Abstract. The physiologic and pathophysiologic importance of natriuretic peptides (NP) has been imperfectly defined. The diminished renal responses to exogenous atrial NP in heart failure have led to the perception that the endogenous NP system might be less effective and thus contribute to renal sodium retention in heart failure. This study tests the hypothesis that in experimental heart failure, the renal responses to an acute volume load are still dependent on the NP system. The specific antagonist HS-142-1 was used to block the effects of NP in a model of high-output heart failure induced by an aortocaval shunt. Plasma cGMP levels and renal cGMP excretion were significantly lower in shunted and sham-operated rats in comparison to control rats (15.2 vs. 27.5 μl/min, P < 0.001). After an acute volume load, the diuretic and natriuretic responses were attenuated by HS-142-1 in control and shunted rats. The renal responses were reduced by HS-142-1 to a significantly greater extent in shunted rats than in control rats. HS-142-1 did not induce any significant systemic hemodynamic changes in either group, nor did it alter renal blood flow. However, the GFR in HS-142-1-treated shunted rats was lower than that in vehicle-treated shunted rats, both at baseline (0.6 ± 0.3 ml/min versus 2.1 ± 0.4 ml/min with vehicle, P < 0.05) and after an acute volume load (1.2 ± 0.4 ml/min versus 2.6 ± 0.4 ml/min with vehicle, P = 0.01), whereas no such effect was observed in control rats. These data indicate that the maintenance of basal renal function and the responses to acute volume loading are dependent on the NP system. The NP seem to be of particular importance for the maintenance of GFR in this model of experimental heart failure. These observations provide new insights into the importance of the renal NP system in heart failure.
injection indicated that NP in heart failure do not act purely via a tubular mechanism but might be relevant in the regulation of GFR (27). In this study, we used an aortocaval shunt, an established model of high-output heart failure (28–31) that (depending on the shunt size) may induce activation of the renin-angiotensin system and is not associated with overt heart failure (14). We examined the contribution of the endogenous NP system to the maintenance of basal renal function and sodium homeostasis and analyzed the renal responses to acute volume load.

Materials and Methods

**Animals**

Male Wistar rats (230 to 250 g) from Moellegaard Animal Farms (Schoenwalde, Germany) were fed normal rat chow and were allowed free access to tap water. The animals were maintained on a 12-h light/dark cycle. All experiments were performed between 7 a.m. and noon. The study was approved by the local authorities and performed according to the Guiding Principles in the Care and Use of Animals, corresponding to American Physiological Society guidelines. Each group consisted of seven or eight animals.

**Shunt Operation**

The aortocaval shunt was introduced under ether anesthesia by a modification of the method developed by Garcia and Diebold (32). Briefly, a laparotomy was performed and the aorta was punctured, with a 1.2-mm (outside diameter) disposable needle (Braun Melsungen, Melsungen, Germany), distal to the renal arteries. The needle was advanced into the adjacent inferior vena cava. After the vessels had been temporarily clamped, the needle was withdrawn and the aortic puncture site was sealed with a drop of cyanoacrylate glue (Instant Krazy Glue; Borden Co., Willowdale, Ontario, Canada). The persistence of the shunt was verified by visual inspection (swelling of the vena cava and color changes resulting from mixture with arterial blood) and by o xo metry, at the end of the experiments. The perioperative mortality rate was <3%. Sham-operated control animals were treated identically, except that no puncture of the vessels was performed.

**Acute Volume Loading**

The study procedures were performed using chloral hydrate anesthesia (400 mg/kg), 30 d after shunt production. For measurements of urine flow rate and sodium and cGMP excretion rates, a PE50 catheter was inserted into the bladder and urine was collected. Sodium chloride (0.9%) was infused at a flow rate of 2 ml/h throughout the experiment. Surgery was followed by a 20-min stabilization period before baseline values were measured during the subsequent 40-min period (t1). Acute volume loading was then performed with 5 ml of sodium chloride (0.9%) infused in 5 min. Urine samples for this period (20 min, t2) were collected during the 5 min of infusion and the subsequent 15 min. The experiment was continued for two additional collection periods of 40 min each (t3 and t4).

