Effects of Atrial Natriuretic Peptide on the Coronary Arterial Vasculature in Humans

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The effects of the synthetic 28-amino-acid α-human atrial natriuretic peptide (ANP) on the proximal coronary arteries and coronary blood flow were evaluated in 17 patients. Proximal coronary dimension was quantitated by digital angiography, and coronary flow was quantitated with 3F Doppler flow catheters. ANP, when given as a 2.5-μg/kg bolus in the left ventricle, caused sustained significant proximal coronary dilations from 3.49±0.57 to 4.09±0.76 mm, lasting more than 30 minutes. The proximal coronary diameter did not increase further after intracoronary injection of 0.3 mg nitroglycerin (4.08±0.79 mm). Coronary flow (resistance coronary dilation) was not significantly increased at 5 minutes after ANP (87±55 to 102±54 vol flow units), indicating that the proximal coronary dilations were not flow dependent. The persistent proximal coronary dilations were associated with minor and transient decreases in aortic pressure and left ventricular end-diastolic pressure and with minor and transient increases in heart rate, cardiac output, and left ventricular contractility. Plasma ANP level increased significantly by more than sixfold from 39.8±8.8 to 245.8±168.5 pg/ml. The time course of proximal coronary dilations was related more closely to the time course of increase in plasma cyclic guanosine monophosphate than that of plasma ANP. This study demonstrates that bolus injection of ANP (2.5 μg/kg), an endogenous vasodilator, caused marked sustained preferential proximal coronary dilations and brief minor changes in cardiac and systemic hemodynamics. Although additional studies are needed to assess its clinical efficacy as a coronary dilator in the treatment of coronary artery disease, these data suggest a potential of ANP in the therapy of ischemia. (Circulation 1989;80:1627–1635)

D eBold et al1 first demonstrated that infusions of extracts from atrial muscle caused natriuresis and diuresis and systemic hypotension in anesthetized rats. Currie et al2 subsequently demonstrated that atrial extracts caused dose-dependent relaxation of rabbit aortic strips. Subsequent studies have characterized the amino-acid sequence of atrial natriuretic peptide (ANP). Biologically active ANP exists in several different chain lengths derived from a 151–152-amino-acid precursor.3–9 Studies from Schwartz et al10 and Sugawara et al11 have suggested that the circulating forms of ANP in rats and humans are 28-amino-acids in length.

Many studies have demonstrated that ANP relaxes vascular strips in a variety of organ systems and animal species. ANP also relaxes preconstricted denuded epicardial coronary artery rings from explanted hearts of patients.12 It is believed to act via activation of particulate guanylate cyclase,13 and ANP-induced smooth muscle relaxation in vitro14 has been related to cyclic guanosine monophosphate (cGMP) formation. Results from studies examining the effects of ANP on the intact coronary vasculature have, however, been conflicting.15–18 Studies from our laboratory19 in chronically instrumented awake dogs demonstrated that bolus injection of ANP (10–150 μg) into the left atrium induced dose-related, sustained proximal coronary dilation. Relatively brief dose-related increases in phasic coronary blood flow were also noted, indicating transient resistance artery dilation. The proximal coronary dilation induced by ANP was not related to the transient increases in coronary flow and was not altered by blockade of the autonomic nervous system. The direct dilation effects of ANP on the

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epicardial vessels were similar to those of nitrates but developed more gradually and were not accompanied by significant changes in systemic hemodynamics. More recent studies from our laboratory in conscious dogs have further demonstrated that ANP dilates intramural coronary arteries during ischemic stimulation in the presence of a critical stenosis, causing redistribution of blood flow to the ischemic subendocardium.\textsuperscript{20}

In normal subjects, intravenous infusion of ANP (0.01–0.10 \(\mu\)g/kg/min) induced significant diuresis and natriuresis and decreases in pulmonary capillary wedge pressure with no significant alterations in heart rate, mean arterial pressure, or cardiac index.\textsuperscript{21} In patients with congestive heart failure, comparable doses of ANP increased cardiac index and stroke volume index, significantly reduced pulmonary capillary wedge pressure and systemic vascular resistance, but did not change heart rate or mean arterial pressure; the natriuresis and diuresis effects were attenuated. Studies have not examined the effects of ANP on the coronary arterial vasculature in patients. Accordingly, the present study was designed to evaluate the effects of ANP on the proximal coronary arteries and coronary blood flow in humans.

