) may play an important role in counteracting the pressor, proliferative, and profibrotic actions of Ang II in the heart. First, systemic administration of Ang-(1-7) attenuates the actions of Ang II vasoconstrictor in spontaneously hypertensive rats [13]. Furthermore, cerebroventricular administration of a monoclonal antibody (mAb) against Ang-(1-7) increased the blood pressure in (mRen-2)27 hypertensive transgenic rats [14]. Finally, we demonstrated that Ang-(1-7) inhibited the hypertrophy and expression of proto-oncogene c-fos in cultured neonatal rat heart myocytes induced by Ang II [15, 16]. Whether Ang-(1-7) also attenuates cardiac hypertrophy in vivo remains to be determined. The present study was conducted to explore the effects of Ang-(1-7) on the development of ventricular hypertrophy and fibrosis by continuous intravenous infusion and measurements of Ang II level in the myocardium and plasma in rat suprarenal aortic coarctation model.

MATERIALS AND METHODS

Animals and reagents

Forty-five 8-week-old male Sprague Dawley (SD) rats (weighing 250 to 300 g) were provided and bred by the Experimental Animal Center of Sun Yat-sen University of Medical Sciences. All the rats were housed in separate cages and fed with standard rat chow and tap water ad libitum. They were maintained in a quiet room (at constant temperature of 20 to 22 °C with humidity of 50% to 60%) with 12 h/12 h light/dark cycles. Ang-(1-7) and osmotic minipumps (model 2004) were purchased from Sigma Chemical Corporation and Alzet Company (USA), respectively. Ang II radioimmunoassay kit was obtained from the Northern Biotechnology Co. (China) with a sensitivity of 10 pg/ml and a confidence of variation less than 5%, and the rate of cross action with Ang I was less than 0.01%.

Surgical procedure and experimental protocol

All experimental procedures and protocols adopted in this study were reviewed and approved by the Ethics Committees of Sun Yat-sen University of Medical Science. The rats were divided into 3 groups, namely the sham operation group with saline infusion (Group 1, n=15), suprarenal abdominal aortic coarctation group with saline infusion (Group 2, n=15), and suprarenal abdominal aortic coarctation group with Ang-(1-7) infusion (Group 3, n=15). After anesthesia induction with intraperitoneal sodium pentobarbital (40 mg/kg), midline laparotomy was performed to expose the abdominal aorta just above the renal artery. The abdominal aorta was carefully isolated, alongside which a wire 0.8 mm in diameter was placed and tied tightly around the artery. A 2-0 suture was then wired around the aorta to yield an approximately 70% stenosis of the luminal diameter when the wire was quickly removed. During the whole procedure, the rectal temperature was maintained at 36.5-37.5 °C with a heating lamp. In the control rats, sham operations were performed without constriction of the suprarenal abdominal aorta. Twenty-four hours after the operation, an osmotic minipump with a pumping rate of 0.25 μl/h lasting for 28 days was implanted subcutaneously for drug delivery via a catheter in the jugular vein. The rats with aortic coarctation received Ang-(1-7) (25 μg·kg⁻¹·h⁻¹) or saline (0.25 μl/h) and the sham-operated rats received saline infusion. With this approach, plasma Ang-(1-7) level was maintained at 917.8±194.1 pmol/L [19], at the concentration of which Ang-(1-7) binds to the Mas receptor and has subsequent functional effects [19]. Three rats died of the surgical procedure of suprarenal abdominal aortic coarctation in Group 2 and 1 in Group 3, while all rats in Group 1 survived the sham operation.

Measurement of blood pressure and LV weight

At 4 weeks after the infusion of Ang-(1-7) or saline, the animals were anesthetized with sodium pentobarbital, and then a 2F polyethylene catheter loaded with heparinized saline solution (25 U·ml⁻¹) was positioned into the right carotid artery and connected to a pressure transducer in-line to a polygraph (7758B System, Hewlett-Packard) to measure systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR) for a consecutive 3 min. The catheter was then advanced into the left ventricle for measurement of LV systolic pressure (LVSP) and LV diastolic pressure (LVEDP), which was then differentiated to obtain the maximum left ventricular pressure increment or reduction rates (±dP/dt). After hemodynamic parameters were obtained, the heart was arrested in diastole with an overdose of potassium chloride (1 mol/L, i.v.). The hearts were rapidly excised and placed intoice cold saline to maintain diastole while removing blood. The LV (including the
interventricular septum) was weighed and the left ventricular mass index (LVMI, mg/g) calculated by dividing left ventricular weight by body weight.

