Elevated Plasma Atrial Natriuretic Peptide Levels After Occlusion of the Thoracic Aorta*

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Study objective: The influence of occlusion of the thoracic aorta by an intraluminal balloon on plasma atrial natriuretic peptide (ANP) levels was evaluated in humans.

Methods: The changes in plasma ANP and plasma norepinephrine levels, and hemodynamic parameters were measured in 10 patients under general anesthesia undergoing regional chemotherapy treatment involving the 15-min inflation and subsequent deflation of an intra-aortic balloon.

Results: The hemodynamic changes observed were similar to those seen during aortic clamping and declamping in patients undergoing vascular surgery. Plasma ANP levels (median \( \pm \) SD) measured 1 min after inflation (146 \( \pm \) 117 pg/mL) and 1 min after deflation (168 \( \pm \) 189 pg/mL) of the aortic balloon were significantly higher than baseline values (83 \( \pm \) 55 pg/mL), with a mean increase, respectively, of 92% and 97% (95% confidence intervals [CI], 50 to 147% and 53 to 152%). Plasma ANP levels were still elevated 30 min after deflation (121 \( \pm \) 94 pg/mL), a 56% increase (95% CI, 21 to 100%), although the hemodynamic parameters had already returned to their baseline levels. There was no evidence that the hemodynamic variables were associated with changes in plasma ANP levels (all p values > 0.30). In addition, there was no evidence of an association between plasma ANP and plasma norepinephrine levels at any of the four individual sampling points (p > 0.17). Thirty minutes after deflation, however, norepinephrine levels were higher than baseline values.

Conclusions: The changes in plasma ANP levels after aortic occlusion and reinstitution of blood flow may be dependent on parameters other than atrial stretch and pressure.

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Key words: aortic clamping; aortic declamping; atrial natriuretic peptide; norepinephrine

Abbreviations: ANOVA = analysis of variance; ANP = atrial natriuretic peptide; CI = confidence interval; CO = cardiac output; CVP = central venous pressure; MAP = mean arterial pressure; PAP = pulmonary arterial pressure; PCWP = pulmonary capillary wedge pressure; SVR = systemic vascular resistance

Occlusion of the thoracic aorta, usually performed by surgical clamping, and the subsequent reinstiution of blood flow (declamping) are followed by dramatic hemodynamic, metabolic, and hormonal changes. Occlusion usually leads to an increase in arterial BP and systemic vascular resistance (SVR), and the declamping may lead to a “declamping shock syndrome” because of profound vasodilatation and hypotension. Humoral factors such as catecholamines, renin, angiotensin,
congestive heart failure. ANP secretion as a response to other stimuli such as catecholamines and vasopressin has been demonstrated in vitro. Moreover, ANP secretion might be affected by oxygen free radicals released by the intestinal ischemia, and reperfusion, as shown in rats.

The present study attempted to clarify whether occlusion of the aorta and its release will influence plasma ANP concentrations. This issue was tested in the past only in hypothermic patients during extracorporeal circulation, when blood flow is diverted from the heart and ANP degradation is diminished. The aim of this study was to examine how changes in heart filling pressures during the occlusion procedure affect plasma ANP levels.

**Materials and Methods**

**Patients**

After obtaining institutional approval and informed patient consent, 10 patients (7 were male and 3 were female) with a mean age of 58 years (range, 31 to 69 years) were included. All patients had inoperable intra-abdominal malignancy and underwent a new procedure of high-dose chemotherapy administration into the isolated intra-abdominal vascular bed. None of the patients had previous significant cardiovascular or respiratory disease.

**Procedure**

General anesthesia was induced with fentanyl, 2 μg/kg; midazolam, 0.015 mg/kg; and thiopental, 2 to 3 mg/kg. Endotracheal intubation was facilitated by succinylcholine, 1.5 mg/kg. Anesthesia was maintained by isoflurane, 0.6 to 1.2%; and 60% nitrous oxide in oxygen, fentanyl, and pancuronium bromide. Patients were monitored with an ECG, pulse oximetry, capnography, and temperature. Radial and pulmonary artery catheters were inserted after the induction of anesthesia.

To isolate the abdominal viscera and facilitate the selective administration of high doses of chemotherapeutic drugs, a specially designed balloon catheter was inserted into the descending thoracic aorta through the femoral artery. Under fluoroscopy, the balloon was placed at the level of the T6–T8 vertebrae and then gradually inflated. Complete occlusion of the aorta was judged to occur when the contour of the balloon showed signs of outside compression. A high dose of chemotherapeutic drugs was injected distal to the balloon. The balloon was kept inflated for 15 min and then gradually deflated.

