Selective and Tone-Dependent Vasodilation of Arterial Segment in Rabbit and Feline Pulmonary Microcirculation in Response to ANP

Mikiyasu SHIRAI, Ishio NINOMIYA*, and Tetsuaki SHINDO

Department of Cardiac Physiology, National Cardiovascular Center Research Institute, Suita, 565 Japan

Abstract Using an X-ray television system, we directly measured the changes in internal diameter (ID; 100–600 μm) of small pulmonary arteries and veins in response to intravenous infusion of atrial natriuretic peptide (ANP) in anesthetized rabbits and cats. Under physiological conditions, ANP (0.01–1 μg/(kg·min) for 3 min) increased the ID of the small arteries in a dose-dependent manner by 4–9% and by 6–14% in the rabbit and cat, respectively. The maximum increase in ID occurred in the 400–600 μm arteries. In the small veins, however, the peptide had no significant effects on the ID. To simultaneously investigate the ANP-induced responses of pulmonary vessels with different vascular tone in a given lung region, we embolized a part of the rabbit pulmonary vascular tree with micro-beads (80–100 μm diameter) and measured ID responses to ANP (1 μg/(kg·min) for 3 min) in the embolized vessels with elevated tone and the nonembolized vessels with baseline tone. In the embolized arteries, which had constricted by 31%, ANP induced 27% increase in ID, while in the nonembolized arteries it caused 8% increase in ID. This indicated that in the small arteries, the vasodilator activity of ANP is greatly enhanced under the conditions of elevated vascular tone. In the small veins, however, no significant vasodilation occurred even under the elevated-tone conditions. We concluded that ANP dilates the arterial segments in the rabbit and cat pulmonary microcirculation selectively and in a dose-dependent manner. Furthermore, the pulmonary vasodilator effect of ANP was dependent on the pulmonary vascular tone.

Key words: ANP, small pulmonary vessels, internal diameter, pulmonary vasodilation, pulmonary vascular tone.

Atrial natriuretic peptide (ANP) is mainly secreted by way of coronary sinus into the right atrium and is delivered first to the pulmonary circulation [1–4].

Received on February 23, 1993; Accepted on May 12, 1993

*Present address: Department of Physiology, Institute of Health Sciences, Hiroshima University School of Medicine, Kasumi-cho, Hiroshima, 734 Japan

485
Specific receptors for ANP exist in the vascular smooth muscle and endothelial cells of pulmonary arteries, arterioles, and veins [5]. Those findings raise the speculation that the released ANP acts on the specific receptors to affect the level of pulmonary vascular tone. In fact, ANP caused relaxation of the isolated pre-constricted pulmonary arteries from various animal species [6–9]. Moreover, ANP reduced pulmonary arterial pressure in the isolated perfused lung at constant flow under conditions of baseline [10, 11] and elevated [10–12] pulmonary vascular tone. In the in vivo lung, however, no direct measurement of vascular diameter has been carried out to determine which pulmonary vascular segment actually dilates in response to ANP and to establish whether the pulmonary vasodilator effect of ANP depends on the degree of pulmonary vascular tone.

In this study, using an X-ray television system [13] on the in vivo rabbit and cat lungs, we measured the internal diameter (ID; 100–600 μm) of the small pulmonary arteries and veins with rich smooth muscle layers [14, 15] and analyzed the ID changes in response to intravenous infusion of ANP under physiological conditions. Furthermore, to elucidate the difference in the ANP-induced ID changes between the vessels with baseline and elevated vascular tone, we embolized a part of pulmonary arterial branches with micro-beads in small doses and induced local vasoconstrictions in the embolized branches [16] before intravenous infusion of ANP; we identified the embolized branch with constricted ID and the non-embolized branch with baseline ID in a given lung region [16] and recorded simultaneously ID changes of those branches in response to infused ANP.

METHODS

Experimental procedure and angiography. The experiments were carried out on 12 rabbits (2.3–2.7 kg bw) and 6 cats (2.8–3.5 kg bw). The rabbit and cat were anesthetized with pentobarbital sodium (30–35 mg/kg) administered intravenously and intraperitoneally, respectively. The level of anesthesia was maintained with supplemental doses of pentobarbital sodium (3 mg/kg, i.v.) given at 20- to 40-min intervals. Each animal was intubated with an endotracheal tube and artificially ventilated with room air enriched with O₂.

