Hyposecretion of Atrial Natriuretic Factor by Prehypertensive Dahl Salt-Sensitive Rat

Michael O. Onwochei and John P. Rapp

Studies were carried out to determine if the release of atrial natriuretic factor (ANF) is altered in the inbred Dahl salt-sensitive (SS/Jr) rat. Isolated heart-lung preparations of prehypertensive young SS/Jr rats (6–8 weeks of age) and age-matched inbred Dahl salt-resistant (SR/Jr) rats were used. At this relatively young age the blood pressure difference between strains (SS/Jr, 108±3 mm Hg; SR/Jr, 103±2 mm Hg) was minor. ANF release was stimulated with preload-induced or afterload-induced atrial stretch. Increased preload produced increases in right and left atrial pressures that were equivalent between young SS/Jr and SR/Jr rats; increased afterload produced increases only in left atrial pressures, which again were equivalent for young rats of the two strains. At any preload-induced change in atrial pressure SS/Jr rat hearts released less ANF than those of SR/Jr rats. Similarly, at any afterload-induced increase in left atrial pressure, SS/Jr rat hearts released less ANF than those of SR/Jr rats. In contrast to the above results in young rats, the strain differences were dramatically reversed when older rats (5–6 months of age) were used; at this age SS/Jr rats were markedly hypertensive (SS/Jr, 211±8 mm Hg; SR/Jr 130±4 mm Hg). Hearts from adult hypertensive SS/Jr rats released more ANF than hearts from adult normotensive SR/Jr rats at any left atrial pressure as afterload was increased. This reversal of SS/Jr rats from hyposecreters to hypersecreters of ANF is probably a consequence of hypertension-induced changes such as cardiac hypertrophy and recruitment of the ventricles to produce ANF. It is concluded that the hyposecretion of ANF by prehypertensive SS/Jr rats may represent a genetic trait relevant to the pathogenesis of genetic hypertension and that this is obscured by adaptive changes in the heart as hypertension progresses. (Hypertension 1989;13:440–448)

Atrial natriuretic factor (ANF) has been reported to increase sodium and water excretion,1–7 relax vascular smooth muscle,8–12 and lower blood pressure.6,7,13,14 ANF concentration in the atrial tissue is higher in Dahl salt-sensitive (SS/Jr) rats, than that of Dahl salt-resistant (SS/Jr) rats.15,16 This strain difference in ANF in the atrial tissue is present when these rats are young (at weaning) and persists for the life of the rats. It is not known why the ANF level is high in the atrial tissue of the SS/Jr rat. Theoretically this could occur as a consequence of increased synthesis and storage of ANF or impairment in its release. It seems unlikely that atrial ANF synthesis is increased in young SS/Jr rats since ANF messenger RNA (mRNA) is present in similar amounts in the atria of young SS/Jr and SR/Jr rats.17 Thus, the alternative that SS/Jr rats have impaired ANF release was investigated in this study. Specifically, we used a heart-lung preparation to investigate ANF release in response to atrial distension or stretch, which is a known potent stimulus for ANF release.18–31 We used young rats at an age when the SS/Jr rat is normotensive to avoid adaptive changes in the heart that occur as a consequence of hypertension.

Materials and Methods

Animals

Age-matched young (6–8 weeks old) or adult (5–6 months old) SS/Jr and SR/Jr rats were used. The development of these inbred strains from the outbred lines obtained originally from Lewis Dahl has been described.32 The official strain designations SS/Jr and SR/Jr33 will be shortened to their generic designations (S and R, respectively) in the rest of this paper. The rats were fed standard rat chow (Wayne Rodent Blox, Continental Grain Co., Chicago, Illinois), which contained 1% NaCl.

