Atrial natriuretic peptide in congestive heart failure in the dog: plasma levels, cyclic guanosine monophosphate, ultrastructure of atrial myoendocrine cells, and hemodynamic, hormonal, and renal effects

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ABSTRACT In an animal preparation of congestive heart failure in the dog, during the development of cardiac failure due to rapid right ventricular pacing we observed significant decreases in cardiac output and arterial pressure and increases in pulmonary arterial and right atrial pressure. We also observed a related increase in right atrial pressure and increases in plasma levels of atrial natriuretic peptide (ANP) and cyclic guanosine monophosphate (c-GMP). Ultrastructure changes in the atrial myoendocrine cells indicated extreme stimulation of the secretory apparatus of ANP. The response of hemodynamic, renal, and hormonal variables was investigated after incremental infusions (0.01, 0.03, 0.1, 0.3, and 0.6 µg/kg/min) of exogenous ANP. In healthy animals ANP significantly decreased mean arterial pressure, cardiac output, stroke volume, and right atrial pressure without changing heart rate or peripheral vascular resistance. As expected, we found a striking increase in urine flow and urinary excretion of sodium, chloride, magnesium and calcium and a smaller increase in potassium excretion. ANP suppressed renin secretion, and increased renal plasma flow, glomerular filtration rate, and filtration fraction. In dogs with heart failure ANP caused a small reduction in mean arterial pressure. No effect was seen on other hemodynamic variables or plasma renin concentration. The excretory effects on the kidneys were completely absent, and smaller increases in glomerular filtration rate and filtration fraction were observed. We found no difference between healthy dogs and animals with heart failure with respect to the secretion of c-GMP during ANP infusions in relation to the plasma levels of ANP. This suggests an intracellular defect that prevents the mediation of the hormonal signal into biological action in the presence of heart failure.


IN 1981 de Bold et al. demonstrated that intravenous administration of atrial extracts to intact rats induced profound natriuresis and diuresis. Injection of atrial natriuretic peptide (ANP) in human subjects causes diuresis and natriuresis and reduces blood pressure. It has been shown that ANP is elevated in the presence of heart failure in proportion to the severity of the disease, suggesting that ANP may be important in the pathophysiology of cardiac failure. It has been reported that in patients with severe chronic congestive heart failure ANP infusions in pharmacologic doses have beneficial effects on cardiac function by reducing preload and afterload. However, in contrast to healthy volunteers, ANP at relatively high doses had no effects on urine and electrolyte excretion, or its effects were considerably attenuated, in these patients. To date, no studies have definitively investigated hemodynamic, renal, and hormonal responses to ANP in an experimental preparation of chronic heart failure.

The present study was designed (1) to determine changes in endogenous ANP during the development of heart failure, (2) to determine whether the response to ANP administration is normal or abnormal in the presence of heart failure, (3) to determine the effect of ANP infusions on plasma renin concentration and cyclic guanosine monophosphate (c-GMP) before and
after heart failure has developed and (4) to describe ultrastructural changes in myoendocrine cells of the atria in dogs with heart failure as compared with those in normal control dogs.

To characterize the effects of ANP more precisely, dose-response studies were performed with the use of synthetic ANP in healthy animals and dogs with congestive heart failure, and hemodynamic, hormonal, and renal changes were measured.