**Inhibition of the NP System**

The NP antagonist HS-142-1 was kindly provided by Pharmaceutical Research Laboratories of Kyowa Hakko Kogyo Co. (Shizuoka, Japan) and was injected intravenously (10 mg/kg dissolved in 100 μl of 0.9% NaCl) after the stabilization period, before the first collection period (t1). The dose of 10 mg/kg was chosen on the basis of previous reports that indicated that lower doses (1 and 3 mg/kg) may not completely block the receptors (22,25), that a higher dose of 8 mg/kg induced additional effects (33), and that 5 and 10 mg/kg were effective in completely abolishing the renal effects of exogenous ANP, brain NP (BNP), and urodilatin (24). Preliminary studies in our laboratory showed that a dose of 10 mg/kg decreased plasma cGMP levels by approximately 80%, indicating complete inhibition of the ANP-dependent particulate guanylate cyclase. To compare the effects of HS-142-1 in normal controls and rats with heart failure, we analyzed the effects of the ANP antagonist in sham-operated and shunted rats. In two additional groups of shunted and sham-operated rats, isotonic NaCl (0.9%, 100 μl) was injected as vehicle.

**Determination of ANP, cGMP, and Angiotensin II Levels**

Blood samples for ANP and cGMP determinations (500 μl for ANP or 200 μl for cGMP) were withdrawn from the carotid artery, into Na-ethylenediaminetetra-acetic acid (EDTA)-preloaded (final concentration, 7 mM) and prechilled tubes, at the end of the baseline observation period (t1). Degradation of ANP was prevented with phenylmethylsulfonyl fluoride (final concentration, 10 μM) and pepstatin (3 μM). The blood was centrifuged at 4°C at 2000 × g for 10 min immediately after withdrawal, and the plasma was maintained at −80°C until extraction. Withdrawn blood was replaced with identical volumes of blood from donor animals (shunted or sham-operated rats, as appropriate). ANP plasma samples were extracted using C18 Sep-Pak columns, which had been equilibrated with acetonitrile and ammonium acetate (0.2%, pH 4.0). After plasma loading, the columns were washed with ammonium acetate and ANP was eluted with acetonitrile (60%)/ammonium acetate (40%), according to a previously described procedure (34). The recovery of ANP was approximately 82% and was taken into account when the ANP plasma values were calculated. Samples were then measured by RIA (34), which was performed with anti-ANP antibodies kindly provided by Dr. J. Gutkowska (Centre Hospitalier de l’Université de Montréal, Montreal, Canada). The inter- and intra-assay variations were <12% and <10%, respectively, with a working range between 5 and 1000 fmol/ml.

Before RIA determinations, plasma cGMP was extracted using alumina (AG7) and Dowex (AG 50W-X8) columns. The recovery of cGMP was approximately 32% and was taken into account when the cGMP plasma values were calculated. Urinary cGMP was determined directly using a specific RIA (35). Anti-cGMP antibodies were kindly donated by Dr. P. Hamet (Centre Hospitalier de l’Université de Montréal, Montreal, Canada). The inter- and intra-assay variations were both <15%, with a working range between 1 and 160 pmol/ml. Renal cGMP production was calculated as follows (26): Renal cGMP generation = (Urinary flow × Urinary cGMP concentration) − (GFR × Plasma cGMP concentration).

For angiotensin II measurements, blood was collected in prechilled Na-EDTA-loaded tubes (final concentration, 7 mM) at the end of the baseline period. o-Phenanthroline (final concentration, 1.25 mM; Merck, Darmstadt, Germany) was added and angiotensin II was measured by RIA (inter- and intra-assay variabilities, 11 and 15%, respectively; working range, 20 to 1000 fmol/ml), as described previously in detail (36,37).

**Hemodynamic Measurements**

A PE50 tubing catheter was inserted into the superior vena cava via the right jugular vein, for measurements of the central venous pressure. Arterial BP was measured by cannulating the right carotid artery. Both pressures were registered with a Statham P23XL transducer and
a Gould AMP 4600 amplifier. Heart rate was derived from the arterial BP signal.

