Differential regulation of cardiac ANP and BNP mRNA in different stages of experimental heart failure

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The natriuretic peptides are a family of three genetically distinct peptide hormones: atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), and C-type natriuretic peptide (CNP). CNP is synthesized in high concentrations in the brain (34) and endothelium (35), and only minor amounts can be detected in atria or ventricles (38). Even though BNP was first described in the mammalian brain (33), ANP and BNP are mainly synthesized in the heart. Under physiological conditions, ANP is synthesized in the atria (11), whereas BNP is produced by atrial and ventricular cardiomyocytes (24, 42). The BNP mRNA expression is more than twofold higher in atria than in ventricles, but the BNP production in the ventricles is considered more important for the contribution to BNP plasma concentrations due to the larger mass of the ventricles (26).

The main actions of ANP and BNP include natriuresis, diuresis, and inhibition of the renin-angiotensin-aldosterone system (6, 26). In heart failure, plasma concentrations of ANP and BNP are elevated (39). Both peptides become important to counteract the water and sodium retention and to decrease the peripheral vasoconstriction, which are induced in heart failure by an activated renin-angiotensin-aldosterone system and by vasopressin (5). When plasma concentrations were compared, BNP had been shown to be increased earlier than ANP in states of acute severe heart failure, giving rise to the concept of BNP as an emergency hormone (16, 21).

In a genetic model of hypertension in the rat (3), in chronic volume overloaded rats (13, 23), in cardiomyopathic hamsters (12), in pacing-induced canine heart failure (30), and in autopsy samples of patients with congestive heart failure (32), the ventricles are recruited to synthesize ANP and contribute to the elevated ANP plasma concentrations. Compared with ANP, plasma concentrations of BNP were shown to be a better marker for impaired left ventricular function (22) and to be of higher prognostic value in heart failure (29, 41).

Previous studies demonstrated that cardiac BNP mRNA was induced in heart failure. In pacing-induced canine heart failure, cardiac BNP mRNA expression was enhanced, but ANP mRNA was not measured in that study (24). In terminal human heart failure, BNP and ANP mRNA in cardiac tissue from explanted hearts were elevated in parallel (36). These results suggested an increased cardiac BNP synthesis in severe heart failure. To the best of our knowledge, no studies have been performed so far to compare the induction of ANP and BNP mRNA in both ventricles during the transition from compensated to overt heart failure. It is still unclear whether the ventricular recruitment of BNP is specific for overt heart failure and whether ANP mRNA is induced in early stages and...
in compensated heart failure when BNP mRNA is still unchanged. To test the hypothesis that cardiac BNP mRNA expression is specifically induced only in severe heart failure, we analyzed atrial and ventricular ANP and BNP mRNA expression in different stages and degrees of experimental heart failure.

**MATERIALS AND METHODS**

**Animals.** Male Wistar rats (230–250 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 12:12-h light-dark cycle. All experiments were performed between 0700 and noon. The studies were approved by the local authorities and were performed according to the Guiding Principles in the Care and Use of Animals corresponding to American Physiological Society guidelines. Experiments were performed with 10–12 animals in each group.

**Shunt operation.** The aortocaval shunt was induced under ether anesthesia by a modification of the method developed by Garcia and Diebold (15). Briefly, a laparotomy was performed, and the aorta was incised distal to the renal arteries with a 1.2-mm (outside diameter) disposable needle (Braun Melsungen, Melsungen, Germany) for the small shunt and with a 1.8-mm disposable needle for the large shunt. The needle was advanced in the adjacent inferior vena cava. After the aorta had been temporarily clamped, the needle was withdrawn, and the puncture site was sealed with cyanoacrylate glue (Instant Krazy Glue; Borden, Willowdale, Ontario, Canada). The presence of the shunt was verified visually by swelling of the vena cava. The perioperative mortality was <3% in the small-shunt group and <5% in the large-shunt group. In sham-operated control rats, a laparotomy was performed, the vessels were dissected free of the surrounding tissue, but no puncture of the vessels was performed.

**Hemodynamic measurements.** Thirty days after induction of either small or large shunt or sham operation and 3 days after induction of large shunt or sham operation, a PE-50 tubing catheter was inserted in the right carotid artery under chloral hydrate anesthesia (400 mg/kg sc) for measurement of the mean arterial pressure (MAP). The catheter was then advanced to the left ventricle for measurement of end-diastolic pressure (LVEDP). Central venous pressure (CVP) was measured by cannulating the right atrium via the right jugular vein. All pressures were registered with a Statham transducer (P23XL) and a Gould AMP 4600 amplifier. Left ventricular contractility was obtained from the left ventricular pressure curves, which were converted with a Gould differentiator (G4615). Heart rate was derived from the arterial blood pressure signal.