Heart-Lung Preparation

Each rat was anesthetized with pentobarbital (30 mg/kg, i.p.), and the heart and lungs were isolated.
and perfused as shown in Figure 1. The rat was tracheotomized and ventilated with 95% O₂ and 5% CO₂ using a rodent respirator (model 683, Harvard Apparatus, South Natick, Massachusetts). The chest was then opened and loose ligatures were placed around the aorta, the jugular veins, and the inferior vena cava. The aorta was catheterized via the brachiocephalic artery using polyethylene tubing. An adjustable clamp was placed on this aortic catheter to control the mean arterial pressure (afterload). Proximal to this clamp, a Y-shaped connector was used to connect the aortic catheter to a pressure transducer, and the mean arterial pressure was recorded on a polygraph (model 79D, Grass Instruments, Quincy, Massachusetts). An in-line flow probe was placed distally to this clamp, and the cardiac output (aortic flow rate, which is cardiac output minus coronary flow rate) was measured with an electromagnetic flow meter (model FM 501, Carolina Medical Electronics, King, North Carolina). Next, the inferior vena cava was catheterized using polyethylene tubing. The other end of this tubing was connected to a water-jacketed reservoir that contained perfusate, which was maintained at 37°C and arranged such that the fluid level (preload) was 4 cm above the heart. By force of gravity, the perfusate was allowed to flow into the inferior vena cava. The jugular veins and the aorta were then tied such that only the heart and the lungs were perfused. Per fusate was then pumped by the heart through the aortic catheter back into the reservoir.

After the above procedure, intramedic polyethylene tubing (P.E. 10, Clay Adams, Parsippany, New Jersey) was placed in the right atrium by catheterizing the right jugular vein proximal to the ligature that had been placed in the earlier procedure. The other end of this catheter was connected to a pressure transducer and the mean right atrial pressure was measured. The mean left atrial pressure was similarly recorded after a direct cannulation of the left atrium with polyethylene tubing (P.E. 10, Clay Adams).

Composition of Perfusate

The perfusate contained Krebs-Ringer bicarbonate buffer (mM): NaCl 127.2, KCl 4.7, CaCl₂ 2.5, KH₂PO₄ 1.2, MgSO₄ 1.2, NaHCO₃ 24.9, glucose 10.0, pyruvate 2.0, 15% rat red blood cells (washed three times in Krebs-Ringer bicarbonate buffer), 0.1% bovine serum albumin, and 1 unit heparin/ml.
**Preload and Atrial Natriuretic Factor Release By Young Rats**

A 20-minute postsurgical equilibration of each heart-lung preparation was carried out at a preload of 3 cm and an afterload of 60 mm Hg mean arterial pressure before the start of the experiment. After this equilibration period, the preload (vertical height above the heart of the surface of the perfusate in the reservoir) was reset to 1.5 cm, the afterload was kept constant at 60 mm Hg, and the preparation was allowed 10 minutes to stabilize at this new preload. At 10 minutes, the recirculated perfusate was replaced with 13.4 ml of fresh perfusate and recirculated for 10 minutes. The reservoir volume was 10 ml; the remaining 3.4 ml was contained in the heart, lungs, and tubings that connected the preparation to the reservoir. This latter volume was measured by pulsatile recording of the pressure signal midway through the experimental 10-minute period. At 10 minutes, a 2-ml perfusate sample was removed from the reservoir for ANF assay. Preloads of 3 cm and 6 cm were then studied in the same manner as described for preload of 1.5 cm (i.e., at each preload the heart was allowed to stabilize for 10 minutes at a constant afterload of 60 mm Hg before the 10-minute experiment was carried out).

**Afterload and Atrial Natriuretic Factor Release By Adult Rats**

A 20-minute postsurgical equilibration of the heart-lung preparation was carried out for each rat at a preload of 4 cm and an afterload of 60 mm Hg mean arterial pressure. After this initial equilibration, the afterload was reset to 40 mm Hg mean arterial pressure, and the preparation was allowed to stabilize for 10 minutes. The recirculated perfusate was then replaced with 13.4 ml of fresh perfusate while the preload was held constant as described above. The perfusate was then recirculated for 10 minutes, and the heart rate and perfusate sample were taken as described for the preload study. This procedure was repeated at a constant preload of 4 cm for other afterloads of 60, 80, 100, and 120 mm Hg mean arterial pressure.

**Radioimmunoassay**

The perfusate samples were placed in ice immediately after collection and were centrifuged (3,000 rpm at 4° C) for 30 minutes to remove the red blood cells. ANF was measured in the supernatant by radioimmunooassay, which was developed in our laboratory and described in detail previously. The sensitivity of the assay was 3 pg and 50% displacement was obtained with 49.9 pg. The coefficients of variation were 8% within assays and 12.2% between assays.