**Methods**

**Patient Selection and Preparation**

The study comprised male patients less than 70 years old undergoing routine coronary angiography at the Durham Veterans Administration Medical Center. Patients with unstable angina, acute myocardial infarction, evidence of pulmonary edema, or recent heart failure were excluded. Informed consent was obtained from each patient before the study. Patients with left main coronary disease or significant (>75%) three-vessel disease documented during catheterization were also excluded. A total of 17 patients were evaluated. The experimental protocol and consent forms were previously reviewed and approved by the Institutional Review Board and conformed with the ethical guidelines prescribed by the National Institutes of Health, including the provision of suitable explanation to human subjects or their guardians concerning the experimental design and all significant hazards. Informed consent was obtained the day before the cardiac catheterization and study protocol. The experimental use of the synthetic 28-amino-acid \(\alpha\)-human ANP in our institution has been approved by the US Food and Drug Administration for use in this study (IND No. 30556).

Patients were admitted at least 24 hours before the study and continued on maintenance medications, including diuretics, \(\beta\)-blockers, and digoxin. All vasodilators including long-acting nitrates, calcium channel blockers, and converting enzyme inhibitors were withheld for more than 24 hours before the study. Diuretics were withheld on the day of the study.

**Experimental Protocol**

The patients were studied in the cardiac catheterization laboratory in the supine position. Right heart catheterization was performed with a balloon-tipped 7F Swan-Ganz catheter equipped with thermodilution-sensing devices for measurement of cardiac output. Coronary angiography was performed with nonionic contrast Isovue (Squibbs Diagnostics, New Brunswick, New Jersey). After completion of each routine coronary angiography, an artery with less than 25% stenosis was selected for study. An 8F left or right coronary guiding catheter was inserted via the right femoral artery and advanced to the aortic root. After administration of 10,000 units heparin i.v., a 3F 20-MHz Doppler flow catheter (NuMed, Inc, Hopkinton, New York) was inserted via the coronary guiding catheter and positioned in the proximal segment of the coronary artery.

After obtaining baseline hemodynamic data including aortic and left ventricular pressures and \(dP/dt\), heart rate, cardiac output, and coronary flow velocity, control digital coronary angiograms were obtained. Images for each patient were obtained in the identical imaging plane with a fixed table height and source-image distance by the Philips Digital Vascular Imaging System (Philips Medical Systems, Shelton, Connecticut) at a fixed pulse width of 6–10 msec with automatically adjusted kilovoltage (range, 60–90 kV) and radiograph tube current (range, 850–1200 mA). Contrast was injected via a programmable automatic injector (Mark V, Med Rad, Pittsburgh, Pennsylvania) at a constant speed of 4 ml/sec, with a constant volume of 7 ml and under a constant injection pressure of 800 psi. At least 10 minutes was allowed between injections. Digital images were acquired at a rate of 1 image per cardiac cycle gated to the R wave. Images were stored in un subtracted format in a 512\(\times\)512 matrix. A 1-cm grid was imaged at the location of the patient at the conclusion of the study for distance calibration. Subsequently, images were analyzed with a Philips APU image analysis system. Coronary diameter quantitation was performed with a combined edge-detection and densitometric profile measurement algorithm developed in our laboratory. The coronary segment at the site of the Doppler crystal was chosen for quantitation. In six patients, duplicate control images were obtained at 2-minute intervals to assess the reproducibility of the quantitative angiographic system. The accuracy of the quantitative angiographic system was also assessed by comparing the diameter measurements obtained from images of contrast-filled Lucite phantoms to actual diameters.

After the control images were obtained, the 28-amino-acid \(\alpha\)-human ANP (Peninsula Laboratories, Inc, Belmont, California) (2.5 \(\mu\)g/kg) was injected...
as a bolus via the left ventricular catheter. ANP was prepared by dissolving in sterile normal saline at a concentration of 200 μg/ml and sterilized by passage through a 0.22-μm millipore filter (Millipore Corp, Bedford, Massachusetts). Systemic hemodynamics and coronary blood flow velocity were continuously recorded for 5 minutes after injection. Hemodynamic measurements were repeated at serial intervals. Cardiac output was measured in duplicate at 1, 5, and 30 minutes after ANP injection. Quantitative coronary angiography was repeated at 5 and 30 minutes after ANP injection. Finally, at 43 minutes after ANP injection, 0.3 mg nitroglycerin was injected via the coronary catheter, and digital coronary angiograms were obtained 2 minutes later to assess the maximal dilation potential of the coronary segments.

