Chronic Administration of Adrenomedullin Attenuates Transition From Left Ventricular Hypertrophy to Heart Failure in Rats

Toshio Nishikimi, Fumiki Yoshihara, Shigeo Horinaka, Naohiko Kobayashi, Yosuke Mori, Kazuyoshi Tadokoro, Kazumi Akimoto, Naoto Minamino, Kenji Kangawa, Hiroaki Matsuoka

Abstract—Acute administration of adrenomedullin (AM) exerts beneficial hemodynamic, renal, and neurohormonal effects in heart failure (HF). However, chronic effects of AM administration on HF remain unknown. This study sought to examine the effect of chronic infusion of AM on progression of HF in rat. Human recombinant AM was administered by osmotic minipump for 7 weeks in the HF model of Dahl salt-sensitive rats. The effect was compared with vehicle and diuretic treatment group. Chronic AM infusion significantly decreased left ventricular end-diastolic pressure, right ventricular systolic pressure, right atrial pressure, and left ventricular weight/body weight (P<0.01 for all). AM significantly attenuated the increase in circulating renin-aldosterone, endogenous rat AM, and atrial natriuretic peptide levels (P<0.01 for all). AM also inhibited the myocardial tissue levels of angiotensin II and atrial and brain natriuretic peptide (P<0.01 for all). These changes were associated with the improvement of cardiac output and systemic vascular resistance (both P<0.05). Furthermore, AM improved left ventricular end-systolic elastance (P<0.01). These improvements were greater in the AM than in the diuretic group, although both drugs similarly decreased systolic blood pressure and increased urinary sodium excretion. Kaplan-Meier survival analysis showed that AM significantly prolonged survival time compared with diuretic (P<0.05) and vehicle (P<0.01) treatment groups. These results suggest that endogenous AM plays a compensatory role in HF and that chronic AM infusion attenuates progression of left ventricular dysfunction and improves survival, at least in part, through inhibition of circulating and myocardial neurohormonal activation. (Hypertension. 2003;42:1034-1041.)

Key Words: adrenomedullin ■ heart failure ■ renin ■ natriuretic peptides ■ angiotensin

Adrenomedullin (AM) is a 52–amino acid peptide that was originally discovered in human pheochromocytoma tissue.1 Subsequent studies demonstrated that AM infusion causes vasodilation, diuresis, and natriuresis and inhibits aldosterone secretion in normal animals.2 In addition, previous studies have shown that plasma AM levels are increased in patients with heart failure in proportion to its severity3 and lungs of rats with heart failure.4 These findings suggest that AM may play an important role as a defense mechanism in volume and pressure homeostasis in the heart failure. Indeed, acute administration of AM improved central hemodynamics and renal function in animal models of heart failure.5,6 Furthermore, we and other groups recently demonstrated that acute intravenous infusion of AM has beneficial hemodynamic, hormonal, and renal effects in patients with heart failure.7,8 However, the effects of chronic infusion of AM on progression of heart failure remains unknown. To address this question, we used Dahl salt-sensitive (DS) rats. In these rats under a high-salt diet, systemic hypertension induces compensated concentric left ventricular (LV) hypertrophy at the age of 11 weeks, followed by marked LV dilation and global hypokinesis at the age of 16 to 19 weeks.9 Therefore, we started chronic AM infusion in DS rats 11 weeks of age and examined the effect on progression of heart failure by measuring central hemodynamics, intrinsic LV function, plasma neurohormonal levels, myocardial biochemical and molecular markers, and survival. Furthermore, we compared the effects of AM with those of a diuretic to investigate whether the beneficial effects of AM are mediated by natriuretic and diuretic effects.

Methods

All procedures were in accordance with institutional guidelines for animal research.

Experimental Animals and Protocols

Male inbred DS rats (Eisai Co, Ltd) were fed a diet containing 8% NaCl (high salt) after the age of 6 weeks and were randomly divided...
into 3 groups: (1) AM treatment group, (2) diuretic treatment group, and (3) vehicle treatment group. The rats in groups 1 and 3 were subcutaneously implanted with an osmotic minipump (model 2ML4, Alza) filled with recombinant human AM dissolved in 0.9% saline in the AM treatment group (500 ng/h) and 0.9% saline in the vehicle group, as previously reported.10 Diuretic (trichlormethiazide; 0.133 mg/dL) was given in drinking water. Age-matched male Dahl salt-resistant (DR) rats fed the same diet served as a control group. All rats had their systolic blood pressure measured by the tail-cuff method before feeding with the high salt diet and at 2-week intervals thereafter.