The secretion of ANF by the heart-lung preparation was expressed as nanograms per 10 minutes for the 10-minute experimental periods described above. This was arrived at by multiplying the concentration of ANF determined in the recirculating medium by the known volume of the recirculating medium.

**Statistical Analysis**

Values were expressed as mean±SEM. Analyses were carried out using Student's t test or analysis of variance with repeated measures. Regression analysis included a test to determine if the data were compatible with a straight line. Differences in the slopes of two regression lines were assessed by analysis of covariance. Statistical analyses were performed on a PDP 11/70 computer (Digital Equipment Corp., Maynard, Massachusetts) using BMD programs (BMDP Statistical Software Inc., Los Angeles, California) or on an Olivetti p6060 with programs supplied by Olivetti (Dallas, Texas).

**Results**

Body weights, blood pressure, and left and right atrial weights for the young S and R rats were not significantly different between strains (Table 1); however, the whole heart of the young S rat was slightly (10.1%) greater than that of the age-matched R rat. The heart weight/body weight ratio was also slightly higher in young S rats. For age-matched adult rats, S rats had slightly higher body weight. The heart weight, heart weight/body weight ratio, left atrial weight, and blood pressure of the adult S rats were markedly higher (by 45.7%, 35.5%, 60.6%, and 62.3%, respectively) than those of the adult R rats. For adults rats, right atrial weights were similar for S and R rats in spite of the marked hypertension and changes in the left atrial and total heart weights. If the heart weight/body weight ratios of the young and the adult rats given in Table 1 are compared it is seen that this ratio stayed relatively constant in the S rats, whereas it decreased with growth in the R rats.

The effects of preload-induced changes on hemodynamic parameters and ANF release by the heart-lung preparations of the young rats are shown in
Table 2. For both strains, increased preload gave rise to increases in cardiac output, heart rate, stroke volume, and right and left atrial pressures. No strain differences or strain-preload interaction was noted for any of these preload-induced hemodynamic changes. Changes in the preload produced similar changes in right atrial pressure and left atrial pressure for each strain, but left atrial pressure was consistently higher than right atrial pressure. ANF release increased significantly with increased preload in both strains. The relations between left atrial pressure and ANF release with changes in preload are given for R and S rats in Figure 2, left panel. Regression lines for the R and S rats had different slopes (p<0.005) and different intercepts (p<0.001). Since the line for R rats is to the left of the line for S rats, R rats released more ANF than S rats at any given left atrial pressure.

The effects of changes in afterload were also studied in young R and S rats and the data are given in Table 3. Cardiac output and stroke volume were significantly lowered by increased afterload. The R rats had higher cardiac output and stroke volume than S rats at the lower afterloads, but the reverse was true at higher afterloads; the strain-afterload interaction was therefore significant for these parameters. Heart rate was slightly lowered for R rats by increasing afterload, but no statistically significant strain differences or strain-afterload interaction were noted. For both strains, left atrial pressure was decreased by increased afterload, but right atrial pressure for each strain was unchanged by the afterload. There were no strain differences in left atrial pressure, or in strain-afterload interaction for left atrial pressure.

Table 2. Effect of Preload on Hemodynamic Parameters and Atrial Natriuretic Factor Release for Isolated Heart-Lung Preparations of Young (6–8 week old) Dahl Rats