**Methods**

**Animal preparation.** The experiments were performed in six female mongrel dogs (15 to 25 kg) in which chronic low-output heart failure was induced by rapid right ventricular pacing.\(^1\) Briefly, under general anesthesia the right jugular vein was exposed and a pacemaker lead was implanted into the right ventricle. This was connected to a pacemaker that was implanted subcutaneously, being programmable by an external magnet to provide a constant heart rate of 260 beats/min. Through the left jugular vein a No. 7F Swan-Ganz thermodilution flow catheter was positioned in the pulmonary artery and a second catheter was placed in the right atrium. Through the left carotid artery a third catheter was inserted into the abdominal aorta distal to the renal arteries. The position of the catheters was controlled by fluoroscopy and pressure tracing. Pressures were measured by use of a Statham P 23 Db pressure transducer and were recorded on a polygraph recorder. Cardiac output was measured by thermodilution after the injection of 5.0 ml of 0.9% saline at about 0°C into the right atrium (cardiac output computer, Hoyer). All measurements were obtained in conscious dogs trained to stand quietly on a table in a cotton mesh support sling. Seventy-two hours after the operation, when the dogs were fully recovered, the bladder of each was catheterized with a Foley catheter under short anesthesia (12.5 mg/kg thiopental sodium). This catheter was used for timed collection of urine for volume and electrolyte measurements. Two hours later, in the fully recovered animal, baseline hemodynamic, hormonal, and renal variables were measured after infusion of 0.9% saline into the pulmonary artery. Thereafter synthetic sterile 28-aminoacid α-ANP (Bissendorf, F.R.G.) dissolved in 0.9% saline, was administered into the pulmonary artery by constant infusions lasting 30 min each. Hemodynamic, hormonal, and renal measurements were obtained at the end of each infusion period. Infusions of ANP covered a whole dose-response curve, with dosages of 0.01, 0.03, 0.1, 0.3, and 0.6 μg ANP/kg/min, and were followed by a 60 min infusion of saline to investigate the effects of ANP withdrawal.

**Renal function studies.** The next day, renal function studies were performed in three dogs. A Foley catheter was placed in the urinary bladder for collection of timed urine samples as already described. A priming dose of 50 mg/kg creatinine and 8 mg/kg para-aminohippurate (PAH) dissolved in saline solution was infused into the pulmonary artery over a 15 min period. This was followed by a constant infusion (1.0 ml/min) of 1.0 mg/kg/min creatinine and 0.3 mg/kg/min PAH.\(^2\) Forty-five minutes later, when plasma concentrations were at a steady state, the bladder of each dog was completely emptied and flushed twice with sterile distilled water before the first of three clearance periods (each of 20 min duration) was started. During the clearance periods urine was collected for the determination of creatinine, PAH, and electrolytes. At the midpoint of each clearance period, blood was sampled from the right atrium. The clearances values were expressed as the mean of three measurements. Creatinine and PAH clearance was measured during a constant infusion of saline and during infusions of 0.03 and 0.1 μg ANP/kg/min for 60 min each. Thereafter the pacemaker was switched on and the same procedures were repeated after 11 days when congestive heart failure was established. During pacing hemodynamic variables and hormonal changes were recorded every third day.

**Analysis of blood and urine samples.** Plasma ANP was measured by radioimmunoassay. Blood samples were taken into plastic tubes containing EDTA (1.5 mg/ml) and aprotinin (500 KIU/ml). One milliliter of plasma was extracted on a C18 Sep Pak cartridge (Waters Associates, Milford, MA). The cartridges were prewashed with 10 ml of methanol and 10 ml of 4% acetic acid. After the plasma was applied, the cartridges were washed three times with 5 ml 0.1% vol/vol trifluoroacetic acid and the absorbed peptide was eluted with 2 ml 60% acetonitrile/0.1% trifluoroacetic acid into plastic tubes. The extracts were dried down and reconstituted in 1.0 ml buffer and measured by radioimmunoassay with use of specific antibody against α-ANP (Peninsula Lab., Inc.).\(^4\)

Plasma levels of c-GMP were measured by radioimmunoassay with use of a highly specific antibody with no cross-reactivity for c-AMP.\(^10\)

Plasma renin concentration was measured as described previously.\(^8\) PAH concentrations were determined by the Britton-Marshall method; serum and urine concentrations of creatinine, sodium, potassium, chloride, magnesium, and calcium were measured by automatic analyzer (SMAC Technicon).

**Electron microscopy.** Five dogs with congestive heart failure and three control dogs were used for electron microscopic and ultrastructural immunohistochemical studies. Three days after the function studies were completed the perfusion fixation was carried out. The animals were anesthetized with thiopental sodium and a laparotomy was performed. The abdominal aorta was cannulated with a plastic catheter. The catheter was advanced up to the aortic arch. The thoracic aorta was perfused retrogradely for 2 min with a rinsing solution containing procaine HCl\(^11\) and then for 10 min with a phosphate-buffered glutaraldehyde solution containing 0.1% picric acid. The heart was then excised and endocrine tissue from the aorta was dissected. Tissue blocks smaller than 1 × 1 mm were cut and washed in phosphate buffer, postfixed with osmium tetroxide, dehydrated in ethanol, and embedded in LR-White. The tissue was cut on a LKB-ultramicrotome and the sections were mounted on nickel grids and stained for immunoelectron microscopy.\(^12\) Electron micrographs were obtained on a Zeiss EM 10.