By use of an X-ray fluoroscopic system (Toshiba), a Swan-Ganz balloon catheter (4-F, Edwards Laboratories) was introduced from the right jugular vein into the left main pulmonary artery for measuring pulmonary arterial pressure (PAP) and injecting the contrast medium. Another balloon catheter (4F) was fluoroscopically introduced from right femoral vein into the inferior vena cava near the right atrium for measuring central venous pressure (CVP) and administering agents. A polyethylene catheter was inserted into the aorta via a femoral artery to measure systemic arterial pressure (SAP). After left thoracotomy, a polyethylene catheter was inserted directly into the left atrium for measuring left atrial pressure (LAP). Airway pressure (AWP) was measured in the tracheal tube. After all the catheters were positioned, partial excision of the left-side rib cage (ribs 6–8) was
conducted to enable the left lower lung to be directly exposed to X-ray. The end-expiratory pressure was adjusted to 3 cmH₂O to prevent lung collapse.

The system and the experimental setup used for angiography have previously been described in detail [13]. Briefly, the animal was put into the X-ray apparatus box and was fixed so that the exposed left lower lung automatically contacted the plate just above the beryllium faceplate of an X-ray-sensitive 1-in. vidicon camera (Hamamatsu Photonics). During a temporary cessation of ventilation at end expiration, the contrast medium (60% Urografin; 2–3 ml) was injected into the left main pulmonary artery at a constant speed (1.5 ml/s) and the passage of the contrast medium through the pulmonary vascular bed was serially recorded at a high speed of 30 frames/s on a video tape recorder (model CR-850; Victor). During the experiment, the temperature in the box was maintained at 25–28°C, and the surface of the exposed lung was kept wet by warm saline at a temperature of 37°C. Blood gases and pH were frequently measured throughout the experiment by a blood gas analyzer (ABL 2, Radiometer). The pH, \( P_{O_2} \), and \( P_{CO_2} \) of systemic arterial blood in the rabbit experiment were 7.39±0.01, 102±3 Torr, and 32±1 Torr, respectively, and those in the cat experiment were 7.38±0.01, 99±2 Torr, and 31±1 Torr, respectively.

**Experimental design.** Protocol 1: effect of ANP on microvessels under physiological condition. Six of the 12 rabbits and six cats were used in this series. The control angiogram was first recorded. The hemodynamic parameters, i.e., PAP, SAP, LAP, and CVP returned to the control values within 15–20 min in all animals. Thereafter, ANP (human, 1–28 or rat, 1–28) was continuously infused at the rate of 0.01 \( \mu g/(kg \cdot min) \) for 3 min into the inferior vena cava. The second angiogram was obtained 3 min after the start of the infusion. The third and fourth angiograms were also recorded 3 min after the continuous infusions of ANP at the rate of 0.1 and 1 \( \mu g/(kg \cdot min) \), respectively. To eliminate influence of the preceding infusion of ANP, there was an interval of about 30 min between each infusion.

Protocol 2: effect of ANP on embolized and nonembolized microvessels. The remaining 6 rabbits were used in this series. The control angiogram was first recorded. Then, to induce pulmonary microembolization, glass beads of 80–100 \( \mu m \) diameter were injected into right atrium in small doses of 20–40 mg/kg that induced no significant changes in PAP and blood gases. By use of the X-ray TV system the distribution patterns of glass beads in the pulmonary vessels were clearly observed. Therefore we could identify the embolized and nonembolized arterial branches [16]. The second angiogram was made to record the ID of the embolized and nonembolized branches. Thereafter, to compare the effects of ANP on the embolized and nonembolized branches which have different vascular tone [16], ANP was continuously infused at the rate of 1 \( \mu g/(kg \cdot min) \) for 3 min into the inferior vena cava. The third angiogram was obtained 3 min after the start of the infusion.

**Measurement of ID.** The serial angiograms recorded on the video tape recorder were transferred to the digital image processor. To obtain the arteriogram
and venogram for measurement of ID, four serial frames, in which arterial and venous tree were extensively filled with the contrast medium, were added and averaged by the digital image processor. The processed image was electrically transferred to the imaging hard copy unit and was clearly copied on the paper. The ID of small pulmonary vessels on the copy paper was manually measured by use of a digitizer coupled with a minicomputer.

Quantitative analysis of ID response. As in our previous study [17], a random selection of many arterial and venous sites for the ID measurement was made. The percentage change in ID in response to ANP under conditions of baseline and elevated vascular tone was calculated at each measured vascular site. The measured sites were classified into five vascular groups with different ID sizes according to their control ID sizes. In protocol 2, the embolized and nonembolized arterial branches were defined according to the method described in our previous study [16].