**Morphological studies**

After physiological studies, a transmural specimen of the left ventricular myocardium was obtained, fixed in 10% formaldehyde for 24 h and embedded in paraffin. Serial sections 5 μm in thickness were cut and stained with hematoxylin-eosin for cell morphometry and with collagen-specific Picrosirius red (Direct Red 80, Aldrich) for detection of fibrosis. The myocyte cross-sectional diameter (CSD, μm) was measured on a longitudinal section across the nucleus of the cells using a micrometer in the microscope. At least two investigators traced the borders of approximately 20 cardiomyocytes in each of the subepicardial, midcardial, and subendocardial region in each cross section, and the results were averaged. In Sirius red stained sections, the connective tissue and muscle areas were identified according to their respective gray level, whereas collagen fibers appeared red, myocytes orange, and interstitial space white. The left ventricular interstitial collagen volume fraction (ICVF) was determined by quantitative morphometry of the Picrosirius red stained sections with an automated image analyzer (IBAS 2000, Carl Zeiss, Oberkochen, Germany). The digitized profiles were transferred to a computer to calculate the collagen volume fraction as the sum of all connective tissues including the perivascular collagen areas in the entire section divided by all connective tissue and muscles areas, expressed as a percentage. The perivascular collagen areas were evaluated as described by Takemoto et al. Briefly, short-axis images of the large coronary arteries (internal diameters ≥200 μm) and small coronary arteries (internal diameters <200 μm) were used to evaluate the thickening of the coronary arterial wall and perivascular fibrosis. The wall-to-lumen ratio (the medial thickness to the internal diameter) and the area of fibrosis immediately surrounding the blood vessels were calculated. Perivascular fibrosis was determined as the ratio of the area of fibrosis surrounding the vascular wall to the total vessel area. All the samples were analyzed in a blinded manner. The intraobserver variabilities (5 determinations of the same sections on 5 different days) for collagen volume fractions and myocyte cross-sectional diameter were 5.3% and 4.1% respectively.

**Determination of Ang II in myocardium and plasma**

Blood sample (2 ml) was collected from the right ventricle before the heart was arrested, and placed into a chilled tube containing enzyme inhibitors and then centrifuged (within one hour) at 4 °C at 2 500 g for 15 min. The supernatant plasma was stored at −20 °C for later measurement. The transmural specimen from the free wall of the LV was weighed and immediately placed into boiling acetic acid (1 mol/L). The tissue samples were boiled for 20 min, homogenized for 1 min, and centrifuged for 15 min at 3 000 g. The supernatant was then transferred to prechilled polyethylene tubes and also stored at −20 °C. The concentrations of Ang II in the plasma and myocardium tissue were determined by radioimmunoassay according to the manufacturer's instructions.

**Statistical analysis**

The data were expressed as Mean ± SE. The between-group difference in myocyte size, heart weight, body weight, and hemodynamic parameters were assessed using one-way ANOVA followed by Bonferroni’s test for multiple comparisons. The difference was considered statistically significant with P<0.05. All data were analyzed using the SPSS10.0 statistical software package.

**RESULTS**

**Effect on hemodynamic parameters**

The values of heart rate, carotid systolic and diastolic blood pressure, LVSP, LVEDP and +dP/dtmax increased significantly in pressure-overloaded groups (Groups 2 and 3). Compared with Group 2, the LVEDP in Group 3 was lower and -dP/dtmax higher (P<0.05). Other hemodynamic parameters were similar between Groups 2 and 3. Ang-(1-7) did not alter the pressor effect of suprarenal abdominal aortal coarctation (Tab.1).

**Effects on left ventricular hypertrophy**

Over 4 weeks, suprarenal abdominal aortal coarctation caused significant increase in the heart size, the weight of LV, LVMI and CSD. Ang-(1-7) partially reversed the increase in these parameters induced by suprarenal abdominal aortal coarctation (Tab.2).