When necessary, the hemodynamic changes induced by the inflation of the aortic balloon were treated with IV nitroglycerin or phenylephrine. Rare occurrences of hypotension (systolic BP < 80 mm Hg) after deflation were treated with IV ephedrine or phenylephrine.

**Measurements**

The following hemodynamic parameters were measured: mean arterial pressure (MAP), pulmonary arterial pressure (PAP), central venous pressure (CVP), pulmonary capillary wedge pressure (PCWP), and cardiac output (CO) that was determined in triplicate by thermodilution. The hemodynamic measurements and arterial blood samples for plasma ANP and plasma norepinephrine levels were obtained at four different times: at baseline (after the insertion of the aortic balloon but before inflation); 1 min after inflation; 1 min after deflation; and 30 min after deflation, but still during general anesthesia.

Data samples obtained to measure plasma ANP levels were placed immediately in chilled tubes containing 2.25 mg of ethylenediaminetetraacetic acid and 1.5 trypsin inhibitor units of aprotinin. Cellular elements were separated by centrifugation at 4°C, and the samples were stored at −70°C until assayed. ANP was determined according to Zamir et al.

The blood samples obtained to measure plasma norepinephrine levels were collected in chilled tubes containing ethyleneglycoltetraacetic acid and glutathione (reduced form), separated by centrifugation at 4°C, and stored at −70°C until assayed. The samples were prepared for analysis by a method reported by Goldstein et al. and plasma norepinephrine concentrations were determined by high pressure liquid chromatography using a μ reverse-phase column (Bonda Pack c-18; Beckman; Fullerton, CA) and an electrochemical detector (Model 460; Waters Corp; Milford, MA). The sensitivity for norepinephrine measurement was 0.04 ng/mL.

**Data Analysis**

Changes over the four time points for each hemodynamic and hormonal variable were assessed using an analysis of variance (ANOVA). Because most variables appeared to be log-distributed, changes in levels were quantified by observing the percentage increase or decrease from baseline levels; variables that were not log-distributed were PCWP, PAP and CVP. At each of the time points, associations between ANP and the other variables were assessed using the Spearman rank correlation.

**Results**

Figures 1–3 show the observations for each of the patients at each of the time points. The solid squares indicate the mean level of the 10 patients at the particular point.

All hemodynamic variables, except CVP, changed significantly during the period from baseline to 30 min after deflation (p < 0.001 for all variables).

The following data are presented as the median (± SD). The inflation of the aortic balloon was followed by an increase in MAP from 74.5 ± 9 to 96 ± 14 mm Hg (p < 0.01); an increase in SVR from 1,042 ± 267 to 1,856 ± 673 dyne · s · cm⁻⁵ (p < 0.01); and a decrease in CO from 5.1 ± 0.7 to 3.2 ± 0.9 L/min (p < 0.01). PAP was significantly elevated from 18 ± 5 to 21.5 ± 5 mm Hg (p < 0.01); as was PCWP, from 13.5 ± 3.6 to 20.5 ± 3.7 mm Hg (p < 0.01). Plasma ANP levels increased significantly from 83 ± 55 pg/mL to 146 ± 117 pg/mL (p < 0.01); however, plasma norepinephrine levels of 290 ± 171 pg/mL were close to their baseline values of 250 ± 142 pg/mL.

The deflation of the aortic balloon, after 15 min of inflation, induced a decrease in MAP to the baseline values of 73 ± 17 mm Hg (p = 0.63); a decrease in
SVR to values significantly lower than baseline, 555 ± 170 dyne·s·cm⁻² (p < 0.001); and an increase in CO to levels higher than baseline, 8.7 ± 2.3 L/min (p < 0.001). PAP remained higher than baseline, 23.5 ± 7 mm Hg (p < 0.01); as did PCWP, 20 ± 7 mm Hg (p < 0.01). Plasma ANP levels of 168 ± 618 pg/mL (p < 0.01) remained higher than baseline and were similar to the levels seen after the inflation of the aortic balloon. Plasma norepinephrine levels of 462 ± 374 pg/mL (p < 0.01) were significantly higher than baseline.

Thirty minutes after the deflation of the aortic balloon, the MAP levels of 80.5 ± 14 mm Hg (p > 0.10), the SVR of 1,055 ± 425 dyne·s·cm⁻² (p > 0.10), PAP of 18 ± 4 mm Hg (p > 0.10), and PCWP of 3.5 ± 5 mm Hg (p > 0.10) were not significantly different from their baseline values. Plasma ANP levels of 121 ± 94 pg/mL (p < 0.01) and plasma norepinephrine levels of 380 ± 334 pg/mL (p < 0.01) remained high.

