
Alan Chu, Adrienne Stakely, Chang-Chyi Lin, and Frederick R. Cobb

The effects of atrial natriuretic peptide (ANP) on transmural myocardial blood flow distribution and the reactive hyperemic response in the presence and absence of flow-limiting coronary stenosis were examined in chronically instrumented conscious dogs. Ten-second coronary occlusion without subsequent flow restriction resulted in marked reactive hyperemic responses (Doppler flow probes), mean flow debt repayment was 481±55%. When the 10-second coronary occlusions were followed by a 20-second partial restriction that allowed normal preocclusion coronary inflow, the subsequent reactive hyperemia was significantly augmented, mean flow debt repayment was 938±91% (p<0.05). Pretreatment with ANP (3 μg/kg) did not alter the flow debt repayment after a 10-second occlusion without restriction (474±30%, NS) but attenuated the augmentation of reactive hyperemia resulting from the 20-second inflow restriction, flow debt repayment (613±66%, NS). Regional myocardial blood flow to the ischemic region was measured during restricted inflow after a 10-second coronary occlusion before and after ANP pretreatment. Before ANP, subendocardial flow decreased (0.54±0.04 ml/min/g) and subepicardial flow significantly increased (1.03±0.12 ml/min/g) when compared with the nonischemic zone (subendocardial, 1.03±0.09 ml/min/g; subepicardial, 0.87±0.09 ml/min/g, p<0.05), indicating maldistribution of the restricted inflow. The resultant subendocardial-to-subepicardial ratio in the ischemic region was significantly decreased when compared with the nonischemic region (0.56±0.03 vs. 1.18±0.04, p<0.05). After ANP pretreatment, subendocardial flow to the ischemic region significantly increased (0.71±0.07 ml/min/g, p<0.05) and the subendocardial-to-subepicardial ratio in the ischemic zone was significantly improved (0.91±0.10, p<0.05). Myocardial flow measured during coronary occlusion was not altered after ANP pretreatment, indicating no change in native collateral flow to the ischemic region. Myocardial oxygen consumption, aortic and left ventricular end-diastolic pressures, dP/dt, and heart rates were also not affected by pretreatment with ANP. These data indicate that ANP favorably redistributed blood flow to the subendocardium and reduced subendocardial ischemia after a transient occlusion in the presence of a flow limiting coronary stenosis. The reversal of subendocardial hypoperfusion by ANP in the absence of alterations of intrinsic vascular reactivity or native collateral flow supports a dilation effect of ANP on the intramural arteries.

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Atrial natriuretic peptide (ANP) induces natriuresis and diuresis. In addition, it has been demonstrated to exert vasorelaxant activity and has been reported to cause mild systemic hypotension. In recent studies, we have demonstrated that ANP injection causes direct, sustained dose-related increases in proximal coronary dimension in chronically instrumented awake dogs. In contrast, ANP injection causes a much more brief direct vasodilation of the distal resistance vessels that results in dose-dependent increases in phasic coronary blood flow. The effects of ANP on the large intramural coronary arteries and native collateral vessels have not been examined.

Previous studies indicate that the large intramural coronary arteries may be an important contributor to coronary resistance that leads to maldistribution of blood flow in the setting of a flow-limiting stenosis and ischemia. The maldistribution of flow results in persistent subendocardial ischemia and augmentation of the reactive hyperemic response. Pretreatment with nitroglycerin (NTG) attenuates the maldistribution of blood flow and consequently reduces both subendocardial ischemia and augmentation of reactive hyperemia without changing native collateral flow during ischemia. These data suggest that NTG dilates the intramural coronary arteries, resulting in a more favorable distribution of transmural blood flow. Subsequent studies have demonstrated that diltiazem and nifedipine also exert similar effects during transient ischemia in the setting of flow limitation, while propranolol is ineffective in redistributing transmural blood flow.

The present study was designed to determine whether ANP would favorably alter the maldistribution of transmural blood flow that occurred after ischemic stimulation in the setting of critical stenosis and whether the effects on regional perfusion would be of sufficient magnitude to reduce ischemia as measured by the reactive hyperemic response. It was reasoned that a favorable effect of ANP on transmural flow after ischemic stimulation without a change in collateral flow or in indexes of myocardial oxygen demand would support an important vasodilator effect of ANP on the intramural coronary vasculature.