To evaluate the relation among plasma ANP, plasma cGMP, and changes in coronary diameter, blood samples (5 ml) were withdrawn before and at 1, 5, 30, and 40 minutes after ANP injection. Blood samples for assay of plasma ANP were collected in chilled polyvinyl tubes containing EDTA (5 mg) and aprotime (3,000 units) and immediately centrifuged at 2,500g for 10 minutes at 4°C. The plasma was then carefully removed, immediately frozen in liquid nitrogen, and stored at −70°C until further assay. Blood samples for plasma cGMP assay were collected in chilled vacutainer tubes containing K-EDTA (7.5 mg) (Becton Dickerson & Co, Rutherford, New Jersey). The tubes were then similarly centrifuged, and the plasma was removed, frozen, and stored.

**Plasma ANP and cGMP Radioimmunoassays**

Radioimmunoassays were performed using a modified technique from that described by Steiner et al. The reagents, antiserum complex, and assay standards for ANP assays were commercially obtained (Peninsula Laboratories, Inc, Belmont, California). Plasma samples (3 ml) were applied to activated C18 Sep-Columns (Peninsula Laboratories, Inc), which were then washed with 0.1% trichloroacetic acid (TCA) (4×5 ml). ANP was then eluted with 60% acetonitrile in 0.1% TCA into polypropylene tubes. The eluant was lyophilized and the residue redissolved in radioimmunoassay buffer (Peninsula Laboratories, Inc). Rabbit anti-α-human ANP serum was then added to duplicate aliquots of the extracted samples or known standards and the mixtures incubated overnight at 4°C. Tracer ANP (125I-α-human ANP, 10,000 cpm) was then added to each mixture and the incubation continued at 4°C for 18 more hours. Bound and free peptide was subsequently separated by the addition of goat anti-rabbit IgG serum and normal rabbit serum, and the centrifuged pellet (2,000g at 4°C for 15 minutes) counted for activity. Results were then calculated for standard curves of bound/free counts per minute compared with log [ANP] standard. Data were reported without correction for recovery. In a separate group of assays, percent recovery was evaluated by subjecting a known amount of 125I-α-human ANP to the C-18 columns and the subsequent radioimmunoassays. The range of recovery was between 62% and 80%.

cGMP levels were determined using a similar principle with commercially available radioimmunoassay kits (EI duPont de Nemours & Co, Inc, New England Nuclear Products, Boston, Massachusetts). Plasma samples were first treated with an equal volume of cold 10% TCA. The suspension was then centrifuged at 2,500g at 4°C for 15 minutes. The supernatant was subsequently extracted four times with 5 ml water-saturated ether. The samples were subsequently evaporated to dryness and reconstituted in sodium acetate buffer (EI duPont) for radioimmunoassay. Succinyl cGMP tyrosine methyl ester-125I combined with normal rabbit serum was added to an equal volume of standard solution or sample in duplicates. Antiserum was then added and the mixture incubated overnight at 4°C. The mixture was subsequently centrifuged at 2,000g at 4°C for 15 minutes, and the pellet was counted for activity. Results were calculated for standard curves of bound/free counts per minute plotted against log [cGMP] standard after correction for internal recovery for individual samples.

Coronary blood flow was calculated from blood flow velocity measurements and expressed in volume flow units after correction for changes in internal coronary diameter at the site of the Doppler crystal. Coronary diameter, coronary blood flow, systemic hemodynamics, and cardiac output measured at various intervals after ANP infusion were compared with control measurements.

| TABLE 1. Hemodynamic Changes Before and After ANP (2.5 μg/kg) Injection (Mean±SD) |
|---------------------------------|---------------------------------|
| Control | Time after ANP injection (min) | 1 | 5 | 30 |
| AoP (mm Hg) | 96±11 | 88±11* | 86±12* | 89±15 |
| LVEDP (mm Hg) | 9±3 | 7±4 | 7±3* | 8±3 |
| dp/dt (mm Hg/sec) | 984±381 | 1,083±410 | 1,095±399* | 1,048±375 |
| Heart rate (beats/min) | 73±22 | 76±17* | 81±20* | 74±23 |
| Cardiac output (l/min) | 5.79±1.39 | 6.37±1.65* | 6.32±1.31* | 5.80±1.45 |

AoP, aortic pressure; LVEDP, left ventricular end-diastolic pressure. *Significant when compared with control.
obtained in the same patients using Student's paired t test after adjusting for multiple comparisons using the Bonferroni method to correct for the multiplicity of tests.