<table>
<thead>
<tr>
<th>Parameters measured</th>
<th>Preload (cm)</th>
<th>Strain</th>
<th>Preload</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.5</td>
<td>3.0</td>
<td>6.0</td>
<td></td>
</tr>
<tr>
<td>Cardiac output (ml/min/g heart)</td>
<td>R</td>
<td>S</td>
<td>R</td>
<td>S</td>
</tr>
<tr>
<td>(14)</td>
<td>(14)</td>
<td>(14)</td>
<td>(14)</td>
<td>(13)</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>R</td>
<td>S</td>
<td>R</td>
<td>S</td>
</tr>
<tr>
<td>(14)</td>
<td>(14)</td>
<td>(14)</td>
<td>(14)</td>
<td>(13)</td>
</tr>
<tr>
<td>Stroke volume (µl/g heart)</td>
<td>R</td>
<td>S</td>
<td>R</td>
<td>S</td>
</tr>
<tr>
<td>(14)</td>
<td>(14)</td>
<td>(14)</td>
<td>(14)</td>
<td>(13)</td>
</tr>
<tr>
<td>Right atrial pressure (cm H2O)</td>
<td>R</td>
<td>S</td>
<td>R</td>
<td>S</td>
</tr>
<tr>
<td>(12)</td>
<td>(13)</td>
<td>(12)</td>
<td>(13)</td>
<td>(12)</td>
</tr>
<tr>
<td>Left atrial pressure (cm H2O)</td>
<td>R</td>
<td>S</td>
<td>R</td>
<td>S</td>
</tr>
<tr>
<td>(12)</td>
<td>(13)</td>
<td>(12)</td>
<td>(13)</td>
<td>(12)</td>
</tr>
<tr>
<td>ANF (ng/10 mm)</td>
<td>R</td>
<td>S</td>
<td>R</td>
<td>S</td>
</tr>
<tr>
<td>(14)</td>
<td>(14)</td>
<td>(14)</td>
<td>(14)</td>
<td>(13)</td>
</tr>
</tbody>
</table>

Values are mean±SEM. Data was analyzed using 2×3 analysis of variance for repeated measures (two strains, three different preloads). Probabilities from 2×3 analysis of variance are shown in the last column. **p<0.001; *p<0.01; NS, not significant.**
ANF release was significantly increased by increasing afterload in young rats (Table 3). The relations between left atrial pressure and ANF release with changes in afterload are given for isolated heart-lung preparations of young inbred Dahl salt-sensitive (S) and salt-resistant (R) rats. Each regression line shown had a slope significantly different from zero ($p<0.001$) and was compatible with fitting a straight line. Left panel, preload experiments: at any left atrial pressure R rats released more ANF than S rats. Slopes ($p<0.005$) and intercepts ($p<0.005$) of S rats and R rats regression lines were significantly different by an analysis of covariance. Right panel, afterload experiments: at any left atrial pressure R rats released more ANF than S rats. Slopes of the S rats and R rats regression lines were not significantly different ($p=0.15$), but intercepts were different ($p<0.005$) by an analysis of covariance.

Next we wanted to determine if the ANF response to changes in atrial pressure was the same when atrial pressure was altered by preload as compared with afterload. When the regression lines for R rats for preload and afterload (Figure 2, left and right panels respectively) were compared, an analysis of covariance showed that the preload for R rats and the afterload lines for R rats had the same slopes ($p=0.15$), and the same intercepts ($p=0.17$), and

### Table 3. Effect of Afterload on Hemodynamic Parameters and Atrial Natriuretic Factor Release for Isolated Heart-Lung Preparations of Young (6–8 week old) Dahl Rats

<table>
<thead>
<tr>
<th>Parameters measured</th>
<th>40</th>
<th>60</th>
<th>80</th>
<th>100</th>
<th>Probabilities from 2x3 or 2x4 analysis of variance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac output (ml/min/g heart)</td>
<td>R</td>
<td>S</td>
<td>R</td>
<td>S</td>
<td>12.1±0.8</td>
</tr>
<tr>
<td></td>
<td>19.1±0.9</td>
<td>16.8±0.9</td>
<td>12.8±1.6</td>
<td>14.4±0.8</td>
<td>0.85 &lt;0.001 0.028</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>R</td>
<td>S</td>
<td>R</td>
<td>S</td>
<td>308±9</td>
</tr>
<tr>
<td></td>
<td>303±11</td>
<td>307±8</td>
<td>286±15</td>
<td>308±6</td>
<td>0.30 0.020 0.120</td>
</tr>
<tr>
<td>Stroke volume (µl/g heart)</td>
<td>R</td>
<td>S</td>
<td>R</td>
<td>S</td>
<td>39.5±3.0</td>
</tr>
<tr>
<td></td>
<td>64.4±4.6</td>
<td>55.8±2.7</td>
<td>52.3±3.1</td>
<td>47.1±2.9</td>
<td>0.25 &lt;0.001 0.014</td>
</tr>
<tr>
<td>Right atrial pressure (cm H2O)</td>
<td>R</td>
<td>S</td>
<td>R</td>
<td>S</td>
<td>1.5±0.6</td>
</tr>
<tr>
<td></td>
<td>2.0±0.3</td>
<td>1.6±0.3</td>
<td>1.9±1.3</td>
<td>1.3±0.4</td>
<td>0.73 0.99 0.393</td>
</tr>
<tr>
<td>Left atrial pressure (cm H2O)</td>
<td>R</td>
<td>S</td>
<td>R</td>
<td>S</td>
<td>16.0±0.6</td>
</tr>
<tr>
<td></td>
<td>8.5±2.4</td>
<td>11.9±4.4</td>
<td>14.2±5.6</td>
<td>15.1±4.6</td>
<td>0.34 0.99 0.567</td>
</tr>
<tr>
<td>ANF (ng/10 min)</td>
<td>R</td>
<td>S</td>
<td>R</td>
<td>S</td>
<td>17.5±3.7</td>
</tr>
<tr>
<td></td>
<td>13.3±1.5</td>
<td>11.5±1.2</td>
<td>12.0±1.3</td>
<td>15.1±2.3</td>
<td>0.059 0.006 0.41</td>
</tr>
</tbody>
</table>