**Measurement of GFR and Renal Blood Flow**

The right femoral artery was cannulated for infusion of 8% inulin and 1% para-aminohippurate in isotonic saline solution, at a rate of 2 ml/h, as described previously (38). Urine samples were analyzed by spectrophotometry for calculation of GFR and renal blood flow at the midpoint of the baseline period and 20 min after acute volume loading. Sodium excretion was measured by flame photometry.

**Statistical Analyses**

Differences between groups were evaluated with the t test, the Wilcoxon rank sum test, and the two-way ANOVA with a posteriori comparison (Bonferroni), as indicated in the figure legends. The significance level was set at \( P < 0.05 \). All data are expressed as mean ± SEM.

**Results**

**Effects of HS-142-1 on Urinary cGMP and Plasma cGMP, ANP, and Angiotensin II Levels**

At baseline, plasma cGMP levels were elevated twofold and plasma ANP levels were increased approximately sixfold in shunted rats, compared with sham-operated controls, as shown in Figure 1. Inhibition of the guanylate cyclase-coupled receptors by HS-142-1 decreased plasma cGMP concentrations by approximately 60% in both groups, confirming the effective inhibition of the NP receptors (Figure 1A). The urinary excretion of cGMP, which was higher in shunted rats than in control animals, was significantly lower in both groups after treatment with HS-142-1 (Figure 1B). The nephrogenous cGMP production was almost completely abolished with HS-142-1 (Figure 1B). A significant positive correlation existed between cGMP and sodium excretion in the control group \( (r^2 = 0.81, P < 0.01) \), whereas no such correlation was found in the shunted group \( (r^2 = 0.22, \text{NS}) \), indicating renal resistance to NP at a post-cGMP level in shunted rats.

As an indicator of the sustained efficacy of HS-142-1, cGMP excretion was determined in the late phase after HS-142-1 application (60 to 100 min). Urinary cGMP excretion after HS-142-1 treatment was decreased in sham-operated rats (vehicle, 45.2 ± 16.2 pmol/min; HS-142-1, 13.8 ± 2.7 pmol/min; \( P < 0.05 \)) and in shunted rats (vehicle, 78.4 ± 21.6 pmol/min; HS-142-1, 20.9 ± 10.5 pmol/min; \( P < 0.05 \)), indi-

![Graphs](image-url)

*Figure 1. Plasma cGMP concentrations (A), cGMP excretion (B), plasma atrial natriuretic peptide (ANP) concentrations (C), and plasma angiotensin II (ANG II) concentrations (D) for control and shunted rats, with either vehicle or HS-142-1 treatment, at baseline. The proportion of nephrogenous cGMP production is indicated by horizontal lines within the bars in B. Data are presented as means ± SEM \((n = 7 \text{ or } 8 \text{ in each group})\). The differences between the groups were evaluated with the t test. *\( P < 0.05 \), **\( P < 0.01 \), compared with vehicle-treated rats; *\( P < 0.05 \), compared with sham-operated rats.*
cating persistent blockade of the guanylate cyclase receptors throughout the study period.

ANP plasma concentrations were higher after HS-142-1 treatment in shunted rats (708 ± 104 versus 454 ± 97 pM with vehicle, \( P < 0.05 \)) (Figure 1C) and sham-operated rats (213 ± 35 versus 94 ± 25 pM with vehicle, \( P < 0.05 \)). Because NP are known to inhibit the renin-angiotensin system by decreasing the release of renin, we determined angiotensin II plasma concentrations (Figure 1D). Angiotensin II in the shunted group was increased after HS-142-1 treatment (733 ± 105 versus 395 ± 74 pM with vehicle, \( P < 0.05 \)), whereas no significant change was observed in the sham-operated group (565 ± 163 versus 316 ± 46 pM with vehicle).