Results

Table 1 summarizes the hemodynamic measurements in all 17 patients before and at serial intervals after ANP injection. ANP induced transient minor decreases in mean aortic pressure (average maximal change, 10%) and left ventricular end-diastolic pressure (16%) and increases in heart rate (11%), left ventricular dP/dt (average maximal increase, 11%), and cardiac output (14%), lasting 5 minutes. By 30 minutes after ANP injection, these measurements were not different from control. In two patients, significant hypotension (>20%) developed during the study and was easily reversed with saline infusions.

Figure 1 illustrates the excellent reproducibility of the digital quantitative angiographic technique. In six patients, coronary angiography was performed in duplicates before ANP injection. The measurements obtained from three selected segments of coronary arteries in the first angiogram (image 1) compare very closely to the measurements obtained in the identical segments in the second angiogram (image 2) from the same patients \((r=0.97, \text{SEE}=0.22)\). To demonstrate the accuracy of our quantitative angiographic technique, diameter measurements from contrast-filled Lucite phantoms are shown in Figure 2. The measured diameters show good agreement with actual diameters over a range of 1.0–5.0 mm \((r=0.99, \text{SEE}=0.10)\).

Figure 3 is a representative coronary angiogram in one patient before and 30 minutes after ANP injection. Coronary dilation is clearly evident throughout the epicardial vessels.

The top portion of Figure 4 illustrates the average diameter and percent change in diameter of the proximal coronary artery of all 17 patients before and at serial intervals after ANP injection. ANP induced significant (15%) proximal coronary dilation from 3.49±0.57 to 3.99±0.68 mm at 5 minutes. The dilation was sustained and remained significant (4.09±0.76 mm [17%]) at 30 minutes after ANP injection. This represents approximately 37% increase in cross-sectional area. In addition, injection of a maximal dose of nitroglycerin (0.3 mg i.c.) 45 minutes after ANP did not further dilate the vessels (4.08±0.79 mm) when compared with diameter at 30 minutes after ANP.

The serial changes in proximal coronary diameter were related to the serial changes in plasma ANP and cGMP levels in the bottom portion of the diagram. Plasma ANP level significantly increased by more than sixfold from 39.8±8.8 to 245.8±168.5 pg/ml and was highest at 1 minute after bolus ANP injection. Plasma ANP subsequently returned to control values by 30 minutes. Plasma cGMP increased significantly by more than threefold from 15.6±12.7 to 54.7±20.4 pmol/ml and reached a peak at 5 minutes. However, unlike the plasma ANP

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**FIGURE 1.** Plots of the measurements obtained from three selected segments of coronary arteries in the first angiogram (image 1) compared with measurements obtained in the identical segments in the second angiogram (image 2) from the same patients \((n=6)\). The close linear relation demonstrates excellent reproducibility.

**FIGURE 2.** Plot of diameter measurements using digital quantitative angiography compared with actual diameters in contrast-filled Lucite phantoms. There is excellent agreement over the range of 1.0–5.0 mm.
levels, the increases in plasma cGMP were more sustained, lasting more than 30 minutes. The time course of proximal coronary dilation was related more closely to the time course of increase in plasma cGMP level than to that of plasma ANP.

The effects of ANP on coronary flow for individual patients are shown in Figure 5. Although mean coronary flow (calculated from flow velocity measurements after correction for diameter changes) increased 18% from 87±55 to 102±54 vol flow units at 5 minutes after ANP injection, the increase was not statistically significant. The lack of a significant increase in flow indicates that the proximal coronary dilation was a direct effect induced by ANP and was not secondary to flow-mediated changes.