Statistical methods. Differences in ID values and hemodynamic data among the conditions of control and ANP infusions in protocol 1 and among the conditions of control, embolism, and embolism+ANP in protocol 2 were determined by ANOVA and modified t-test [18]. The statistical significances for ID responses to ANP among the five vascular groups were also determined by ANOVA and a modified t-test. Differences in ID change and percent ID change to ANP between embolized and nonembolized arteries were assessed by an unpaired t-test. All results were expressed as mean±SE, and p<0.05 was considered significant.

RESULTS

ID response to ANP under physiological condition

Figure 1 shows typical arteriograms and venograms before (control) and during infusion of ANP at the rate of 0.1 μg/(kg·min) in the same rabbit. During the infusion the ID of the arteries increased in many branches, particularly in the larger branches (solid arrows). The ID of the veins, however, did not change obviously.

The relationships between infusion rates and magnitudes of ID increase in the small pulmonary arteries and veins (100–600 μm) are shown in the rabbit (Fig. 2A) and the cat (Fig. 2B). During the infusions of ANP at the rates of 0.01, 0.1, and 1 μg/(kg·min), the ID of rabbit pulmonary arteries increased significantly in a dose-dependent manner by 4±1, 7±1, and 9±1%, respectively. With the three infusion rates of ANP, the ID of feline pulmonary arteries also increased significantly in a dose-dependent manner by 6±1, 11±1, and 14±1%, respectively. In both rabbit and feline pulmonary veins, however, the ID did not significantly change with the three infusion rates of ANP. The results indicated that exogenous ANP selectively dilates the arterial segments in a dose-dependent manner in the rabbit and feline pulmonary microcirculation.

Japanese Journal of Physiology
Fig. 1. Typical changes in internal diameter (ID) of small pulmonary arteries and veins in response to ANP (0.1 μg/(kg·min)) in rabbits. Solid arrows indicate apparent increases in ID.

The relationships between vessel sizes and magnitudes of ID increase during the ANP infusion at the rate of 1 μg/(kg·min) are shown in the rabbit (Fig. 3A) and feline (Fig. 3B) small pulmonary arteries. In both cases of the rabbit and cat, the ID significantly increased in all the arteries ranging from 100–600 μm ID and, moreover, the magnitude of ID increase was significantly (p < 0.05) larger in the arteries of 400–600 μm than in those of 100–300 μm. This indicated that the 400–600 μm arteries are more responsive to exogenous ANP than the smaller arteries.

Comparison of ID responses to ANP between embolized and nonembolized arteries in rabbits

Figure 4 shows typical arteriograms under the conditions of control, embolization, and embolization + ANP infusion (1 μg/(kg·min)) in the same rabbit. Appar-
Fig. 2. Dose-response effects of ANP on ID of small pulmonary vessels (100–600 μm) in rabbits (A) and cats (B). **Significantly different from control (p < 0.01). Vertical bars, SE.

ent ID reductions (solid arrows) occurred in the arteries upstream from the sites of the emboli. In the nonembolized arteries, however, no apparent ID changes were seen as compared with control. With the ANP infusion, the decreased ID of the embolized arteries greatly increased to almost the control level; on the other hand, the ID of the nonembolized arteries with the control size showed a small increase.

The mean values of ID under the conditions of control, embolism, and embolism + ANP infusion (1 μg/(kg·min)) are shown in the nonembolized and embolized arteries (Fig. 5). In the nonembolized arteries, the mean values under the three conditions were 290±12, 293±10, and 318±10 μm, respectively; in the

Japanese Journal of Physiology
embolized arteries, those were $283 \pm 12$, $198 \pm 13$, and $251 \pm 11 \mu m$, respectively. The mean values during control and embolism were significantly different in the embolized arteries but not in the nonembolized arteries. This indicated that the ID reduction occurred locally in the embolized arteries. The mean values during embolism and embolism + ANP were significantly different in both embolized and nonembolized arteries, indicating that ANP has a potency of dilating both arteries.

The changes and percent changes in ID with ANP infusion ($1 \mu g/(kg \cdot min)$) are shown in the nonembolized arteries with baseline ID and embolized arteries with constricted ID (Fig. 6). Both the change and percent change in ID were significantly larger in the embolized arteries ($52 \pm 8 \mu m$, $27 \pm 2\%$) than in the
nonembolized arteries (24±6 μm, 8±1%), indicating that the ANP-induced dilator effect on small pulmonary arteries was greatly enhanced in the presence of ID constriction.