**Effect on myocardial fibrosis**

There was only a few collagen deposits in the perivascular areas in Group 1 (Fig.1). Suprarenal abdominal aortal coarctation caused pronounced
Tab.1 Effect of Ang-(1-7) on the hemodynamics in rats (Mean±SE)

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n=15)</th>
<th>Group 2 (n=12)</th>
<th>Group 3 (n=14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (bpm)</td>
<td>393.5±22.4</td>
<td>432.1±26.7*</td>
<td>428.4±14.8*</td>
</tr>
<tr>
<td>Carotid BP (mmHg)</td>
<td></td>
<td></td>
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<tr>
<td>SBP</td>
<td>121.3±8.1</td>
<td>142.1±11.7*</td>
<td>139.5±10.9*</td>
</tr>
<tr>
<td>DBP</td>
<td>84.9±7.3</td>
<td>110.2±8.3*</td>
<td>107.5±10.3*</td>
</tr>
<tr>
<td>LVSP (mmHg)</td>
<td>125.6±9.6</td>
<td>146.5±12.7*</td>
<td>143.5±10.5*</td>
</tr>
<tr>
<td>LVEDP (mmHg)</td>
<td>6.46±0.5</td>
<td>6.93±1.02*</td>
<td>5.99±0.94*</td>
</tr>
<tr>
<td>+dp/dt (mmHg/s)</td>
<td>4.79±0.5</td>
<td>5.61±0.84*</td>
<td>5.41±0.62*</td>
</tr>
<tr>
<td>-dp/dt (mmHg/s)</td>
<td>4.73±0.5</td>
<td>3.69±0.41*</td>
<td>4.21±0.51*</td>
</tr>
</tbody>
</table>

*P<0.01 vs Group 1; **P<0.05 vs Group 2. HR: Heart rate; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; LVSP: Left ventricular systolic pressure; LVEDP: Left ventricular end-diastolic pressure. 1 mmHg=0.133 kPa.

Tab.2 Effects of Ang-(1-7) on left ventricular hypertrophy and myocardial fibrosis in rats (Mean±SE)

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n=15)</th>
<th>Group 2 (n=12)</th>
<th>Group 3 (n=14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BW (g)</td>
<td>270.7±18.3</td>
<td>264.3±17.8</td>
<td>265.1±20.5</td>
</tr>
<tr>
<td>LVW (mg)</td>
<td>616.4±80.7</td>
<td>745.3±70.4*</td>
<td>677.1±74.1**</td>
</tr>
<tr>
<td>LVMI (mg/g)</td>
<td>2.31±0.18</td>
<td>2.84±0.25*</td>
<td>2.58±0.2*</td>
</tr>
<tr>
<td>CSD (µm)</td>
<td>13.9±1.1</td>
<td>16.0±1.8*</td>
<td>14.6±1.2*</td>
</tr>
<tr>
<td>ICVF (%)</td>
<td>10.4±2.23</td>
<td>15.8±2.22**</td>
<td>13.8±2.78**</td>
</tr>
</tbody>
</table>

*P<0.05 vs Group 1; **P<0.05 vs Group 2. BW: Body weight; LVW: Left ventricular weight; LVMI: Left ventricular mass index; CSD: Cardiomyocyte cross-sectional diameter; ICVF: Left ventricular interstitial collagen volume fraction.

Fig.1 Photomicrograph showing myocardial fibrosis in the groups (Original magnification: ×400)
A, B and C indicates the photomicrographs of Groups 1, 2 and 3, respectively, showing myocardial fibrosis induced by aortic coarctation, which was inhibited by Ang-(1-7).

Fig.2 Effects of aortic coarctation with and without Ang-(1-7) on left ventricular interstitial collagen volume fraction (ICVF)

*P<0.05 vs Group 1; **P<0.05 vs Group 2. The values are presented as Mean±SE. The number in the bar represents the number of hearts.

Effect on the Ang II levels in myocardium and plasma

Suprarenal abdominal aortal coarctation caused an approximately two-fold increase in the concentration of Ang II in the LV myocardium. Ang-(1-7) did not alter the effect of suprarenal abdominal aortal coarctation on Ang II levels in LV myocardium. There was no difference in the plasma concentration of Ang II among the groups (Tab.3).