**Determination of ANP and BNP plasma concentrations.** Blood samples for ANP and BNP determinations were withdrawn from the aorta in Na- and EDTA-preloaded tubes. The blood was centrifuged at 4°C at 2,000 g for 10 min immediately after withdrawal, and the plasma was stored at −80°C until extraction. ANP and BNP plasma samples were extracted using C18 Sep-Pak columns that 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 and BNP were eluted with acetonitrile (60%)-ammonium acetate (40%), following a previously described procedure (17). The recovery for both peptides was ~80% and was taken into account when the plasma values were calculated. Samples were then measured by RIA (17), which was performed with ANP antibodies kindly provided by Dr. J. Gutkowski (Montreal, Canada). BNP plasma concentrations were measured with a commercially available kit (Peninsula, Paesel und Lorei, Hanau, Germany).

**RNA analysis.** Under chloral hydrate anesthesia (400 mg/kg sc), the entire heart was rapidly removed, rinsed in RNase-free NaCl (0.9%, 4°C), and weighed. The atria were dissected from the ventricles. To not contaminate ventricular tissue with atrial tissue and vice versa, special care was taken, and the ventricular tissue was separated distinctly from the atria. The remaining tissue (including the valvular areas and the septum) was discarded. The tissue parts were weighed and rapidly frozen in liquid nitrogen and were stored at −80°C until RNA extraction. RNA was isolated according to the method described by Chomczynski and Sacchi (9). In brief, tissues were homogenized in guanidinium thiocyanate solution (pH 7.4) and extracted by addition of phenol/chloroform. RNA from the aqueous phase was precipitated by addition of 1/10 vol of 4.0 M sodium acetate (pH 5.2) and 2.5 vol of ethanol. After centrifugation, the pellet obtained was dissolved in 30 µl of diethyl pyrocarbonate-treated water. The concentration of isolated RNA was determined spectrophotometrically at 260 nm. The RNA was ethanol precipitated on a 1.2% agarose gel for subsequent Northern blotting or was directly transferred in the slot-blot apparatus for blotting on a nylon membrane (Hybond N+ Nucleic Acid Transfer Membrane; Amersham). The cDNA probes for ANP, BNP, and glyceraldehyde-3-phosphate dehydrogenase (GAPDH) were synthesized by PCR with specific primer pairs (ANP: Ar-CTGCTTAGACCACTTTGGAGGA/Br-CCAGAGGGTATCCACCACC; BNP: Ar-CACCTCTGCAAGTTCGTATCCTGCAAGGA/Br-CTGTTCCAGAGCTGGGAAAGAGAG; GAPDH: Ar-CATGGGAAAGGCTGGGG/Br-CAGAATGGTACAGTAG-ACC; Biometra, Göttingen, Germany) and were labeled with digoxigenin using the DIG DNA Labeling and Detection Kit (Boehringer-Mannheim). After hybridization for 20 h at 42°C with the specific probes, the mRNA was detected by chemiluminescence and exposure to an X-ray film. To control for the amount of RNA loaded on the gels and the slot-blot apparatus, all membranes were rehybridized with the GAPDH probe. All results were normalized to the GAPDH mRNA expression. One RNA sample of each tissue (left and right atria and ventricles) of each animal was measured.

**Statistical analysis.** Differences between the groups were evaluated with the ANOVA and post hoc analysis (Fisher). The significance level was set at P < 0.05. All data are expressed as means ± SE.

**RESULTS**

Heart and lung weights and hemodynamic characterization of rats with aortocaval shunt. Total and relative heart weights, as well as the weights of all four heart chambers, were elevated in rats with small shunt and increased further in rats with a large shunt of 30 days duration (Table 1). The lung weights were unchanged in animals with small shunt and increased by ~60% in rats 30 days after large shunt, indicating pulmonary congestion. The MAP was decreased in rats with small or large aortocaval shunt.

To characterize more precisely the degree of heart failure in the models used, CVP, LVEDP, and contractility were measured. CVP was elevated in rats with small shunt (Fig. 1A) and after 3 days of large shunt and was increased further in rats after 30 days of large shunt. Although the CVP indicates the increased venous blood flow due to the shunt-induced volume
Table 1. Heart and lung weights and hemodynamic parameters