Recombinant Human AM

Human recombinant AM was kindly provided by Shionogi & Co, Ltd (Osaka, Japan). The method of production of human recombinant AM has been described previously.10

Urine Collection

Twenty-four-hour urine samples were collected from rats in metabolic cages 7 weeks after treatment with AM, diuretic, or vehicle, as previously reported.11 Urine electrolytes were analyzed by standard methods.

Central Hemodynamic Measurements

After approximately 7 weeks of treatment of AM, diuretic, or vehicle, mean arterial pressure (MAP), LV end-diastolic pressure (LVEDP), right atrial pressure (RAP), and right ventricular systolic pressure (RVSP) were measured under anesthesia, as previously reported.10–12

Plasma Neurohormonal Analysis

For the measurements of myocardial peptides levels, other rat groups were used (each n = 6). After the heart was excised, it was perfused with cold phosphate-buffered saline (pH 7.4), as previously reported.13 The radioimmunoassays for ANP, brain natriuretic peptide (BNP), aldosterone, and atrial natriuretic peptide (ANP) concentrations were measured by radioimmunoassay, as previously reported.10–12

Myocardial Neurohormonal Analysis

For the measurements of myocardial peptides levels, other rat groups were used (each n = 6). After the heart was excised, it was perfused with cold phosphate-buffered saline (pH 7.4), as previously reported.13 The radioimmunoassays for ANP, brain natriuretic peptide (BNP), and angiotensin II in myocardial tissue were performed as described previously.11–15

RNA Preparation and Northern Blot Analysis

All procedures were performed as described in detail in our previous reports.5,11

Serial Measurement of Cardiac Output and Systemic Vascular Resistance

For the serial measurement of cardiac output and systemic vascular resistance (SVR), other rat groups were used (each n = 3 to 6). Cardiac output was measured in 11-, 14-, and 17-week-old treated DS rats and DR by thermodilution methods with the use of a computerized cardiac output monitor (Cardiotherm-500, Columbus Instruments), as previously reported.6 MAP, LVEDP, and RVSP were also measured. SVR was calculated by standard formula.

LV End-Systolic Pressure-Volume Relation

We obtained the slope of the LV end-systolic pressure-volume relation (Ees) in another rat group (each n = 5 to 8) by a gradual inferior vena cava occlusion with the use of the conductance catheter technique, as previously reported.16–18

Effect on Survival Rate

To examine the effect of treatment on survival, DS rats were randomly divided into 3 groups: AM, trichlormethiazide, and vehicle treatment group, as described above. A DR group was also produced. Animals were carefully monitored, and deaths were recorded every day. Survival rates were compared among the groups at 19 weeks after the start of drug treatment.

Statistical Analysis

All values are expressed as mean ± SD. The data on blood pressure were analyzed by 2-way ANOVA, and the differences between each group at each time point were determined by the least-squares mean test. Statistical comparisons between more than 2 groups were carried out by ANOVA followed by the Bonferroni test for multiple comparisons. Comparisons between 2 groups were performed by an unpaired Student t test. Survival was analyzed by the standard Kaplan-Meier analysis with a log-rank test. A probability value < 0.05 was considered statistically significant.

Results

We performed 4 series of experiments. In experiment 1, DR and DS rats at 11 weeks and DR, AM-, diuretic-, and vehicle-treated DS rats at 18 weeks were killed for the determination of central hemodynamics, neurohormonal factors, and myocardial biochemical and molecular markers. In experiment 2, serial changes of cardiac output, SVR, MAP, RVSP, and LVEDP were determined in DR and DS rats at 11 weeks and DR, AM-, diuretic-, and vehicle-treated DS rats at 14 and 18 weeks. In experiment 3, the LV pressure-volume relation was measured in DR and AM-, diuretic-, and vehicle-treated DS rats at 18 weeks. In experiment 4, survival was determined in AM-, diuretic-, and vehicle-treated DS rats.