There was no evidence that the hemodynamic variables were associated with ANP (all p values > 0.30 are from ANOVA) after allowing for the effect of inflation and deflation of the balloon.

There was also no evidence of an association between ANP and norepinephrine at any of the individual four time points using Spearman rank correlation: baseline, r = 0.01 (p = 0.97); 1 min after inflation, r = 0.31 (p = 0.38); 1 min after deflation, r = −0.47 (p = 0.17); 30 min after deflation, r = −0.20 (p = 0.60); or overall (p = 0.36 from ANOVA).

**Discussion**

In this study, the 15-min occlusion of the thoracic aorta by an inflated intraluminal balloon and its subsequent deflation induced hemodynamic changes similar to those described after external aortic clamping and declamping in patients undergoing vascular surgery.² ³ A similar model was used previ-
ously in dogs by Puri et al, but its longer period of aortic occlusion and different timing of measurements (30 min after occlusion and deflation) prevents a comparison to the present study.

Considering that ANP is secreted in situations of increased atrial stretch and elevated PCWP, such as blood volume expansion, acute myocardial ischemia and congestive heart failure, it is not surprising to find elevated ANP levels in the presence of increased heart filling pressures after the inflation of an aortic balloon. In this situation, ANP may act as a counter-regulatory hormone to renin, angiotensin, and catecholamines, and their effects on BP and renal perfusion.

The presence of higher-than-baseline plasma ANP concentrations after balloon deflation was also to be expected because filling pressures remained somewhat elevated. At this stage, ANP may contribute to the low BP and vasodilatation present after aortic declamping in patients undergoing vascular surgery.

However, the persistent elevation of plasma ANP levels 30 min after deflation cannot be explained on a hemodynamic basis alone, because at that time the filling pressures had returned to baseline values. Alternative mechanisms for these sustained high plasma ANP levels could be prolonged ANP half-life or secretion caused by factors other than atrial stretch, such as renin, angiotensin, catecholamines, metabolites secreted from the ischemic abdominal compartment, or chemotherapeutic drugs.

Prolonged ANP half-life, which normally is about 2 min, was demonstrated only during hypothermic cardiopulmonary bypass. The mechanism is most probably a decrease in ANP degradation as part of the generalized decreased metabolism induced by hypothermia. Nevertheless, renal ischemia during the aortic occlusion may induce impairment in ANP metabolism by endopeptidase located in the brush border of the proximal tubules, or ANP binding by C receptors in the renal cortex.

ANP secretion as a response to stimuli other than atrial stretch has already been described. Sorrenberg et al demonstrated ANP secretion as a response to vasopressin in an in vitro model. Manning et al found similar results in anesthetized rats. Since the effect was abolished in the presence of a specific pressor antagonist, the authors concluded that ANP secretion was related to the increase in BP, and not directly to vasopressin. Shackford et al showed that plasma ANP was elevated in a model of severe hemorrhagic shock, in the presence of low cardiac filling pressures. Proposed mechanisms included a response to elevated plasma norepinephrine and epinephrine levels, significant tachycardia, or a decrease in ANP metabolism during shock. In the present study, both plasma ANP and norepinephrine levels were elevated 30 min after the aortic balloon had been deflated; therefore, the increase in plasma ANP levels at this time might also be dependent on the persistent increase in catecholamines.

ANP secretion as a response to tissue hypoxemia was demonstrated during reperfusion after 20 min of gut ischemia in rats, during myocardial ischemia, and 3 h after the induction of septic shock.

Another possible mechanism for the ANP secretion is the effect of chemotherapy treatment itself, although Fiorica et al in a previous study demonstrated that platinum-based chemotherapy did not induce elevation of plasma ANP levels above baseline in humans.

In summary, our study demonstrated that ANP secretion after occlusion of the thoracic aorta, as well as after the reinstatement of blood flow, may indeed be influenced by the associated hemodynamic changes. However, ANP levels 30 min after the reinstatement of blood flow remained higher than baseline values, even after all the hemodynamic parameters returned to baseline values. This suggests that elevated plasma ANP levels may

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**Figure 3.** The ANP and norepinephrine plasma level observations for each of the patients at each of the time points. The solid squares indicate the mean level of the 10 patients at the particular point (calculated on a log scale).
be a result of factors other than those associated with atrial stretching, such as elevated plasma levels of catecholamines, with or without regional ischemia, and reperfusion or decrease in ANP clearance.

**References**

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