Discussion

The present study demonstrates that in patients, bolus injections of ANP (2.5 µg/kg) caused sustained preferential epicardial coronary dilation without accompanying significant sustained increases in coronary blood flow. The epicardial coronary dilation was not further increased by a subsequent large dose of nitroglycerin. The striking sustained epicardial coronary dilation was associated with brief minor reductions in mean aortic pressure and left ventricular end-diastolic pressure and minor increases in heart rate and cardiac output. Minor increases in left ventricular contractility persisted for more than 30 minutes. The duration of epicardial coronary dilation followed the time course of
Results

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An increase in plasma cGMP, suggesting continuous production and release of cGMP into the circulation during the period of vasodilation. In contrast, plasma ANP returned to control levels earlier than the duration of vasodilation and cGMP elevation.

The preferential sustained proximal epicardial dilations seen in patients in this study are comparable to the results from previous studies performed in awake dogs in our laboratory. Bolus ANP injections in chronically instrumented awake dogs at a dose similar to the dosage used in the current study (0.3–5 μg/kg) induced sustained increase in proximal coronary diameter, reaching a peak at 10 minutes after ANP injection and lasting an average of 70.2±28.6 minutes at the highest dose. Coronary blood flow increased only briefly, lasting 1–5 minutes. Nitroglycerin induced similar effects on epicardial coronary dimension and coronary blood flow. Studies from our laboratory have demonstrated that ANP also dilates intramural vessels, causing favorable redistribution of flow to the subendocardium during ischemic stimulation in the presence of a critical stenosis, similar to the effects of nitroglycerin. Although continuous recordings of coronary blood flow in patients were not possible in the present study, the insignificant increase in coronary flow seen 5 minutes after ANP injection is consistent with the previous finding in dogs that vasodilation of the distal coronary resistance vasculature is brief. Because epicardial coronary dilation persisted long after coronary flow returned to baseline values, the proximal dilation resulted from a direct effect of ANP rather than secondary to changes in coronary flow. The prolonged effect on epicardial dimensions indicated it is unlikely that the response was mediated via a reflex. These views are supported by animal studies in our laboratory demonstrating that the combined autonomic blockade did not alter the epicardial vasodilation response and that the effects of ANP on epicardial dimensions were not altered when flow was held constant. The findings of the present study are also consistent with results from conscious rats by Garcia et al and with observations in anesthetized dogs by Bache et al and Bauman et al, who observed increases in myocardial blood flow after ANP injections, but are contrary to results of Pegram et al and Wangler et al, who observed reductions in coronary flow in rats and Langendorff-perfused guinea pig hearts.

In the present study, bolus injection of ANP (2.5 μg/kg, left ventricle) induced only transient and minor reductions in aortic pressure and left ventricular end-diastolic pressure and a brief increase in heart rate. It is likely that the minor changes in pressures did not result from cardiac depression because the changes were associated with small increases in cardiac output and left ventricular dP/dt. Only two patients experienced a 20% reduc-
tion in mean aortic pressure requiring volume replacement. Previous studies in experimental animals have reported conflicting effects of ANP on aortic pressure, cardiac output, and indexes of left ventricular contractility. The different responses may have been influenced by different experimental models and conditions and different protocols for ANP infusions. Studies by Kleinert et al. with chronically instrumented conscious dogs demonstrated a significant decrease in mean arterial pressure, heart rate, cardiac output, and left ventricular dP/dt after bolus ANP (3 μg/kg) followed by a continuous ANP infusion (0.3 μg/kg/min i.v.). Lappe et al. also showed that continuous intravenous infusion of ANP (0.25–4 μg/kg/min) induced a dose-dependent reduction in mean arterial pressure and cardiac output and increases in regional vascular resistance in conscious rats. They concluded that ANP directly reduced cardiac output, leading to a reflex increase in resistance. Studies by Koike et al. however, demonstrated no significant change in cardiac output in conscious rats after an intravenous bolus injection of ANP (30 μg/kg). Reports of systemic hemodynamic responses to ANP infusions in patients are also conflicting. Weidmann et al. observed significant reductions of arterial pressure when ANP was given as a bolus (50 μg) followed by a continuous infusion (6.25 μg/min) in normal subjects. In contrast, constant intravenous infusion of ANP (0.1 μg/kg/min) did not significantly alter mean arterial pressure or heart rate in either normal volunteers or heart failure patients. In the latter study, cardiac index actually increased significantly in the heart failure group and remained unchanged in the normal volunteers.