Effects of HS-142-1 on Baseline Renal Function and Hemodynamics

Baseline urine flow rates were not significantly different between shunted and control rats, before HS-142-1 administration. However, rates were lower in the HS-142-1-treated sham-operated rats (15.2 ± 1.1 versus 27.5 ± 3.1 µl/min with vehicle, \( P < 0.001 \)) and in the HS-142-1-treated shunted rats (8.1 ± 1.3 versus 19.9 ± 2.3 µl/min with vehicle, \( P < 0.001 \)) (Figure 2A and B), compared with the respective vehicle-treated groups. For HS-142-1-treated rats, the sodium excretion rates for both groups were decreased to less than one-third of baseline values (t1) (Figure 3A and B). The values for the mean arterial BP are shown in Table 1 and indicate that baseline values were not different for shunted rats, compared with controls, and did not change with HS-142-1. Similarly, the renal blood flow was not different at baseline (7.1 ± 0.9 ml/min in shunted rats versus 9.6 ± 1.5 ml/min in controls) and remained unaffected by HS-142-1 in shunted and sham-operated control rats. Central venous pressure was elevated in shunted rats, compared with controls (3.7 ± 1.5 versus 1.7 ± 0.5 mmHg, \( P < 0.05 \)). HS-142-1 administration did not significantly affect the central venous pressures in either shunted rats (6.1 ± 0.6 mmHg) or controls (2.7 ± 0.9 mmHg).

Effects of HS-142-1 on Excretory Responses to Acute Volume Loading

The excretory responses to an acute volume load (5 ml of isotonic NaCl) for the different collection periods are shown in Figure 2A and B. The total diuretic response during 100 min after volume loading was 4343 ± 449 µl in control rats and 3036 ± 499 µl in shunted rats (\( P = 0.09 \)). In rats treated with HS-142-1, the diuretic response was attenuated to 2512 ± 241 µl (\( P < 0.01 \)) in controls and to 1240 ± 170 µl (\( P < 0.05 \)) in shunted rats. The reduction in urine flow rate was highly significant at each collection period in both groups. The attenuation of the diuretic response to volume loading (at t3 and t4) by HS-142-1 was significantly more pronounced in shunted rats than in controls. The urine flow rate that persisted after HS-142-1 administration was 37 ± 9% of that of vehicle-treated rats for rats with aortocaval shunts and 68 ± 6% for sham-operated controls (t4, \( P < 0.001 \)) (Figure 2C).

The sodium excretion rate after an acute volume load was significantly increased in vehicle-treated control rats (807 ± 94 µl/min) versus 454 ± 97 pM with vehicle) compared with control rats (94 ± 25 pM with vehicle, \( P < 0.05 \)). The responses to acute volume loading were compared using two-way ANOVA with \( a posteriori \) comparison (Bonferroni). \( *P < 0.05, **P < 0.01, ***P < 0.001 \), compared with vehicle treatment. (C) Urine flow rates after HS-142-1 (HS) (expressed as percentages of rates for vehicle-treated rats) for shunted and control rats. Differences in urine flow rates were evaluated with the Wilcoxon rank-sum test. \( **P < 0.01, ***P < 0.001 \), compared with control. Data are presented as means ± SEM (n = 7 or 8 in each group).
184 to 1855 nmol/min, \( P < 0.01 \), as well as in shunted rats (395 ± 110 to 691 ± 168 nmol/min, \( P < 0.05 \)). After HS-142-1 treatment, the natriuretic responses to an acute volume load were significantly less in both groups, as shown in detail in Figure 3, A and B. The inhibitory effects of the NP antagonist are compared between the two groups in Figure 3C. The attenuation of the natriuretic responses induced by HS-142-1 was similar in the two groups immediately after volume loading, as was the absolute decrease later after volume expansion. However, after 20 to 100 min, the relative inhibition of natriuresis with HS-142-1 was more pronounced in shunted rats (13 ± 4% of the value for vehicle-treated rats) than in controls (64 ± 13% of the value for vehicle-treated rats, \( P < 0.001 \)).