**Statistical analysis.** Data are presented as the mean ± SEM. Analysis of variance for repeated measures was performed to determine the significance of changes of hemodynamic, renal, and humoral variables. Dose-response curves were analyzed by a multivariate analysis of variance analog of the univariate repeated measures analysis of variance described by Grizzle and Allen.\(^13\) This procedure allows testing of differences in the dose-response curves obtained before and after the induction of heart failure.\(^9\) To test the significance of single comparisons a nonparametric procedure (Wilcoxon matched pairs signed-ranks test) was applied. Correlation coefficients were obtained by linear regression analysis (method of least squares). Statistical significance was accepted at the p<.05 level.

**Results**

The data collected during the development of heart failure (9 days) are summarized in figure 1. Rapid right ventricular pacing resulted in a significant fall in cardiac output (F = 9.9; p < .001) and mean arterial pressure (F = 37.8; p < .001), and a significant
A decrease in oxygen saturation of the mixed venous blood in the pulmonary artery (F = 6.6; p < .007). We also observed a significant increase of mean pulmonary arterial pressure (F = 6.6; p < .007) and right atrial pressure (F = 10.4; p < .001). Plasma ANP levels increased during the development of congestive heart failure to levels about six to seven times higher than those at baseline (F = 16.3; p < .001). We found a significant correlation between right atrial pressure and plasma ANP (r = .75; p < .001; n = 24). There was a significant increase in plasma c-GMP parallel to the stimulated secretion of ANP (F = 4.8; p < .02).

**Dose-response studies.** Figure 2 shows hemodynamic data obtained during the dose-response study of constant infusions of synthetic ANP and after withdrawal of ANP for 60 min. After 10 days of rapid right ventricular pacing, baseline values of mean arterial blood pressure, cardiac output, and stroke volume were significantly decreased and right atrial pressure was significantly increased. Both in healthy animals and in those in cardiac failure incremental infusions of ANP resulted in a significant decrease in mean arterial blood pressure. Before pacing ANP reduced cardiac output significantly. This was due to a significant reduction in stroke volume based on a significant reduction in right atrial pressure. Heart rate and peripheral vascular resistance remained unchanged. In the dogs with cardiac failure ANP caused no significant changes in cardiac output, stroke volume, peripheral vascular resistance, or right atrial pressure. The plasma ANP levels measured at baseline, during the incremental ANP infusions, and 1 hr after ANP was withdrawn are indicated in figure 2. At baseline, plasma ANP values are significantly (p < .03) elevated in dogs with heart failure. One hour after stopping the ANP infusion the ANP levels were restored to baseline, in contrast to the hemodynamic variables, which had not reached preinfusion values.

Figure 3 shows the renal variables in the same experiment. Plasma creatinine levels were not significantly different in healthy dogs (0.72 mg/dl) and in the animals with heart failure (0.62 mg/dl). At baseline we found significantly (p < .03) reduced urine flow, as shown on figure 3, but the reductions in urinary sodium and chloride excretion were not significant in dogs with heart failure. In the healthy control animals the incremental infusion of ANP induced a profound increase in urine flow and urinary sodium, magnesium, and calcium excretion. The same was found for urinary chloride excretion (data not shown). The urinary excretion of potassium was only significantly elevated at the highest infusion rate. Similar to the hemodynamic results, we found that urine flow and urinary sodium, calcium, and chloride excretion were not restored to basal values 60 min after stopping the ANP infusion, a time at which ANP plasma levels had reached preinfusion values. In contrast to healthy dogs, we found no effect of exogenous ANP on renal excretory function in dogs with heart failure, even at the high infusion rates of ANP.
Renal function studies. The results of studies of renal function are summarized in table 1. In the healthy animals the infusion of 0.03 and 0.1 μg/kg/min ANP induced an increase of renal plasma flow, glomerular filtration rate, and filtration fraction in each dog. In dogs in cardiac failure we found a marked reduction in renal plasma flow at baseline, a well-preserved glomerular filtration rate, and an increase in filtration fraction in each animal. In contrast to the healthy animals, ANP decreased renal plasma flow at the high infusion rate, possibly due to the reduction in blood pressure. As in the healthy controls, ANP increased glomerular filtration rate and filtration fraction in
dogs with heart failure, although to a small extent.