Experiment 1

Cardiac Weight, Lung Weight, Urinary Excretion of Sodium and Potassium, and Blood Pressure

The physiological profiles of the 6 experimental groups are summarized in the Table. Right and left ventricular weight/body weight (RVW/BW and LVW/BW, respectively) was higher in the DS than in the DR rats at both 11 and 18 weeks. LV/BW were further elevated in DS rats at 18 weeks compared with that in DS rats at 11 weeks. Lung weight, as an index of pulmonary congestion, was increased only in DS rats at 18 weeks compared with the other 3 treatment groups. AM and diuretic treatment reduced LVW/BW and lung weight/BW (all P < 0.01) compared with DS at 18 weeks.

AM and diuretic treatment significantly increased daily sodium excretion without changing potassium excretion compared with the vehicle treatment group.

As shown in Figure 1, DS rats fed a high-salt diet from 6 weeks of age had progressive development of hypertension. AM and diuretic treatment reduced systolic blood pressure in DS rats at 13, 15, and 17 weeks to a comparable degree.

Central Hemodynamic Responses to Chronic AM Therapy

As shown in Figure 2, DS rats at 11 weeks had higher MAP, but they had normal RAP and RVSP with a slight increase in LVEDP compared with DR at 11 weeks, indicating a compensated hypertrophy against increased afterload. DS rats at 18 weeks were characterized by obviously higher MAP, LVEDP, RAP, and RVSP compared with DR. Chronic AM infusion and diuretic therapy significantly reduced the LVEDP, RAP, and RVSP without changing the MAP. Chronic AM infusion therapy was more effective in reducing LVEDP than diuretic therapy.
Plasma Neurohormonal Responses to Chronic AM Therapy

As shown in Figure 3, DS rats at 11 weeks had higher plasma total AM, AM-mature, and ANP levels than the other two DR groups, and these indexes were further elevated in DS rats at 18 weeks. In contrast, DS rats at 11 weeks had normal plasma aldosterone and PRC; however, these indexes were increased in DS rats at 18 weeks. Chronic AM infusion significantly inhibited the activation of circulating renin-aldosterone system and further increase of AM and ANP. In contrast, chronic diuretic treatment significantly reduced PRC and total AM compared with vehicle-treated DS rats at 18 weeks; however, it did not significantly reduce ANP, AM-mature, or aldosterone levels. Human AM immunoreactivity was only detected in AM-treated DS rats (2.3 ± 1.5 pmol/L), which was comparable to AM-mature levels of DS rats at 11 weeks.

Myocardial Neurohormonal Responses to Chronic AM Therapy

As shown in Figure 4, the LV tissue level and gene expression of ANP was markedly increased and LV tissue levels of angiotensin II and BNP were moderately increased in DS rats at 18 weeks compared with DS rats at 11 weeks or the other two DR. Chronic AM infusion significantly decreased the LV tissue level and gene expression of ANP and myocardial levels of BNP and angiotensin II. Chronic diuretic treatment significantly reduced LV tissue level and gene expression of ANP but not LV tissue levels of angiotensin II or BNP.