Effects of HS-142-1 on GFR

Because NP have effects on glomerular hemodynamics as well as on sodium transport, we studied the effect of HS-142-1 on GFR in shunted and control rats. Whereas no significant effect of HS-142-1 was observed in control rats (Figure 4A), the GFR in shunted rats was dramatically lower at baseline in the HS-142-1-treated group than in the vehicle-treated group (0.6 ± 0.3 versus 2.1 ± 0.2 ml/min, \( P < 0.05 \)). After an acute volume load, the GFR was only 1.2 ± 0.4 ml/min in rats receiving HS-142-1, compared with 2.6 ± 0.4 ml/min in vehicle-treated shunted rats (\( P = 0.01 \)) (Figure 4B). Therefore, the GFR appears to be dependent on NP only in the shunted group. Interestingly, after HS-142-1, there was a nonsignificant tendency toward an increase in GFR in shunted rats after volume expansion (0.6 ± 0.3 to 1.2 ± 0.4 ml/min, \( P = 0.07 \)), whereas there was no such tendency in control rats. Similar to the analysis of urine flow and sodium excretion, we calculated the relative GFR after administration of HS-142-1 (Figure 4C). The relative GFR that remained after HS-142-1 treatment was 67.3 ± 20.2% in control rats, in contrast to 29.0 ± 6.5% in shunted rats.

Discussion

These experiments demonstrated that the blockade of NP receptors with the specific antagonist HS-142-1 decreased basal renal function and greatly impaired the renal responses to an acute volume load in normal rats. In rats with heart failure, the impairment of the renal responses was more dramatic.
These findings indicate that the endogenous NP play a vital role in the maintenance of GFR in heart failure and that the renal responses to an acute volume load remain highly dependent on NP. The effects of HS-142-1 after an acute volume load were significantly more pronounced in aortocaval shunt-treated rats than in controls. Using this maneuver to stress the NP system, we have been able to show clearly that the contribution of endogenous NP to sodium and water homeostasis is increased in heart failure. Consequently, our observations support the notion that renal function in heart failure is highly dependent on the activity of endogenous NP, which contrasts with previous reports discussing a minor contribution of the NP system in fluid and electrolyte homeostasis in heart failure (reviewed in references (4, 6, and 39)).

Diuresis and natriuresis were significantly decreased in response to blockade of the guanylate cyclase-coupled NP receptors in sham-operated control rats. Renal blood flow and GFR, however, were unaffected. Depending on the experimental conditions, ANP is known to modify renal hemodynamics, tubular reabsorption of sodium, and GFR (reviewed in references (4 and 6)). Only high doses of exogenous ANP seem to increase the GFR, whereas low-dose infusions exert their renal effects apparently by selectively influencing tubular reabsorption (4). In our study, the NP antagonist had no effect on GFR in control rats under basal conditions, suggesting that the decreased diuresis and natriuresis in control rats were the result of altered tubular sodium reabsorption.

Previous reports on the effects of HS-142-1 on renal function under resting baseline conditions are contradictory. An earlier study of Stevens et al. (26) showed that intrarenal infusion of HS-142-1 decreased the urine flow rate and sodium excretion rate, supporting a functional role for endogenous ANP in the regulation of basal sodium excretion. However, NP antagonists have also been reported to have little effect on basal diuresis and natriuresis (25, 27, 40–42). Such differences may be the result of species variability (dog versus rat) and different drug dosages, as well as differences in the degree of existing NP system stimulation, e.g., euvolemic versus hydropenic conditions (43). In a previous study using 20 mg/kg HS-142-1, no decrease in sodium excretion was observed in control animals (27), which might be explained by the different continuous-infusion rate (1.2 ml/h NaCl versus 2.0 ml/h in our study). A higher infusion rate, as in our study, might have induced some stimulation of the endogenous NP system. Only high concentrations of HS-142-1 (at least 3 mg/kg) seem to be successful in completely inhibiting activation of the NP receptors (27, 42). Lower concentrations may not completely block the NP system, which could explain the failure to observe an influence of HS-142-1 on basal renal function in some studies (21, 44). The dose used in this study was 10 mg/kg, which decreased the plasma concentrations and the urinary excretion of the second messenger cGMP to approximately one-third of previous levels. Before the development of HS-142-1, antibodies against ANP were used to investigate the contribution of NP to hemodynamic and volume homeostasis. As in our study, no changes in hemodynamics were observed under physiologic conditions (45). Only antibodies against ANP were used, and
the effects of other NP were not considered. HS-142-1 is known to block the effects of BNP, C-type NP, and urodilatin as well (24,46). BNP has been shown to be secreted in increased amounts in chronic heart failure (where it exerts beneficial effects) and seems useful for risk stratification for patients with heart failure (47). Therefore, the observed effects of HS-142-1 may be attributed not only to ANP but also to the other NP. The clear and significant renal responses to HS-142-1 that we observed in normal rats indicate that the NP system is essential for the maintenance of renal excretory function, although possible effects of the experimental design, anesthesia, and surgical stress on the renal responses to the NP antagonist cannot be excluded.