Humoral changes. Plasma renin concentration (figure 4) was significantly (p < .03) elevated in dogs with heart failure. In the healthy control dogs the infusion of ANP decreased plasma renin secretion significantly. One hour after stopping the ANP infusion we observed a striking increase in plasma renin concentration (p < .05) that amounted to doubling preinfusion values. Plasma renin concentration did not change significantly during the infusion of ANP in the animals with cardiac failure, showing instead a tendency to increase. As has been shown in figure 1, there was significant increase in c-GMP levels in dogs in heart failure. In figure 5,
the c-GMP levels are plotted against the ANP values obtained at baseline and at the end of each infusion period during the ANP dose-response study. There was significant difference between the plasma levels of c-GMP in relation to the measured plasma levels of ANP before and after heart failure was established, indicating that even when the hemodynamic and renal response to ANP infusion is attenuated, c-GMP production is not affected by the infusion of ANP.

**Electron and immunoelectron microscopy.** The ultrastructure of the control hearts was as described in an earlier article by Kaczmarczyk et al.\(^\text{15}\) In dog atria, as compared with that of other species, a relatively discrete endocrine secretory apparatus of myoendocrine cells is found. The Golgi complex is most frequently observed in the area next to the poles of the elongated nucleus of the myoendocrine cell, exhibiting flat cisternae, vesicles, and very few progranules. A scarce number of secretory granules can be found around this perinuclear Golgi complex and occasionally some cisternae of the rough endoplasmatic reticulum are seen. Few secretory granules are observed in the interfibrillar or subsarcolemmal space. A further location of the Golgi complex is seen subjacent to the sarcolemma or in the interfibrillar space, and this has been termed the "telenuclear" location. These Golgi complexes are poorly developed. The secretory granules and some progranules can be labeled by the immunogold method when antibodies against human C-terminus of ANP are used.\(^\text{12}\)

In this study, in dogs with heart failure a distinct hypertrophy of the Golgi apparatus was induced at its perinuclear, paranuclear, and telenuclear locations (figures 6 and 7). The cisternae of the Golgi apparatus increased in number and size. More frequently, progranules and Golgi vesicles were observed. A strongly developed rough endoplasmatic reticulum was found in many myoendocrine cells (figure 9). The Golgi complexes in the subsarcolemmal or interfibrillar location were particularly evident in the hypersecretory active

**FIGURE 5.** Plasma levels of c-GMP in relation to plasma levels of ANP at baseline and during incremental infusions of ANP before (— — —) and after (— — —) heart failure was established.
phase (figure 8). New Golgi apparatuses were possibly formed during ventricular pacing. The stainability of granules and sometimes the Golgi vesicles by the immunogold method also demonstrated the extreme stimulation of the secretory apparatus (figure 7).

Discussion

This study demonstrated, in an animal preparation of congestive heart failure, an increase in ANP and c-GMP during the development of heart failure related to an increase in right atrial pressure. It also demonstrated ultrastructural changes in atrial myoendocrine cells indicating an extreme stimulation of the secretory apparatus of ANP release. In healthy control dogs we found a significant decrease in mean arterial blood pressure, cardiac output, stroke volume, and right atrial pressure, with no changes in mean pulmonary arterial pressure or total peripheral vascular resistance after incremental infusions of synthetic ANP covering a whole dose-response range. Our data in conscious control dogs confirm previous findings,16, 17 that ANP decreases cardiac output via a reduction in stroke volume due to reduced venous return. Possible mechanisms include venodilatation and a reduced circulating blood volume. It has been shown that the infusion of ANP decreases blood volume but does not increase circulatory capacitance in rats,18 indicating that a reduced blood volume participates in the reduction of venous return but not supporting an important role for venodilatation.19 It has also been demonstrated19 that the preload reduction is dissociated from the renal effects of ANP, such as diuresis and natriuresis. These authors also showed that the infusion of ANP at a pharmacologic dose increases calculated resistance to venous return, which may be an important mechanism by which ANP decreases stroke volume. A fluid compartment shift from the vascular to the extravascular space20 due to an increase in capillary hydrostatic pressure or capillary permeability may be another mechanism. Our data indicate that mean arterial pressure is lowered by ANP in the animal preparation by a reduction in stroke volume and cardiac output rather than by a reduction in total peripheral resistance, which did not change.