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**Physiological Profiles of the 6 Experimental Groups**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>DR 11W</th>
<th>DR 18W</th>
<th>DS 11W</th>
<th>DS 18W</th>
<th>DS AM</th>
<th>DS Diu</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>BW, g</td>
<td>391 ± 16</td>
<td>452 ± 25†</td>
<td>356 ± 19§</td>
<td>356 ± 34†§</td>
<td>395 ± 23§ ††</td>
<td>403 ± 20§ ††</td>
</tr>
<tr>
<td>LW, g</td>
<td>0.75 ± 0.07</td>
<td>0.82 ± 0.08</td>
<td>1.03 ± 0.15§</td>
<td>1.25 ± 0.11†§</td>
<td>1.17 ± 0.12†§</td>
<td>1.20 ± 0.20§#</td>
</tr>
<tr>
<td>LV/BW, g/kg BW</td>
<td>1.91 ± 0.14</td>
<td>1.81 ± 0.10</td>
<td>2.89 ± 0.37†§</td>
<td>3.54 ± 0.49†§</td>
<td>2.98 ± 0.32†§††</td>
<td>2.99 ± 0.61†§††</td>
</tr>
<tr>
<td>RW, g</td>
<td>0.19 ± 0.02</td>
<td>0.24 ± 0.03†</td>
<td>0.23 ± 0.02†§</td>
<td>0.23 ± 0.05†</td>
<td>0.23 ± 0.04†</td>
<td>0.23 ± 0.03†</td>
</tr>
<tr>
<td>RV/BW, g/kg BW</td>
<td>0.48 ± 0.05</td>
<td>0.52 ± 0.05</td>
<td>0.65 ± 0.03†§</td>
<td>0.67 ± 0.21†§</td>
<td>0.60 ± 0.09*</td>
<td>0.57 ± 0.09**</td>
</tr>
<tr>
<td>Lung weight, g</td>
<td>1.75 ± 0.11</td>
<td>1.67 ± 0.13</td>
<td>1.44 ± 0.14</td>
<td>2.56 ± 0.70†§#</td>
<td>1.64 ± 0.37††</td>
<td>1.72 ± 0.33††</td>
</tr>
<tr>
<td>Lung/BW/kg BW</td>
<td>4.48 ± 0.19</td>
<td>3.61 ± 0.24</td>
<td>4.04 ± 0.30</td>
<td>7.50 ± 2.92†§</td>
<td>4.17 ± 0.93††</td>
<td>4.28 ± 0.97††</td>
</tr>
<tr>
<td>UV, mL/d</td>
<td>42.2 ± 14.9</td>
<td>32.3 ± 11.2</td>
<td>47.0 ± 20.6</td>
<td>68.1 ± 25.6†§$</td>
<td>70.2 ± 14.6†§#</td>
<td>53.4 ± 25§**</td>
</tr>
<tr>
<td>UNaV, mEq/d</td>
<td>10.7 ± 6.3</td>
<td>10.7 ± 5.8</td>
<td>13.3 ± 7.5</td>
<td>15.6 ± 7.6†</td>
<td>21.2 ± 4.6§$††</td>
<td>20.7 ± 6.9§$††</td>
</tr>
<tr>
<td>UKV, mEq/d</td>
<td>3.1 ± 0.9</td>
<td>3.0 ± 1.0</td>
<td>3.1 ± 1.0</td>
<td>2.9 ± 0.8</td>
<td>3.5 ± 0.5</td>
<td>3.2 ± 1.1</td>
</tr>
</tbody>
</table>

BW indicates body weight; LW, left ventricle weight; RVW, right ventricle weight; DR 11W, DR at 11 weeks; DR 18W, DR at 18 weeks; DS 11W, DS at 11 weeks; DS 18W, DS treated with vehicle at 18 weeks; DS AM, DS treated with AM 500 ng/h at 18 weeks; DS Diu, DS treated by methylchrolothiazide 0.133 mg/mL at 18 weeks.

*P<0.05 vs DR 11W; †P<0.01 vs DR 11W; ††P<0.05 vs DR 11W; §P<0.01 vs DR 18W; ¶P<0.05 vs DS 11W; ††P<0.01 vs DS 11W; ‡P<0.05 vs DR 18; #P<0.01 vs DR 18; **P<0.05 vs DS 11W; †††P<0.01 vs DS 18; ††††P<0.01 vs DS 18.

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**Figure 2.** Central hemodynamics in DR and DS rats at 11 and 18 weeks. Right atrial pressure (RAP) (A), left ventricular end-diastolic pressure (LVEDP) (B), mean arterial pressure (MAP) (C), and right ventricular systolic pressure (RVSP) (D). Abbreviations and number of rats in each group as in the Table. *P<0.05 vs DR 11; **P<0.01 vs DR 11; †P<0.05 vs DR 18; ††P<0.01 vs DR 18; ¶P<0.05 vs DS 11; †††P<0.01 vs DS 11; ‡P<0.05 vs DS 18; ††††P<0.01 vs DS 18; #P<0.05 vs DS AM.