Tab.3 Effect of Ang-(1-7) on Ang II levels in the myocardium and plasma of rats (Mean±SE)

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n=15)</th>
<th>Group 2 (n=12)</th>
<th>Group 3 (n=14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardium AngII(pg/g)</td>
<td>291.2±109.9</td>
<td>512.1±155.7*</td>
<td>457.7±126.6*</td>
</tr>
<tr>
<td>Plasma AngII(pg/L)</td>
<td>1 478.2±57.3</td>
<td>1 511.1±45.4</td>
<td>1 493.3±49.6</td>
</tr>
</tbody>
</table>

*P<0.05 vs Group 1

DISCUSSION
In the present study, significant cardiac hypertrophy was induced with an increment of left ventricular thickness and fibrosis accompanied by high level of myocardium Ang II 4 weeks after suprarenal abdominal aortic constriction in this cardiac hypertrophy model. In this model, the effects of
chronic intravenous infusion of Ang-(1-7) on the development of left ventricular hy- pertrophy and fibrosis were examined. The main findings of this study are as follows: (1) Chronic administration of Ang-(1-7) attenuates cardiac hypertrophy and fibrosis and preserved the impaired left ventricular function caused by supraprenal abdominal aortic constriction in rats; (2) This effect is not associated with the changes in systemic blood pressure and the concentration of Ang II in LV myocardium or plasma.

Although the precise mechanisms that govern the myocardial hypertrophy and accumulation of fibrillar collagen in hypertensive LV hypertrophy are still not fully elucidated, the local and circulating activation of RAS seems to play a dominant role, with Ang II and aldosterone as the mediators [22-25]. Long-term infusion of Ang II in pressor and subpressor doses induced LV hypertrophy and cardiac fibrosis in animals [22, 24], and in the renovascular hypertensive [25] or aortic banding rat model [26], it has been reported that ACEIs induced prevention or regression of pressure-overload hypertrophy unrelated to its blood pressure-lowering effect, suggesting the possible involvement of plasma or locally formed cardiac Ang II in the development of LV hypertrophy. The current findings provide additional support for this hypothesis by indicating an increase in myocardial Ang II level in LV hypertrophy induced by supraprenal abdominal aortic constriction. However, since there was no significant difference in the level of plasma Ang II between the pressure-overload (Groups 2 and 3) and control groups, the plasma Ang II might not be responsible for the difference in the degree of hypertrophy observed in this study. Our finding is consistent with that yielded from coarctation of either the ascending aorta or supraprenal abdominal aorta [27]. In addition, in pressure-overloaded animals, Tokuda et al [28] reported that Ang II had pressure-independent effects and acted as a strong inflammatory mediators, indicating that Ang II induces reactive fibrosis and cardiomyocyte hypertrophy partially through the mechanisms that are independent of the pressor effect. These findings suggest that increased Ang II in the myocardium may trigger LV hypertrophy.

Ang-(1-7) could represent a mechanism that functions within the renin-angiotensin system to oppose the pressor and trophic actions of Ang II. Ang-(1-7) was shown to be a potent vasodilator in isolated vascular preparations including the coronary arteries [29], hind limb [8, 30], and human subjects [31]. Recently, the vasodilator effect of Ang-(1-7) was shown in mature skin and sponge- induced neovascularization in mice [32]. The increased blood flow produced by Ang-(1-7) was blocked by D-Ala7- Ang-(1-7), a nitric oxide synthase inhibitor, or the cyclooxygenase inhibitor, indomethacin [32, 33]. These studies suggest that Ang-(1-7) may contribute to chronic inflammatory processes.

There are few studies addressing the effects of chronic infusion of Ang-(1-7). Loot et al [18] reported that an 8-week infusion of Ang-(1-7) following coronary artery ligation prevented the deterioration of cardiac function, as indicated by a 40% reduction in left ventricular end-diastolic pressure. The Ang-(1-7)-mediated improvement in cardiac function was associated with a significant decrease in myocyte cross-sectional area, suggesting a role of Ang-(1-7) in the regulation of myocyte growth, but they did not evaluate the effect of Ang-(1-7) on myocardial fibrosis within the infarct and non- infarct regions. In the present study, our findings indicated that Ang-(1-7) treatment prevented the deterioration of left ventricular hypertrophy, and preserved the impaired left ventricular function. Furthermore, we found, for the first time, that 4 weeks of Ang-(1-7) administration significantly diminished the myocardial fibrosis induced by aortic coarctation. Our previous study showed that Ang-(1-7) reduced Ang II-induced protein synthesis in the myocytes as well as DNA and protein production in cardiac fibroblasts, indicating that the heptapeptide inhibits hypertrophy of the cardiomyocytes and hyperplasia in cardiac fibroblasts [34], and reduces interstitial collagen matrix deposits, which leads to the improvement of the impaired cardiac function.