In our experiments all hemodynamic changes induced by ANP infusions in healthy control dogs were completely absent in the animals with congestive heart failure with the exception of a small reduction in mean arterial blood pressure. The six- to sevenfold increase in ANP in the presence of chronic heart failure can be mainly explained by an increase in atrial wall tension,21-23 which results in a strong stimula-

tion of the secretory activity in the atrial myoendocrine cells, as documented in our electronmicroscopic study. As was demonstrated in the original article of De Bold et al.1 ANP infusions induced a striking increase in urinary flow and renal excretion of sodium, chloride, magnesium, and calcium, with a smaller increase in urinary potassium excretion in healthy control dogs. These stimulating effects on renal excretion could be demonstrated not only when pharmacologic doses of ANP were infused but also by use of ANP infusion rates that increased plasma ANP levels within a range of endogenous ANP measured in animals with heart failure. As was demonstrated in patients with severe congestive heart failure,4-6 we found in our experiment a marked diminution of the renal response to exogenous ANP in the dogs with heart failure, even at the highest infusion rates.

In healthy control animals infusions of ANP in the physiologic and pharmacologic range led to a small increase in renal plasma flow and considerable increase in glomerular filtration rate and filtration fraction in each dog. In dogs with congestive heart failure the increase of renal plasma flow was blunted, but increases in glomerular filtration rate and filtration fraction were observed that were somewhat smaller than in healthy control animals. The mechanism for the increase in glomerular filtration rate is not exactly known. Constriction of the efferent and dilatation of the afferent glomerular arterioles may lead to an elevation in hydraulic pressure together with an increase in glu-

merular capillary permeability and a relaxing effect on the glomerular mesangial cells.24, 25 The increase in glomerular filtration rate does, however, not fully account for the increased natriuresis and diuresis. Urinary excretion may be enhanced by a shift of blood flow toward the superficial and midcortical regions of the kidney26 and may be due to a specific inhibition of sodium reabsorption from the medullary collecting ducts.27-29

It has been reported that ANP produces a fall in renin secretion in animals and in man.6, 27 In our experiment we found a significant suppression of renin secretion in the control animals. Stopping the ANP infusion for 1 hr resulted in a significant stimulation of renin secretion, as expressed by a twofold increase in plasma levels in comparison with preinfusion values. A similar effect was reported in normal volunteers after a 4 hr infusion of synthetic ANP.30 There is recent evidence31, 32 that an increase in the sodium load delivered to the macula densa is not essential for the inhibition of renin secretion by ANP. The suppression of renin production may be mediated through renal vascular receptors and recep-

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tors in the macula densa for ANP. Renin may also be suppressed by a direct inhibitory action on the juxtaglomerular cells. As has been shown in patients with severe heart failure, we found no significant effect of ANP on plasma renin secretion when heart failure was induced in our experiment.

The marked diminution of hemodynamic and renal responses to exogenous ANP in dogs in heart failure suggests that this could contribute significantly to the pathogenesis of the disease because of the attenuation

FIGURES 6 to 9. For legend, see opposite page.
of counterregulating properties of ANP in relation to vasoconstrictor and fluid- and sodium-retaining systems such as the renin-angiotensin system, sympathetic nervous activity, and vasopressin, all of which stimulated in the presence of heart failure. Downregulation of binding sites for ANP in platelets of patients with congestive heart failure has been demonstrated. Similar effects have been shown in cultured vascular smooth muscle cells without a change in affinity of the ANP receptors after exposure with ANP. Renal glomerular ANP receptor density has been shown to be downregulated in rats after mineralocorticoid administration, causing a sustained increase of ANP secretion.