Values are mean ±SEM. Data were analyzed using a factorial analysis of variance for repeated measures; the design was 2x4 for atrial pressures (two strains, four afterloads) and 2x3 (two strains, three afterloads) for other parameters. The number in parenthesis below each mean is the number of heart-lung preparations used. Preload was set at 4 cm for each different afterload condition. Afterloads are given as mean arterial pressure in mm Hg. R, Dahl salt-resistant rats; S, Dahl salt-sensitive rats; ANF, immunoreactive atrial natriuretic factor in atriopeptin III equivalents.
thus the two lines were identical for R rats. Similarly comparing the regression lines for preload and afterload for S rats (Figure 2, left and right panels, respectively), an analysis of covariance showed that the preload for S rats and the afterload lines for S rats had the same slopes ($p=0.80$) and intercepts ($p=0.32$), and thus the two lines were identical for S rats. Thus, for both strains the relation of ANF to left atrial pressure was the same regardless of whether left atrial pressure was altered by preload or by afterload.

The effect of afterload on ANF release from heart-lung preparations was also studied in adult 4–6 month old rats, at which age the S rats are markedly hypertensive. Data was obtained from adult S rats for afterloads from 60 to 160 mm Hg mean arterial pressure, but hearts from adult R rats failed (cardiac output approached zero and pulmonary edema developed) at afterloads above 120 mm Hg. This is reflected in a marked rise in left atrial pressure that occurred at 120 mm Hg afterload in adult R rats, but did not occur in adult S rats until 160 mm Hg (Figure 3). This situation in adult rats contrasted with the young rats in Figure 3, where it is seen that hearts from both young S and R rats showed similar increases in left atrial pressure, and hearts from both strains failed at the relatively low afterload of 100 mm Hg. It is also interesting that at any given afterload in the range of 60 to 100 mm Hg the young rats of both strains (Figure 3) showed a greater left atrial pressure than the adult rats; we have no explanation for this age difference.

Table 4 gives hemodynamic and ANF data for heart-lung preparations from the adult rats. The 2x4 factorial analysis of variance in Table 4 is for data up to 120 mm Hg of afterload. Within this range, afterload did not significantly influence the heart rate, cardiac output, or stroke volume, but significant strain differences were noted for cardiac output and stroke volume where R rats had higher cardiac output and stroke volume than S rats. Heart rate and stroke volume showed significant strain-afterload interactions. Afterload had no effect on right atrial pressure and no strain differences were noted in right atrial pressure. Left atrial pressure, however, was markedly increased for both strains by increased afterload. Strain differences and strain-afterload interaction were noted for afterload-induced changes in left atrial pressure because R rats showed a sharp increase in left atrial pressure at lower afterloads than S rats (as already noted in Figure 3). Because of this differential response, strain-afterload interaction was significant.

ANF release increased with increasing afterload in adult rats of both strains, and ANF release by the adult S rat was significantly ($p=0.041$) higher than that of the adult R rat at any afterload (Table 4). The relation between left atrial pressure and ANF release is shown in Figure 4 for the adult rats. Significant regressions ($p<0.001$) were found for each strain and an analysis of covariance showed that the slopes ($p<0.001$) and intercepts ($p<0.001$) of the regression lines for S and R rats (Figure 4) were significantly different. Obviously the adult S rats in Figure 4 were much more sensitive than were adult R rats in releasing ANF in response to changes in left atrial pressure. This higher release of ANF by the adult S rat is the opposite of the effect that was noted in the young rats where R rats released more ANF than S rats (compare Figures 2 and 4).