Materials and Methods

Seventeen healthy mongrel dogs (25-30 kg) were used in this study. Twelve (Group A) were anesthetized with thiopental sodium (60-80 mg/kg i.v.) and subjected to left thoracotomy. The heart was suspended in a pericardial cradle. Heparin-filled polyvinyl catheters were inserted into the left atrium via the left atrial appendage, in the left ventricular cavity via the apex, and in the ascending aorta via the left internal thoracic artery. A 10-MHz cuff-type pulsed Doppler flow probe (Dr. C.J. Hartley, Houston, Texas) was implanted on the proximal circumflex coronary artery. An inflatable pneumatic snare was placed around the circumflex artery distal to the flow probe. The catheters, tubings, and wires were tunneled to a subcutaneous pouch at the base of the neck.

The postoperative period was a 7-14-day recovery period, during which the dogs were sedated lightly with morphine sulfate (0.3-0.5 mg/kg i.m.) and studied while loosely restrained and lying awake on their right sides. The laboratory was dimly illuminated, and the noise level was kept to a minimum. Catheters, wires, and tubings were exteriorized under local lidocaine infiltration anesthesia. Aortic pressure, left ventricular pressure and dP/dt, heart rate, and coronary flow were monitored throughout the experiment.

The dogs were initially subjected to a 60-second coronary occlusion. Those that failed to demonstrate significant S-T segment elevation and increased heart rate were excluded since significant collateral circulation may have been present in these animals. The dogs were further subjected to a transient 10-second coronary occlusion and, later, to a transient 10-second coronary occlusion followed by 20 seconds of inflow restriction to preocclusion level. The delayed reactive hyperemic flow after release of a 10-second coronary occlusion followed by a 20-second inflow restriction (after release of a 10-second coronary occlusion followed by a 20-second inflow restriction) was compared with the reactive hyperemic flow after a simple 10-second occlusion. Previous studies using a similar model demonstrated augmentation of the delayed reactive hyperemia in the presence of flow restriction. Dogs that failed to demonstrate an augmented delayed reactive hyperemic response were also excluded. Four dogs were excluded from the data analyses using these criteria.

Myocardial blood flow distribution was evaluated in all eight Group A dogs using the radioactive microsphere technique. Microspheres (9 ± 1 μm) labeled with NaI, Co57, Tc99m, Sn113, Sc95, Ru103, or Nb95 (New England Nuclear, Boston, Massachusetts) were injected via the left atrial catheter. Before each injection, the microspheres were vortexed throughly and agitated in an ultrasonic bath for at least 15 minutes. For each injection, 1 ml of the diluted microsphere suspension (approximately 3 × 10^6 microspheres) was infused via the left atrial catheter. Before each injection, the microsphere suspension and continued for 90 seconds, a reference sample was collected from the aortic catheter at a precalibrated constant rate of approximately 17 ml/min using a Harvard withdrawal apparatus (South Natick, Massachusetts).

Dogs were subjected to a 10-second coronary occlusion, and the reactive hyperemia was recorded to establish the intrinsic reactive hyperemic response to a standard ischemic stimulation. Five minutes later, they were subjected to a 10-second occlusion followed by 20 seconds of flow restriction before complete release. The restricted flow was carefully adjusted to exactly equal the preocclusion level. The subsequent augmented delayed reactive hyperemic response was also recorded. Previous studies demonstrated that in conscious dogs, a transient 5-second coronary artery occlusion induced reactive hyperemia resulting in threefold to fourfold repay-
ment of flow debt. If the occluder was only partially released after a transient occlusion so that coronary artery inflow was held at the preocclusion level for 20 seconds before complete release, the delayed reactive hyperemia was markedly augmented. Each dog was then given a 3 μg/kg bolus of ANP (α-human, 28-amino acids, Peninsula Laboratories) via the left atrial catheter (total volume, <2 ml infused in <5 seconds). To avoid any potential effects of ANP on the distal autoregulatory vasculature, studies were performed 10 minutes after ANP injection, when phasic blood flow had returned to preinfusion level. At this time, the 10-second occlusion followed by reactive hyperemic response was repeated. Five minutes after the phasic coronary flow returned to preocclusion level, the 10-second occlusion/20-second flow restriction/delayed reactive hyperemia sequence was again carried out. All measurements were made in duplicate, and the occlusions were at least 10 minutes apart. Duplicate measurements deviating by >10% were excluded. The sequence of occlusion was randomized.