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**Figure 1.** Time course of systolic blood pressure of DS and DR rats. DS and DR (n=15) rats were fed a high-salt diet from 6 weeks of age (left arrow). DS rats were treated with vehicle (DS vehicle, n=15), adrenomedullin (DS AM, 500 ng/h, n=13), and trichlormethiazide (DS Diu, 0.133 mg/mL, n=11) from 11 weeks of age.
Experiment 2
Serial Measurement of Cardiac Output and SVR
The serial changes in cardiac output, SVR, MAP, LVEDP, RVSP, and LVW/BW were assessed in other experiment groups (Figure 5). At 11 weeks, DS rats had higher MAP as the result of increased SVR than DR; however, there was no difference in cardiac output between DS rats and DR. After 14 weeks, DS rats had lower cardiac output than DR. Chronic AM infusion treatment significantly increased cardiac output and reduced SVR without changing MAP. In contrast, diuretic did not change them significantly.

Experiment 3
LV End-Systolic Elastance
Representative results of LV pressure-volume relations in DR and DS rats treated with vehicle, AM, and diuretic and the results of Ees in four groups are shown in Figure 6. Ees was significantly lower in vehicle-treated DS rats than in DR. Chronic AM and diuretic treatment significantly prevented the fall in Ees seen in DS rats; however, its effect was greater in AM than in diuretic.

Experiment 4
Survival Rate
As shown in Figure 7, survival rate was analyzed at 8 weeks after the start of treatment. All DS rats treated with vehicle died of congestive heart failure between 12 and 19 weeks of age. Kaplan-Meier survival analysis showed that long-term AM infusion and diuretic treatment significantly prolonged the survival of DS rats ($P<0.01$ and $P<0.05$, respectively); however, the effect was greater in the AM than in the diuretic group ($P<0.05$).

Discussion
The circulating renin-angiotensin-aldosterone system is known to be excessively activated in patients with heart failure, leading to adverse effects. In this study, plasma renin was not activated at 11 weeks; however, DS rats at 18 weeks had higher plasma renin and aldosterone concentrations than DR, indicating activation of the circulating renin-angiotensin-aldosterone system in the transition from LV hypertrophy to heart failure in DS rats. Interestingly, chronic AM infusion significantly inhibited the activation of circulating renin in DS rats. In previous studies, the acute effects of AM on plasma renin activity were controversial in vivo because excessive reduction of blood pressure induced by AM may induce renin secretion. However, Khan et al. reported that chronic administration of AM significantly reduced plasma renin activity despite the reduction of blood pressure in renovascular hypertensive rats, suggesting an inhibitory effect of chronic AM infusion on renin secretion. Furthermore, AM significantly inhibited the activation of aldosterone in the transition from LVH to heart failure in this study. AM has been shown to inhibit production of angiotensin II–induced aldosterone by dispersed rat adrenal zona glomerulosa cells.

Acute inhibitory effects of AM on aldosterone secretion was also reported in human and experimental heart failure. Thus, beneficial effects of AM may be partly mediated by an inhibitory effect of the activation of the circulating renin-angiotensin-aldosterone system.

In the present study, DS rats with heart failure exhibited not only increased LV weight but also myocyte phenotypic modulation, as shown by the upregulation of ANP genes and increased myocardial ANP and BNP levels. Interestingly, long-term AM infusion was effective in reduction of ANP gene expression and ANP and BNP myocardial levels. In addition, previous studies have shown that the cardiac renin-angiotensin system plays a critical role in progression of heart failure in DS rats fed a high-salt diet. Furthermore, myocardial angiotensin II is also involved in the development of heart failure induced by myocardial infarction or hemodynamic overload. In the present study, the myocardial angiotensin II level was significantly higher in DS rats with heart failure than in DR. Importantly, this increase in myocardial angiotensin II level was significantly attenuated by chronic AM administration. These findings suggest that not only the reduction of circulating renin-angiotensin levels but also inhibition of the intracardiac renin-angiotensin system may be involved in the amelioration of heart failure by chronic AM therapy.