The renal response to an acute volume load in normal rats was reported to be diminished after application of antibodies against ANP (48). Infusion of HS-142-1 (3 mg/kg) was reported to reduce diuresis and natriuresis as well as cGMP excretion after massive acute volume expansion in barbiturate-anesthetized rats (41). In agreement with these earlier reports on volume expansion in control rats, we observed nearly complete abolition of the renal excretory response to an acute volume load using a higher dose (10 mg/kg) of HS-142-1.

The main focus of this work was to investigate the importance of NP in heart failure. The diminished efficacy of exogenous ANP and impaired water and sodium handling in heart failure have led to the misperception that the NP system is of less importance in heart failure. Resistance to exogenous ANP in experimental heart failure, decreased cGMP production after ANP infusion, and blunted responses to endopeptidase inhibition have been reported by our group and others (14,19). However, our present findings suggest that the role of the NP system is much more important than previously recognized. We observed that water and sodium excretion in control and shunted rats depended on endogenous NP and that blockade of the NP system evoked major effects in both groups under baseline conditions. These observations indicate that the contribution of NP to the maintenance of basal renal excretory function is not decreased in experimental heart failure. These results are in agreement with previous reports on heart failure secondary to myocardial infarction, which suggested that the basal urine flow and sodium excretion rate were to some extent dependent on the NP system (27,42). In a model of pacing-induced heart failure, Burnett and coworkers could demonstrate a significant role for the endogenous NP system in renal function (40,49) and in left ventricular relaxation and coronary flow (50). In our study, the decrease of the natriuretic and diuretic responses to an acute volume load by NP receptor blockade was significantly more pronounced in rats with heart failure than in control rats, suggesting that the relative contribution of NP to the regulation of sodium and volume homeostasis is enhanced.

NP are known to inhibit the renin-angiotensin system via inhibition of renin and aldosterone synthesis and secretion (reviewed in reference (51)). We observed increased angiotensin II plasma levels in shunted rats after administration of HS-142-1, suggesting that the effect of NP might be partially mediated by inhibition of the renin-angiotensin system.

To the best of our knowledge, this study is the first assessing the effects of HS-142-1 in rats with high-output heart failure. No other study has included assessment of the renal responses to acute volume loading with HS-142-1. The GFR was reduced by HS-142-1 only in shunted rats. Although no data on the metabolism of HS-142-1 are currently available, it is conceivable that the lower GFR might have induced higher HS-142-1 levels in shunted rats. Our findings indicate that NP are important in sustaining the GFR in experimental high-output heart failure, and they shed new light on the role of endogenous NP in heart failure.

An unexpected and important observation was the increase in plasma ANP levels after NP receptor blockade in control as well as shunted rats. In severe heart failure, NP inhibition has been reported to increase ANP plasma concentrations, in contrast to observations in controls; however, only a small number of animals (n = 4) were studied (52). Although it was not the aim of this study, our observations suggest that an effect of cardiac NP receptors on ANP synthesis or release may exist. An autoregulatory ANP release mechanism was recently suggested in an in vitro study using atrial myocytes (53). It is possible that stimulation of cardiac NP receptors could inhibit cardiac ANP synthesis; inhibition of these receptors could then lead to enhanced ANP synthesis or release.

In summary, this study demonstrated that blockade of the NP system induced diminished renal excretory function in control rats and rats with experimental heart failure. Moreover, blockade of NP receptors reduced the GFR only in rats with heart failure and produced a greater effect on renal function after an acute volume load in rats with experimental heart failure, compared with control animals. These data suggest a functional role for the NP system in the maintenance of GFR and the regulation of volume homeostasis, which appears to be of greater importance in heart failure than under physiologic conditions.

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