Myocardial blood flow was measured in the same dogs on the following day. After reproducing comparable reactive hyperemic responses to a single 10-second occlusion and comparable augmented delayed reactive hyperemia after the 10-second occlusion/20-second flow restriction sequence, myocardial blood flow was quantitated by injecting the radioactive microspheres. Previous studies demonstrated that the vasodilating effects of ANP on the epicardial conductance vessels were maximal under local lidocaine infiltration anesthesia while the dogs were lying awake on their right side. A 7-F multipurpose catheter was advanced under fluoroscopy to the coronary sinus, and a 7-F right coronary catheter was advanced to the aortic root. Arterial and coronary sinus venous blood samples were simultaneously withdrawn before and at 10 minutes after injection of 3 μg/kg ANP bolus into the left atrium. The oxygen content of the arterial and venous samples were determined and the myocardial arteriovenous oxygen difference calculated.

Data were analyzed as follows using the same dog as its own control. Reactive hyperemic flow (KHz · sec) = total flow during reactive hyperemia (KHz · sec) – [control flow (KHz) × duration of reactive hyperemia (sec)]. Blood flow debt (KHz · sec) = control flow (KHz) × duration of occlusion (sec). Blood flow debt repayment (%) = [(reactive hyperemic flow/blood flow debt) × 100%].

Blood flow debt repayment in the presence of 20-second flow restriction was compared with the flow debt repayment after a single 10-second occlusion. The same comparison was made after ANP injection. Each flow debt repayment before ANP injection was further compared with its counterpart measured after ANP injection. The corresponding myocardial blood flow measurements were similarly compared for both the normal (anterior wall)
TABLE 1. Mean Resting Hemodynamic Measurements Before Each Intervention

<table>
<thead>
<tr>
<th></th>
<th>No ANP</th>
<th>After ANP</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Before 10-sec occlusion</td>
<td>Before 10-sec occlusion/20-sec constant flow</td>
</tr>
<tr>
<td>Aortic pressure (mm Hg)</td>
<td>97±3</td>
<td>99±3</td>
</tr>
<tr>
<td>LV end-diastolic pressure (mm Hg)</td>
<td>8±1</td>
<td>8±1</td>
</tr>
<tr>
<td>LV dP/dt (mm Hg/sec)</td>
<td>2,080±170</td>
<td>2,060±210</td>
</tr>
<tr>
<td>Heart rate (beat/min)</td>
<td>76±7</td>
<td>73±7</td>
</tr>
<tr>
<td>Coronary flow (KHz)</td>
<td>1.82±0.12</td>
<td>1.80±0.11</td>
</tr>
</tbody>
</table>

ANP, atrial natriuretic peptide; occ, occlusion; LV, left ventricular. Values are mean±SEM.

and ischemic (posterior wall and posterior papillary) regions. Statistical analyses were performed using Student’s paired t test.

**Results**

Mean aortic and left ventricular end-diastolic pressures, dP/dt, heart rates, and rest coronary blood flow of all dogs in Group A are illustrated in Table 1. There were no significant differences in rest hemodynamic parameters before the 10-second occlusion or before the 10-second occlusion/20-second restricted flow sequence. In addition, these resting parameters were not significantly different from rest measurements obtained before the occlusions performed after ANP was given.

Figure 1 illustrates a representative reactive hyperemic response after a 10-second transient occlusion (A), and following 10-second occlusion with subsequent 20-second flow restriction before (B) and then after (C) pretreatment with 3 μg/kg ANP. As shown in Table 2, the delayed percent blood flow debt repayment was significantly augmented in the presence of 20 seconds of flow restriction after 10 seconds of coronary occlusion (938±91%) when compared with 10 seconds of coronary occlusion alone (481±55%, p<0.05).