We compared the effect of AM with a diuretic to determine whether the beneficial effects of AM are mediated solely through its natriuretic and antihypertensive actions. Although AM and diuretic treatment similarly decreased systolic blood pressure and increased sodium excretion in DS rats, the beneficial effects were greater in AM than in the diuretic group. This may be explained in part by the direct effects of AM on the cardiovascular and endocrine systems. Previous studies have shown that AM inhibits angiotensin II–induced cardiac hypertrophy in cardiac myocytes as well as angiotensin II–induced collagen synthesis and proliferation in cardiac fibroblasts, suggesting an inhibitory effect of AM in...
cardiac remodeling. In fact, AM gene therapy significantly reduced cardiac hypertrophy and fibrosis in a model of hypertension. In addition, antiproliferative effects of AM in vascular smooth muscle cells and mesangial cells has also been reported. Indeed, AM(+/−) mice, the plasma and organ AM concentrations of which were almost half of those in AM(+/+) mice, have marked coronary arterial perivascular fibrosis and intimal hyperplasia in angiotensin II and salt-loaded conditions, suggesting a protective action of endogenous AM against cardiovascular damage. Thus, direct anticardiac remodeling, antiatherosclerotic, and/or renoprotective effects of AM may have been associated with the beneficial effects of chronic administration of AM.
Rademaker et al. very recently reported that intravenous infusion of AM for 4 days increases cardiac output with a decrease of SVR in sheep with pacing-induced heart failure. They showed the improvement of cardiac function after 4 days of AM treatment; however, whether chronic treatment of AM has beneficial effect on cardiac function remains unknown. In the present study, an increase in cardiac output and decrease in SVR were still observed after 7 weeks of treatment with AM. Furthermore, from the analysis of LV pressure-volume relations, DS rats treated with AM exhibited an increase in Ees, suggesting the improvement of LV contractility by AM. Thus, long-term administration of AM improves cardiac output not only by the reduction of afterload but also by the preservation of LV contractility.

Interestingly, chronic human recombinant AM infusion significantly decreased the elevated plasma endogenous rat AM levels. Although the plasma level of human AM was low, the beneficial effects of chronic AM infusion therapy on progression of heart failure were significant. Previous studies have shown that chronic AM infusion significantly reduced plasma renin activity in renovascular hypertensive rats, attenuated progression of pulmonary hypertension in rats, attenuated cardiac remodeling in myocardial infarct rats, and had a renoprotective effect in severe hypertensive rats, with an increase of plasma AM levels in the pathophysiological range. These findings were consistent with the present results. The fact that this slight increase in plasma AM was effective may be attributable to an increase of AM-mature, an active form of AM. Recent studies have shown that major molecular form of plasma AM is AM-glycine, an inactive molecular form of AM, and that AM-mature only constitutes ~10% of plasma AM. In the present study, we also demonstrated that AM-mature is not the

Figure 6. LV end-systolic pressure-volume relations by gradual occlusion of inferior vena cava and Ees. Data show typical results in DR 18 (A), DS 18 (B), DS AM (C), and DS Diu (D). Abbreviations as in Figure 1. Number of rats in each group is DR (n=8), DS (n=8), DS AM (n=5), and DS Diu (n=5).
Figure 7. Kaplan-Meier survival curves. DS fed a high-salt diet were treated with vehicle (DS, n=20), AM (DS AM, n=23), and trichlormethiazide (DS Diu, n=17).

major molecular form of rat plasma AM and that increased human AM was comparable to rat AM-mature levels. Thus, the finding that exogenous AM administration reduces endogenous AM levels may support the hypothesis that increased plasma AM may play a compensatory role in the pathophysiology of heart failure.

In conclusion, chronic administration of AM had beneficial hemodynamic, plasma neurohormonal, myocardial biochemical, and cardiac functional effects and thereby improved survival in DS rats with heart failure. Chronic AM administration may be a new therapeutic approach for the treatment of heart failure.

Perspectives

The current study provides insight into the role of increased plasma AM in heart failure. Our results suggest that AM behaves as a beneficial endogenous peptide for hemodynamic and cardiac function in heart failure, partly through inhibition of circulating and tissue renin-angiotensin-aldosterone system. Furthermore, this study suggests that long-term infusion of AM may be a new therapeutic approach to the treatment of heart failure. Currently, infusion of ANP or brain natriuretic peptide is clinically used for the treatment of heart failure. Currently, infusion of ANP or brain natriuretic peptide is clinically used for the treatment of heart failure. Currently, infusion of ANP or brain natriuretic peptide is clinically used for the treatment of heart failure. Currently, infusion of ANP or brain natriuretic peptide is clinically used for the treatment of heart failure. Currently, infusion of ANP or brain natriuretic peptide is clinically used for the treatment of heart failure.

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