Comparison of ID response to ANP between veins distal to nonembolized and embolized arteries

The mean values of ID under the conditions of control, embolism, and embolism+ANP infusion are shown in the veins which located distal to the nonembolized and embolized arteries (Fig. 7). In the veins distal to the nonembolized arteries, the mean values under the three conditions were 300±11, 295±12, and 302±10 μm, respectively; in the veins distal to the embolized arteries, those
were 296±10, 266±12, and 273±11μm, respectively. The mean values during control and embolism were significantly different in the veins distal to the embolized arteries but not in the veins distal to the nonembolized arteries, indicating that the ID reduction occurred locally in the veins distal to the embolized arteries. In neither vein distal to nonembolized arteries nor vein distal to embolized arteries a significant difference was present between the mean values during embolism and embolism + ANP. This indicated that ANP had no significant vasomotor effects on the small pulmonary veins under the conditions of baseline and constricted ID.
Veins Distal to Nonembolized Arteries

Veins Distal to Embolized Arteries

Fig. 7. Mean values of ID under conditions of control, embolism, and embolism + ANP (1 μg/(kg·min)) are shown in veins located distal to nonembolized and embolized arteries. *p < 0.05. Vertical bars, SE.

Table 1. Hemodynamic data.

<table>
<thead>
<tr>
<th>Condition</th>
<th>n</th>
<th>PAP (mmHg)</th>
<th>CVP (mmHg)</th>
<th>LAP (mmHg)</th>
<th>SAP (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protocol 1 (rabbit)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>6</td>
<td>16.1±0.4</td>
<td>2.3±0.3</td>
<td>5.3±0.3</td>
<td>96±5</td>
</tr>
<tr>
<td>ANP (0.01 μg/(kg·min))</td>
<td>6</td>
<td>16.0±0.4</td>
<td>2.1±0.3</td>
<td>5.2±0.3</td>
<td>92±5</td>
</tr>
<tr>
<td>ANP (0.1 μg/(kg·min))</td>
<td>6</td>
<td>15.3±0.5*</td>
<td>1.9±0.5</td>
<td>4.8±0.5</td>
<td>87±6**</td>
</tr>
<tr>
<td>ANP (1 μg/(kg·min))</td>
<td>6</td>
<td>15.0±0.6*</td>
<td>1.4±0.6*</td>
<td>4.4±0.5*</td>
<td>82±6**</td>
</tr>
<tr>
<td>Protocol 1 (cat)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>6</td>
<td>17.2±0.4</td>
<td>3.1±0.3</td>
<td>5.8±0.4</td>
<td>98±6</td>
</tr>
<tr>
<td>ANP (0.01 μg/(kg·min))</td>
<td>6</td>
<td>17.1±0.4</td>
<td>2.9±0.4</td>
<td>5.6±0.4</td>
<td>95±6</td>
</tr>
<tr>
<td>ANP (0.1 μg/(kg·min))</td>
<td>6</td>
<td>16.4±0.5*</td>
<td>2.7±0.4</td>
<td>5.5±0.6</td>
<td>88±6**</td>
</tr>
<tr>
<td>ANP (1 μg/(kg·min))</td>
<td>6</td>
<td>16.1±0.5*</td>
<td>2.2±0.5*</td>
<td>4.9±0.6*</td>
<td>82±7**</td>
</tr>
<tr>
<td>Protocol 2 (rabbit)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>6</td>
<td>16.3±0.4</td>
<td>2.6±0.3</td>
<td>5.6±0.3</td>
<td>92±6</td>
</tr>
<tr>
<td>Embolism (E)</td>
<td>6</td>
<td>16.4±0.6</td>
<td>2.6±0.3</td>
<td>5.5±0.3</td>
<td>94±6</td>
</tr>
<tr>
<td>E+ANP (1 μg/(kg·min))</td>
<td>6</td>
<td>15.4±0.6*</td>
<td>1.6±0.6*</td>
<td>4.7±0.6*</td>
<td>81±6**</td>
</tr>
</tbody>
</table>

Values are mean±SE. n, No. of animals; PAP, mean pulmonary arterial pressure; CVP, mean central venous pressure; LAP, mean left atrial pressure; SAP, mean systemic arterial pressure. Significant difference from control: *p < 0.05; **p < 0.01.