**Figure 1.** Representative recordings of phasic coronary reactive hyperemic response in a dog after a 10-second transient occlusion (A), and after a 10-second occlusion with a subsequent 20-second flow restriction before (B) and then after (C) pretreatment with ANP (3 μg/kg). Reactive hyperemic response after a 10-second coronary occlusion was significantly augmented in the presence of a subsequent 20-second flow restriction. This augmented response was substantially attenuated after pretreatment with ANP.
At 10 minutes after ANP, resting coronary flow had returned to control values (Table 1), and the percent flow debt repayment after a single 10-second occlusion (474 ± 30) was not different from that before ANP (Table 2), indicating that ANP did not alter basic vascular reactivity to ischemic stimulation. However, in the presence of ANP, the delayed percent flow debt repayment after the 10-second occlusion/20-second restricted flow sequence (613 ± 66) was only minimally augmented and was not statistically different from the percent flow debt repayment after a single 10-second occlusion.

Table 3 illustrates regional myocardial blood flow to the nonischemic and ischemic regions measured during restricted flow after 10 seconds of coronary occlusion before and after ANP pretreatment. Before ANP injection, blood flow to the ischemic regions was significantly decreased in the subendocardium (0.54 ± 0.04 ml/min/g) and was significantly increased in the epicardium (1.03 ± 0.12 ml/min/g) when compared with the nonischemic zone (subendocardial and subepicardial flows were 1.03 ± 0.09 and 0.87 ± 0.09 ml/min/g, respectively). As a result, the subendocardial-to-subepicardial flow ratio in the ischemic region was significantly decreased as compared with the nonischemic region (0.56 ± 0.03 vs. 1.18 ± 0.04, respectively). ANP pretreatment reduced the maldistribution of blood flow resulting from the restriction of flow following the 10-second occlusion. As compared with control, ANP pretreatment increased subendocardial flow (0.54 ± 0.04 vs. 0.71 ± 0.07 ml/min/g), reduced subepicardial flow (1.03 ± 0.12 vs. 0.82 ± 0.09 ml/min/g) and improved the subendocardial-to-subepicardial flow ratio in the ischemic region (0.56 ± 0.03 vs. 0.91 ± 0.10). The resultant increase in subendocardial flow to the ischemic region after ANP narrowed the difference between the ischemic and nonischemic regions. However, blood flow to the subendocardium was still significantly less than in the nonischemic region (0.71 ± 0.07 vs. 0.93 ± 0.09 ml/min/g).

After ANP treatment, myocardial blood flow to the subepicardium of the ischemic zone was not significantly different from the nonischemic region (0.82 ± 0.09 vs. 0.76 ± 0.08 ml/min/g).

Table 4 illustrates the myocardial blood flow measured during coronary occlusion before and after ANP. ANP pretreatment did not change subendocardial or subepicardial blood flow in the ischemic region, indicating that pretreatment with ANP did not alter native collateral flow to the ischemic region. The mean arterial oxygen content, coronary sinus oxygen content, and arteriocoronary sinus oxygen difference of all five dogs in Group B were listed in Table 4. ANP pretreatment did not significantly alter any of these parameters. Since ANP did not alter rest coronary flow (Table 1), myocardial oxygen consumption also was unchanged.

**Discussion**

In previous studies, we observed preferential effects of ANP on different segments of the coronary vasculature. ANP caused a direct sustained dose-related vasodilation of proximal coronary arteries and a much briefer dilation of the distal resistance vessels of less than 10 minutes. The present study provides new data concerning the effects of ANP 1) on the reactive hyperemic response after transient myocardial ischemia with and without blood flow restriction, 2) on the distribution of blood flow after transient ischemia in the presence of a flow-limiting severe coronary stenosis, and 3) on blood flow via innate collateral vessels. ANP reduced the augmented delayed reactive hyperemic response observed after transient ischemia in the presence of initial flow restriction, and favorably redistributed blood flow to the subendocardium. In contrast, ANP did not alter the basic reactive hyperemic response to a simple occlusion and did not alter collateral blood flow during coronary occlusion. These data provided strong support for an important vasodilation effect of ANP on the intramural vasculature. The data also demonstrated that ANP exerts no effect on the innate collateral vessels. The reactive hyperemic response after transient myocardial ischemia is a function of metabolic demands and the degree of ischemia during the period of coronary occlusion.9-11 In the present

**TABLE 2. Blood Flow Debt Repayment**

<table>
<thead>
<tr>
<th></th>
<th>After 10-sec occlusion</th>
<th>After 10-sec occ/20-sec constant flow</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before ANP</td>
<td>481 ± 55%</td>
<td>938 ± 91%*</td>
</tr>
<tr>
<td>After ANP</td>
<td>474 ± 30%</td>
<td>613 ± 66%</td>
</tr>
</tbody>
</table>

ANP, atrial natriuretic peptide.