It has been shown that Ang-(1-7) attenuates the pressor response of Ang II in rabbit aortic rings and anaesthetized rats [35]. A similar blocking action of Ang-(1-7) on Ang II vasoconstrictor response was also reported in healthy humans [36] and in isolated human arterial rings [37]. In the current study, Ang-(1-7) did not alter arterial blood pressure, heart rate and contractile function, indicating that the inhibitory effects of
Ang-(1-7) on cardiac hypertrophy and fibrosis are not likely to depend on systemic hemodynamics. Moreover, Ang-(1-7) infusion did not alter the concentrations of Ang II in the left ventricular myocardium and plasma, suggesting that anti-hypertrophic and anti-fibrotic effect of Ang-(1-7) is not associated with the reduction in the formation and release of Ang II in the plasma and myocardium. The beneficial effects of Ang-(1-7) on left ventricular hypertrophy and fibrosis in our study may be related to an intracardiac mode of action for Ang-(1-7) [20, 38, 39]. Ang-(1-7) exerts direct effects on cardiomyocytes and cardiac fibroblasts to attenuate their hypertrophy and hyperplasia and maintain the mechanical function of the cardiomyocytes. Another possibility is that Ang-(1-7) directly inhibits the actions of Ang II by altering the signaling mechanisms of Ang II through its specific receptor. More recently, the receptor responsible for the transduction of the Ang-(1-7) response has been considered as Mas proto-oncogene protein [39]. With regard to these observations, more work is needed for further investigation.

In summary, our findings demonstrated, for the first time, that chronic administration of Ang-(1-7) attenuated cardiac hypertrophy, fibrosis and preserved the impaired left ventricular function caused by pressure-overload in rat in vivo. This study suggests that Ang-(1-7) may attenuate of the development of left ventricular hypertrophy in the patients with hypertension and other cardiovascular diseases.

REFERENCES


血管紧张素-(1-7)对腹主动脉缩窄大鼠心肌肥厚和纤维化的影响

王立军，何建桂，马 虹*，蔡乙明，廖新华，曾武涛，柳 俊，王礼春（中山大学附属第一医院心内科，广东 广州 510080）

摘要: 目的 探讨血管紧张素-(1-7)(Ang-(1-7)]对腹主动脉缩窄所诱导的大鼠心肌肥厚和纤维化的影响。方法 对8周龄雄性SD大鼠行腹主动脉缩窄术并随机分为假手术组、模型对照组和Ang-(1-7)治疗组, 对1 d后仍存活者皮下植入微量泵持续静脉输注Ang-(1-7)或生理盐水, Ang-(1-7)组(n=14)输注Ang-(1-7)(25 μg·kg⁻¹·h⁻¹), 假手术组(n=15)及模型对照组(n=12)则输注等量的生理盐水。术后检测血流动力学参数, 血压和心肌Ang II浓度、左心室重量指数、心肌细胞横径和心肌胶原容积分数。结果 (1)模型对照组动脉收缩压、舒张压、心率、左室内压最大上升速率(±dp/dtmax)、左心室重量指数(25.6±4.8 g·kg⁻¹)、左心室重量指数与基底水平无明显差异(P>0.05)。与模型对照组比较, Ang-(1-7) 治疗组LVDEP显著增高(1001±35 mmHg, P<0.05), LVMI显著显著下降(296±30 mmHg, P<0.05), 但收缩压、舒张压、心率、LVSP及±dp/dtmax在两组间无明显差异。2)在腹主动脉缩窄术后4周, 模型对照组左心室重量指数、左心室重量指数与基底水平无明显差异(P>0.05)。与模型对照组比较, Ang-(1-7) 治疗组LVDEP显著增高(1001±35 mmHg, P<0.05)。与模型对照组比较, Ang-(1-7) 治疗组左心室重量指数显著减弱(296±30 mmHg, P<0.05)。3) 模型对照组与Ang-(1-7) 治疗组收缩压、舒张压、心率、LVSP及±dp/dtmax在两组间无明显差异。4)左心室重量指数(Ang-(1-7) 治疗组与模型对照组比较, P<0.05)。结论: 长期静脉输注Ang-(1-7) 对腹主动脉缩窄引起的动脉高压和心肌纤维化水平的升高无影响, 但使心肌肥厚和纤维化程度显著减轻, 并保护受损的心肌功能。

关键词: 血管紧张素-(1-7); 左心室肥厚; 纤维化; 腹主动脉缩窄