It was recently reported that bovine aortic smooth muscle cells and bovine adrenal cortex contain two subpopulations of ANP receptors. The predominant ANP receptor subpopulation was not coupled to c-GMP metabolism, while the second minor ANP receptor subpopulation was tightly coupled to the stimulation of particulate guanylate cyclase. c-GMP can be actively processed through the cell membrane, possibly by a process similar to that described for c-AMP. Since c-GMP increases in proportion to the stimulation of ANP receptors, the determination of c-GMP may allow conclusions about the ANP receptor regulation state. In our experiment we found no significant difference between the production of c-GMP, as measured by plasma levels in the pulmonary artery, during incremental infusion of the hormone in normal healthy dogs and that in dogs with congestive heart failure. In this context it is interesting that despite a normal stimulation of c-GMP by ANP, the physiologic responses of ANP were very much attenuated in dogs with heart failure. Hirata et al. recently demonstrated in cultured rat vascular smooth muscle cells that human ANP causes a marked reduction of ANP receptor number, but they also demonstrated that ANP was capable of stimulating intracellular c-GMP formation to the same extent in ANP-pretreated and control cells. This is in accordance with our findings. These results suggest that ANP receptors may be heterogenous and it may be speculated that the ANP binding sites coupled to guanylate cyclase are affected little by receptor downregulation after chronic exposure to increased endogenous levels of ANP, whereas the number of the ANP receptors not coupled to guanylate cyclase may be considerably reduced. There is preliminary evidence that the majority of specific renal binding sites for ANP are biologically ineffective and can be characterized as receptors noncoupled to guanylate cyclase. In this context the results of our experiment suggest a defect in the intracellular regulating mechanism, beyond the production of c-GMP, that causes a marked reduction in the biologic action of ANP.

Clinical implications. The decreased responsiveness of the vascular system and the complete absence of renal excretory effects in the presence of heart failure suggest that ANP may not be very important as a counterregulating system in the pathogenesis of chronic heart failure in relation to the importance of the stimulated renin-angiotensin system, sympathetic nervous activity, and vasopressin. The blunted renal effects may be one factor in the retention of sodium and water.

We can draw an analogy between results in our experimental preparation and findings reported in patients with severe congestive heart failure, in whom a similar attenuation of responses after exogenous ANP has been observed.

These results do not support the treatment of patients with ANP as long-term therapy for chronic heart failure. However, the hemodynamic effects may be beneficial in those with acute severe heart failure because the drug induces unloading of the heart by reducing preload and afterload. With respect to a possible new, more effective therapy for heart failure, it is important

FIGURES 6 to 9. Electron microscopic slides of cardiac myoendocrine cells from a dog heart after 14 days of ventricular pacing. 6, A nuclear region of a left atrial myoendocrine cell with a hypertrophic Golgi apparatus. In comparison with that in control dogs, the Golgi is strongly extended, exhibiting two perinuclear dictiosomes (G) with the cisternae and vesicles. Progranules (PG) and mature secretary granules (SG) as well as cisternae of the rough endoplasmic reticulum (RER) are also increased in number. Note further the nucleus (N), mitochondria (MI), myofibrils (MY), and some lysosomes (LY). Original magnification × 18,000. 7, Immunoelctron microscopic slide showing the localization of cardiac peptide (CDD-IR, cardioldilatin immunoactivity) that antibodies directed against CDD-99-126/a-hANP. The protein A immunogold method was used. The secretory granules (SG) are intensely labeled (5 to 10 particles per sectioned secretory granule) by the colloidal gold particles, but a few labels are also seen in the Golgi cisternae (arrows). Original magnification × 50,400. 8, A teleuomere, interfibrillar Golgi complex in the same cell as in 6 exhibits several progranules (PG) adjacent to the vesicles (V) and cisternae (CI). This type of Golgi complex (G) is rarely seen in control dogs, but develops frequently in cardiomyopathic dog atrial myoendocrine cells. Original magnification × 29,500. 9, Perinuclear zone of a left atrial myoendocrine cell from a cardiomyopathic dog. In this well-preserved cell, a strong proliferation of the rough endoplasmic reticulum (RER) is seen as a sign of intensely activated protein synthesis. Note further the cell nucleus (N), some normal mitochondria (MI), and a giant mitochondrion (gMI) and myofibrils (MY). Original magnification × 32,300.
to clarify the possible intracellular defect preventing the mediation of the hormonal signal into biological action in these patients.

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