Blood pressure and ANP

The values of PAP, CVP, LAP, and SAP during the experiment with all the protocols are summarized in Table 1. All those parameters measured just before the injection of the contrast medium. In protocol 1 on the rabbit, PAP decreased significantly by 0.8 and 1.1 mmHg with ANP infusions at the rates of 0.1 and 1 μg/(kg·min), respectively. CVP and LAP decreased significantly by 0.9 mmHg with

Japanese Journal of Physiology
ANP infusion, 1\(\mu g/(kg\cdot min)\). SAP decreased significantly by 9 and 14 mmHg with ANP infusions, 0.1 and 1\(\mu g/(kg\cdot min)\), respectively. In protocol 1 on the cat the patterns of changes in PAP, CVP, LAP, and SAP were similar to those on the rabbit.

In protocol 2, none of the parameters showed significant changes in response to embolism. ANP infusion, 1\(\mu g/(kg\cdot min)\), under the condition of embolism significantly decreased PAP, CVP, LAP, and SAP by 0.9, 1.0, 0.9, and 11 mmHg, respectively. AWP under all the experimental conditions showed the same value (3 ± 0 cmH2O), because the ventilation was stopped just at end expiration whenever angiography was performed.

DISCUSSION

Using an X-ray television system, we directly measured the internal diameter (ID) of the small pulmonary arteries and veins in the in vivo lung. We analyzed ID changes in response to intravenous infusion of ANP under baseline conditions to elucidate which pulmonary vascular segment this peptide dilates. Furthermore, we administered ANP to the pulmonary vascular bed embolized with micro-beads to determine whether the pulmonary vasodilator effect of this peptide depends on the pulmonary vascular tone. The rabbit and cat were used in this study. This is because there is little information on the pulmonary vasomotor effect of ANP in the rabbit and cat, although those animals have been commonly used for studying the humoral control of pulmonary circulation [19, 20].

Site of vasodilation to ANP. There is no general agreement regarding the site of pulmonary vasodilation in response to ANP [7, 11, 12]. By recording tension of an isolated bovine vascular strip, it has been shown that intrapulmonary arteries, but not intrapulmonary veins, relax in response to ANP [7]. In the in situ porcine autoperfused lung lobe, ANP has been shown to decrease lobar arterial and venous pressures [11]. They suggested that the decreased lobar arterial pressure is due to pulmonary arterial vasodilation, whereas the decreased venous pressure is possibly caused by decreased cardiac filling pressures. In the isolated perfused lamb lungs with constant LAP, it has been shown that ANP infusion induces a fall in pressures in the pulmonary artery and the 20-80 \(\mu\)m venules [12]. They suggested that ANP relaxes both pulmonary arteries and veins. Among the above studies, opinions differ as to the vasomotor effect of ANP on the pulmonary veins. Moreover, it is still obscure from those results which segment of the pulmonary arteries is most responsive to ANP.

The small pulmonary arteries and veins (100-600 \(\mu\)m) observed in the present study have thicker layers of smooth muscle than do pulmonary vessels of other sizes [14, 15] and show great responses to various neurohumoral stimuli [13, 16, 17, 21, 22]. Therefore, we considered it important to directly measure the ID changes of the small pulmonary vessels in response to ANP for a better understanding of the vasomotor effect of this peptide in the pulmonary arteries and veins. Our results
clearly indicated that ANP dilates arterial segment selectively and dose dependently in the rabbit and cat pulmonary microcirculation. Moreover, the magnitude of the arterial vasodilation was larger in the 400–600 µm arteries than the 100–300 µm arteries.

**Possible factors responsible for nonuniform vasodilation to ANP.** A histochemical study, by recording radioautographic localization of 125I-ANP in rats, has shown that specific binding sites for ANP exist in the vascular smooth muscle and endothelial cells of pulmonary arteries, arterioles, and veins [5]. In our study ANP induced a vasodilation locally in the pulmonary arterial segment, suggesting that the relaxant effect of ANP is selective for arterial smooth muscle receptors. It is possible that ANP receptors in the venous segment have effects other than pulmonary vasomotion.

The reason for the greater vasodilator effect of ANP on larger pulmonary arteries than on smaller ones (Fig. 3) remained to be elucidated. In the previous study, the vasodilation to prostacyclin was uniform in the small pulmonary arteries of 100–500 µm in the cat [21]. Therefore, the nonuniform arterial vasodilation to ANP cannot be ascribed to differences in relaxant ability of vascular smooth muscle between the larger and smaller pulmonary vessels. Since ANP is endothelium-independent vasodilator [7], the nonuniform vasodilation cannot be explained by differences in the nature of the endothelial relaxant factor. A difference in ANP receptor number may partly have contributed the nonuniform response.