*p < 0.05 compared with 10-second occlusion.

**TABLE 3. Regional Myocardial Blood Flow (ml/min/g) Measured During Restricted Flow After 10-Second Coronary Occlusion**

<table>
<thead>
<tr>
<th></th>
<th>Nonischemic</th>
<th>Ischemic</th>
<th>Nonischemic</th>
<th>Ischemic</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Endocardial</strong></td>
<td>1.03 ± 0.09</td>
<td>0.54 ± 0.04*</td>
<td>0.93 ± 0.09</td>
<td>0.71 ± 0.07*</td>
</tr>
<tr>
<td><strong>Epicardial</strong></td>
<td>0.87 ± 0.09</td>
<td>1.03 ± 0.12*</td>
<td>0.76 ± 0.08†</td>
<td>0.82 ± 0.09†</td>
</tr>
<tr>
<td><strong>Endo/epi</strong></td>
<td>1.18 ± 0.04</td>
<td>0.56 ± 0.03*</td>
<td>1.24 ± 0.05</td>
<td>0.91 ± 0.10†</td>
</tr>
</tbody>
</table>

ANP, atrial natriuretic peptide; Endo/epi, subendocardial-to-subepicardial flow ratio.

*p < 0.05 compared with corresponding normal region.

†p < 0.05 compared with same region before ANP.
study, ANP when injected as a bolus did not significantly change indexes of myocardial oxygen consumption including heart rate, blood pressure, dP/dt, total coronary flow, or arteriocoronary sinus oxygen differences. It is thus unlikely that a reduction in myocardial oxygen demands contributed significantly to the reduced reactive hyperemia. An increase in flow via collateral vessels during occlusion may be expected to reduce the reactive hyperemic response. Microsphere measurements during a complete coronary occlusion, however, demonstrated no significant change in native collateral flow after ANP pretreatment, making this an unlikely explanation. Certain vasoactive agents including nifedipine and diltaizem have been reported to directly depress the reactive hyperemic response by producing a partial dissociation between the ischemic stimulation and coronary vasodilation. This partial dissociation was thought to in part contribute to the reduced augmented reactive hyperemic response. Pretreatment with NTG did not alter the reactive hyperemic response to a 5-second transient occlusion(s) and thus did not induce a similar partial dissociation. As in the case in NTG but unlike the calcium channel blockers, ANP did not reduce the reactive hyperemic response to a 10-second occlusion. Thus, the reduced augmentation of the delayed reactive hyperemia after 10 seconds of occlusion and 20 seconds of flow restriction in the presence of ANP was not due to a partial dissociation effect of ANP between the ischemic stimulus and coronary vasodilation.