**Discussion**

The main focus of this work was to test the hypothesis that, with young animals, the prehypertensive heart of S rats is hyporesponsive to ANF release induced by atrial stretch. This concept is
FIGURE 4. Relation between afterload-induced changes in left atrial pressure and release of atrial natriuretic factor (ANF) by isolated heart-lung preparations of the adult (4-6 month old) Dahl rats.

Values are mean±SEM. Data were analyzed using a factorial analysis of variance for repeated measures; the design was 2x4 factorial (two strains, four afterloads) and used the data only up to an afterload of 120 mm Hg since R hearts failed at that preload. Preload was set at 4 cm for each afterload. ANOVA, analysis of variance; R, Dahl salt-resistant rats; S, Dahl salt-sensitive rats; ANF, immunoreactive atrial natriuretic factor in atriopeptin III equivalents.
In our studies in young S and R rats, we have emphasized the relation between left atrial pressure and ANF in the heart-lung preparation, but not with right atrial pressure. Theoretically ANF could be released from both atria by the preparation. The reasons for our emphasis on left atrial pressure are as follows: In the afterload study, only left atrial pressure changed significantly so presumably ANF secretion reflects ANF released from the left atrium. In the preload study, both left atrial pressure and right atrial pressure changed, but changes in left atrial pressure were much greater. Moreover, within a given strain, the regression lines relating ANF to left atrial pressure were identical for the preload and afterload studies. If the right atrium were releasing much ANF with changes in preload, then the preload regression line of ANF versus left atrial pressure (where both left atrial pressure and right atrial pressure increase) would be shifted higher than the similar afterload regression line (where only left atrial pressure changes). The fact that it was not shifted significantly suggests that the right atrium was releasing very little ANF with changes in preload. This is not to imply that the right atrium does not release ANF in vivo, it only means that, with the heart-lung preparation as used here, most of the ANF released is probably from the left atrium.

Our present study gives no insight into the potential mechanism whereby hearts from young S rats are hyporesponsive to increased atrial pressure. On the assumption that atrial stretch, as demonstrated by several workers\(^{21,26,29}\) with atrial strips in vitro, and not atrial pressure per se, is a likely proximal stimulus for ANF release, it is reasonable to ask if atria of young S and R rats stretch similarly under a given pressure. Perhaps they are not equally compliant. Alternately, an underlying secretory defect could exist in S rats at the biochemical level. This issue is not resolved.

Our previous data\(^20\) showed that adult hypertensive S rats were not hyporesponsive to changes in atrial pressure with regard to ANF release compared with adult normotensive R rats, but were in fact hyperresponsive. This was true for both preload-induced and afterload-induced changes in atrial pressure. In our previous afterload study in hypertensive S rats,\(^20\) the range of afterloads studied was, however, too narrow to appropriately challenge the hypertrophied heart from S rats. The afterload experiments were, therefore, repeated here with an expanded range of afterloads, and the same conclusion was reached, (i.e., adult hypertensive S rats are hyperresponsive to stretch-induced atrial ANF release).

The dramatic age-related reversal of ANF secretion in S rats, from hyporesponsive to hyperresponsive, in response to changes in atrial pressure is likely to be related to the cardiac hypertrophy of the hypertensive S rats. The exact mechanism for this reversal is unclear, but it could be related to production of ANF by the ventricle, as shown by marked increases in ventricular ANF and ANF mRNA in hypertensive S rats.\(^17\)

In Langendorff preparations of rat and rabbit hearts, severe hypoxia (no oxygen) has been shown to cause ANF release.\(^26\) One hypothesis could be that the working heart preparation experiences hypoxia as oxygen demand goes up with increased workload, and this may initiate ANF release. This might be exacerbated in the hypertrophied heart of the hypertensive S rat, possibly explaining the increased ANF release from such hearts.

References


**KEY WORDS** • genetic hypertension • atrial natriuretic factor • cardiac output • isolated heart-lung preparation
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