ANP is believed to mediate its effects via activation of particulate guanylate cyclase closely associated with the cell membrane. Cyclic GMP formation has been reported to generally correlate with the vasorelaxant activity in vitro. In the present study, we observed that the duration of epicardial dilation was related more closely to the duration of elevation of plasma cGMP than the duration of increase in plasma ANP levels. In recent preliminary studies in chronically instrumented awake dogs, we demonstrated a similar relation between plasma cGMP levels and epicardial coronary dilation. Discordance between duration of epicardial dilation and the much shorter duration of plasma ANP elevation was also observed. Furthermore, in previous studies, we demonstrated a selective increase in plasma cGMP with ANP, an activator of particulate guanylate cyclase. In contrast, activators of soluble guanylate cyclase, including nitroglycerin and endothelium-derived relaxing factor, did not increase plasma cGMP despite a similar or greater epicardial coronary dilation. Gerzer et al. studied the effects of bolus injections of 50 μg ANP in eight normal subjects. They also observed a short-lived threefold increase in plasma ANP that rapidly returned to baseline within 10 minutes. As in our present study, plasma cGMP elevation was more sustained, lasting more than 30 minutes. The authors suggested that cGMP may be a biological marker for circulating ANP in humans, although a direct correlation with a physiologic response such as rate and duration of diuresis, natriuresis, or vasodilation was not studied. Our data demonstrate for the first time an in vivo relation between the elevated plasma cGMP level and epicardial coronary dilation in humans. This relation may be selective for conductance vessels because both coronary flow and arterial pressure changes were much more brief than the duration of plasma cGMP elevation or duration of epicardial coronary dilation. The correlation between plasma cGMP elevation and the duration of epicardial dilation does not necessarily indicate that the dilation was induced by the plasma cGMP. In fact, the plasma cGMP was probably from sources other than the vascular smooth muscle such as the endothelium. Our demonstration in animal studies of a selective increase in plasma cGMP in response to ANP but not activators of soluble guanylate cyclase such as nitroglycerin or endothelium-derived relaxing factor further lends support to the notion that the plasma cGMP itself is not the cause of the dilation. The actual mediator of the dilation may be an increase in cGMP production in the vascular smooth muscle. The present study does not establish a cause-and-effect relation between epicardial dilation and changes in plasma cGMP. It also has not established that the increase in plasma cGMP was related to changes in cGMP in vascular smooth muscle. However, the data do indicate continuous production of cGMP during the period of epicardial coronary dilation and thus provide support for the view that cGMP may be mediating the dilation.

Because ANP shares certain vascular effects of nitrates, it has been considered as an “endogenous nitrate.” It is tempting to speculate that ANP may play an important role in the response to ischemia. Myocardial ischemia may cause an increase in ventricular filling pressures and both left and right atrial pressures. The increase in atrial pressures stretches atrial myocytes and increases ANP release, which may, in turn, reduce ischemia by dilation of the stenotic epicardial coronary arteries and increasing total flow and/or dilation of intramural coronary arteries, leading to favorable redistribution of flow to the ischemic subendocardium. The ANP dose (2.5 μg/kg) used in the present study caused a more than sixfold increase in plasma ANP level. Although the level observed in the present study may exceed normal physiologic responses, similar levels may occur during stressful pathologic states such as acute ischemia and abrupt increase in filling pressure. Fivefold increases in ANP have been observed in patients with marked edema and severe heart failure. Threefold to 13-fold increases in plasma ANP level have also been observed in patients during supraventricular tachycardia. Studies performed in our laboratory...
in chronically instrumented awake dogs have demonstrated significant epicardial coronary dilation after less than one eighth of the ANP dose used in the present study (0.3 μg/kg). This study demonstrates for the first time the effects of ANP, an endogenous vasodilator, on coronary arterial vasculature in humans. Although additional studies are needed to assess the clinical efficacy of ANP as a coronary dilator in the treatment of coronary artery disease, these data do suggest a potential of ANP in the therapy of ischemia and raise the intriguing question of whether endogenous release of ANP may play an important role in the response to ischemia.

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References

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