We used a model of brief transient ischemia followed by flow restriction to preocclusion levels to examine potential effects of ANP on the intramural vasculature. This model is characterized by severe coronary stenosis and maldistribution of transmural blood flow as measured by the microsphere technique, despite normal total inflow of blood during the period of flow restriction. This maldistribution of blood flow results in an augmentation of the reactive hyperemic response after relief of the partial stenosis. The maldistribution of blood flow is thought to be secondary to a significant resistance imposed by the intramural vasculature. Under normal coronary perfusion pressures, the primary site of resistance is the more distal vasculature; the proximal and larger intramural vessels impose minimal resistance to flow. During myocardial ischemia, the distal resistance vessels become dilated but the proximal conductance arteries are not affected. In the setting of ischemia plus a partial stenosis as used in the present study, the pressure distal to the occluder decreases markedly after transient ischemia and subsequent dilation of the resistance vessels. Consequently, the normally insignificant resistance in the intramural conductance vessels becomes significant, leading to maldistribution of blood flow with subendocardial hypoperfusion and subepicardial hyperperfusion, as observed in the present study. The maldistribution of blood flow is thus a result of vasodilation of autoregulatory resistance vessels in a setting in which total flow cannot increase, resulting in a decrease in perfusion pressure and a relative increase in the resistance imposed by more proximal intramural conductance vessels that differentially affect endocardial and epicardial perfusion. In this setting, agents that preferentially dilate the conductance vasculature may be expected to improve the maldistribution of flow; further preferential dilation of the distal resistance vasculature may further decrease perfusion pressure and worsen or not improve the maldistribution of flow. The present study was performed at 10 minutes after ANP, at a time when the effect of ANP on the distal vasculature had subsided, while its effects on proximal conductance vessels were still maximal. Our data demonstrate that at this time ANP not only reduced the maldistribution of blood flow, resulting in improvement of subendocardial ischemia, but it also reduced the reactive hyperemic response indicating a reduction in ischemic stimulation. These data provide support for an important vasodilator effect of ANP during ischemia on the intramural vasculature in the presence of a critical stenosis. Previous studies from our laboratory and others using this model have demonstrated that NTG and calcium channel blockers produce comparable effects in conscious dogs.

| TABLE 4. Regional Myocardial Blood Flow (ml/min/g) Measured During Coronary Occlusion |
|-----------------------------------------------|-----------------|-----------------|-----------------|-----------------|
| No ANP                  | Ischemic       | After ANP       |                 |                 |
| Endocardial             | 1.03±0.10      | 0.11±0.02*      | 0.90±0.06       | 0.12±0.03*      |
| Epicardial              | 0.76±0.05      | 0.22±0.02*      | 0.70±0.05       | 0.23±0.02*      |
| Endo/epi                | 1.36±0.08      | 0.52±0.10*      | 1.29±0.05       | 0.53±0.12*      |

ANP, atrial natriuretic peptide; Endo/epi, subendocardial-to-subepicardial flow ratio.
*p<0.05 compared with corresponding normal region.

| TABLE 5. Mean Arterial O2 Content, Coronary Sinus O2 Content, and Arteriocoronary Sinus Oxygen Difference in All Group B Dogs (ml/100 ml) |
|---------------------------------------------------------------|-----------------|-----------------|-----------------|-----------------|
|                   | No ANP          | After ANP       |                 |                 |
| Arterial O2 content | 17.97±0.52      | 17.72±0.63      |                 |                 |
| Coronary sinus O2 content | 6.81±1.09      | 7.10±1.08      |                 |                 |
| Arteriocoronary sinus O2 difference | 11.16±0.64      | 10.61±0.80      |                 |                 |

ANP, atrial natriuretic peptide.
In a recent study, we have demonstrated that vasodilating effects of ANP on the proximal epicardial and distal resistance arteries are very similar to that of NTG. Both agents exert a preferential, more sustained, direct increase in dimension of proximal coronary vessels and a relatively brief dilation of distal resistance arteries. Both agents are believed to act via stimulation of the guanylate cyclase system, although ANP acts through the particulate enzyme, while NTG acts via the soluble isoenzyme. Indeed, this preferential proximal dilation appears to be a consistent property of vasodilating agents mediated via the guanylate cyclase pathway, including endothelium-derived relaxing factor. Our study provides further support for the view that ANP behaves like an "endogenous nitrate" and is consistent with the previous observation that the penetrating intramural arteries behave like the epicardial conductance vessels during ischemia.

In summary, our present study demonstrates that in the presence of a flow-limiting stenosis, ANP is capable of favorably reversing the subendocardial hypoperfusion resulting from maldistribution of transmural blood flow induced by transient myocardial ischemia. The reversal of subendocardial hypoperfusion reduces ischemic stimulation as measured by the reactive hyperemic response without affecting intrinsic vascular reactivity or native collateral flow, indicating that this favorable effect on transmural flow probably results from dilation of the penetrating intramural arteries.

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References


Key Words: atrial natriuretic peptide • coronary dilation, intramural • coronary blood flow, transmural • reactive hyperemia • coronary stenosis
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