Extraction of circulating ANP occurs during passage across the lung [23–25]. It is therefore conceivable that blood concentration of exogenous ANP was lower on the venous side than on the arterial side of the pulmonary circulation in our preparations; this factor might contribute partly to the present result that the small veins did not significantly dilate during ANP infusion. In view of previous studies with radioimmunoassay techniques [11, 26, 27], however, the higher dose of ANP we used would have provided circulating ANP levels far greater than the physiological range. We considered that ANP receptors in the small pulmonary veins were extensively activated during the infusion of ANP.

**Effects of change in vascular tone on vasodilator activity of ANP.** There are different opinions as to whether the pulmonary vasodilator activity of ANP is dependent on the existing level of pulmonary vasoconstrictor tone. In the feline and porcine pulmonary vascular bed under conditions of controlled blood flow, decreases in lobar arterial pressure in response to ANP were greater when lobar arterial pressure was increased by U46619 [10] and PGF2α [11] than when the pressure was at baseline level. In the intact porcine pulmonary circulation pulmonary vascular resistance (PVR) remained unchanged in response to ANP but significantly decreased when PVR was increased by hypoxia [26]. Those studies have suggested that the pulmonary vasodilator activity of ANP is enhanced when pulmonary vascular tone is elevated. In the isolated perfused lamb lungs, on the other hand, the decrease in PVR and pulmonary venous resistance in response to ANP was similar in lungs with moderate and high vasomotor tone [12]. They
suggested that the pulmonary arterial and venous vasodilation to ANP is independent of the degree of vasomotor tone.

Our study showed, in the rabbit lung preparation with microembolism, that the magnitude of ID dilation in response to ANP is larger in the embolized arteries with constricted ID than in the nonembolized arteries with baseline ID (Fig. 6). In the intact rabbit lung, on the other hand, the magnitude of ID dilation to ANP was smaller in the arteries with smaller ID than in those with larger ID (Fig. 3). The results indicate that the vasodilator effect of ANP is increased in the embolized arteries as compared to the nonembolized arteries. The increase in the vasodilator effect in the embolized arteries is independent of the ID size; it is dependent on the level of vascular tone.

We previously showed that during pulmonary microembolism, the volume flow \( (V) \) to the embolized arteries decreases, whereas \( V \) to the nonembolized arteries increases [16]. Assuming that intravenously-infused ANP is thoroughly mixed up in the cardiac chamber and reaches the embolized and nonembolized arteries with the same plasma concentration \((C)\), a total ANP delivery \((V \times C)\) is smaller in the former than in the latter. In the present study, the ID dilation to infused ANP was nonetheless greater in the embolized arteries than in the nonembolized arteries. This suggests that the enhancement of vasodilation in the embolized arteries occurs independently of the change in the volume flow.

We found that ANP has no significant effect on the ID-constricted small pulmonary veins which located distal to the embolized arteries. There is a possibility that this result is partly explained by a decrease in the ANP delivery due to decreased volume flow in those veins. However, there is an extensive network of pulmonary arterial collaterals originating at the level of 100- to 200-\(\mu\)m diameter arteries [28]; therefore, embolization of a part of the 80–100\(\mu\)m ID arteries would allow for sufficient perfusion of the downstream small veins. We considered that the possibility is small, if any.

Taken together, the present results indicate that ANP dilates the arterial segment selectively and tone dependently in the rabbit pulmonary microcirculation.

Possible role of ANP in pulmonary hemodynamics. A previous chemical study has shown that patients with pulmonary arterial hypertension have elevated circulating ANP levels, in proportion to their increased PAP and PVR [29]. A pronounced and rapid increase in plasma ANP has been shown during acute hypoxic pulmonary hypertension [26,27]. Physiological studies have indicated that ANP reduces venous return [30,31]. The present study has shown that the ANP-induced ID dilation of small pulmonary arteries is greatly enhanced when those vessels are under the vasoconstrictive states. Considering those results together, it is possible that during pulmonary arterial hypertension increased plasma ANP serves to reduce the right ventricular preload and afterload by reducing venous return and attenuating the level of pulmonary vasoconstrictor tone, respectively.
This study was supported in part by Grants-in-Aid for Scientific Research from the Ministry of Education, Science, and Culture and by research grants for Cardiovascular Diseases from the Ministry of Health and Welfare of Japan.

REFERENCES


*Japanese Journal of Physiology*