<table>
<thead>
<tr>
<th></th>
<th>Control 3 Days</th>
<th>Control 30 Days</th>
<th>Small Shunt 3 Days</th>
<th>Small Shunt 30 Days</th>
<th>Large Shunt 3 Days</th>
<th>Large Shunt 30 Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight, g</td>
<td>236 ± 4</td>
<td>312 ± 9</td>
<td>313 ± 6</td>
<td>227 ± 4</td>
<td>312 ± 18</td>
<td></td>
</tr>
<tr>
<td>Heart weight, mg</td>
<td>822 ± 27</td>
<td>1,079 ± 35</td>
<td>1,496 ± 45*</td>
<td>1,002 ± 31*</td>
<td>2,111 ± 100*†</td>
<td></td>
</tr>
<tr>
<td>Relative heart weight, mg/g</td>
<td>3.5 ± 0.1</td>
<td>3.5 ± 0.1</td>
<td>4.9 ± 0.1*</td>
<td>4.5 ± 0.1*</td>
<td>6.6 ± 0.3*‡</td>
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<tr>
<td>Right atrium, mg</td>
<td>32 ± 3</td>
<td>38 ± 3</td>
<td>73 ± 7*</td>
<td>59 ± 6*</td>
<td>118 ± 11*‡</td>
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<tr>
<td>Left atrium, mg</td>
<td>26 ± 2</td>
<td>31 ± 3</td>
<td>51 ± 3*</td>
<td>43 ± 3*</td>
<td>80 ± 6*‡</td>
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<tr>
<td>Left ventricle, mg</td>
<td>134 ± 8</td>
<td>170 ± 9</td>
<td>246 ± 8*</td>
<td>170 ± 5*</td>
<td>379 ± 29*‡</td>
<td></td>
</tr>
<tr>
<td>Right ventricle, mg</td>
<td>442 ± 11</td>
<td>520 ± 22</td>
<td>708 ± 24*</td>
<td>494 ± 16†</td>
<td>931 ± 35*‡</td>
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<tr>
<td>Lung, mg</td>
<td>1,151 ± 45</td>
<td>1,330 ± 48</td>
<td>1,466 ± 32</td>
<td>1,353 ± 77†</td>
<td>2,113 ± 197*‡</td>
<td></td>
</tr>
<tr>
<td>Heart rate, min⁻¹</td>
<td>442 ± 7</td>
<td>428 ± 9</td>
<td>457 ± 9</td>
<td>431 ± 8</td>
<td>485 ± 27*</td>
<td></td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>83 ± 3</td>
<td>108 ± 2</td>
<td>89 ± 1*</td>
<td>60 ± 3*</td>
<td>74 ± 1*‡</td>
<td></td>
</tr>
<tr>
<td>dP/dt_{max}, 10⁻² mmHg/s</td>
<td>4.8 ± 0.2</td>
<td>5.0 ± 0.2</td>
<td>5.3 ± 0.5</td>
<td>4.2 ± 0.3</td>
<td>3.8 ± 0.2‡</td>
<td></td>
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</tbody>
</table>

Data are means ± SE. Heart and lung weights and hemodynamic parameters are shown for controls and rats with small and large shunt. MAP, mean arterial pressure; dP/dt_{max}, left ventricular contractility. *P < 0.01 and †P < 0.05 vs. corresponding control; ‡P < 0.01 and §P < 0.05 vs. small shunt.

overload, the LVEDP and contractility are considered to be more specific markers of heart failure. LVEDP was not significantly different in rats with either small shunt or 3 days of large shunt, whereas it increased after 30 days of large shunt (Fig. 1B). Cardiac contractility was unchanged in rats with small shunt and after 3 days of large shunt and decreased in rats with large shunt (Table 1).

ANP and BNP plasma concentrations. ANP plasma concentrations were elevated approximately threefold in rats with small shunt compared with controls and increased further in rats with large shunt (Table 2). Similarly, BNP plasma concentrations were elevated in animals with small shunt and were significantly higher in rats with large shunts compared with controls and rats with small shunt.

Ventricular ANP and BNP mRNA expression. Figure 2 shows a typical Northern blot (using a slot-blot apparatus) of three samples of three left ventricles of either controls or rats with small or large shunt, which were hybridized with either ANP (Fig. 2A) or BNP probes (Fig. 2B). Left ventricular ANP mRNA expression was induced approximately fivefold in rats with small shunt (Fig. 3A) and in rats after 3 days of large shunt. The elevation of left ventricular ANP mRNA in rats after 30 days of large shunt did not exceed the levels observed after 30 days of small shunt. In contrast to ANP mRNA, the left ventricular BNP mRNA expression was unchanged in rats with small shunt and after 3 days of large shunt, whereas it increased significantly in rats after 30 days of large shunt (Fig. 3B).

Right ventricular ANP mRNA expression was increased in rats with small shunt (Table 3), and no further elevation was measured in rats with large shunt. The right ventricular BNP mRNA expression in rats with small shunt was not significantly different from controls and increased significantly only in rats with large shunt, indicating a similar pattern of BNP induction in both ventricles.

Recently, GAPDH has been disputed as a constant housekeeping gene, and a possible upregulation in some disease states has been proposed (44). We did not find any significant changes in GAPDH expression between any of the shunt groups and the sham-operated controls. When we calculated the ANP mRNA expression without normalizing to GAPDH, the expression was 355 ± 18% of controls (small shunt, P ≤ 0.001), 334 ± 46% of controls (large shunt/3 days, P ≤ 0.001), and 361 ± 38% of control (large shunt/30 days, P ≤ 0.001). Similar to the data obtained when mRNA expression was normalized to GAPDH, BNP mRNA expression was induced only in the large-shunt/30 days model (285 ± 47%, P ≤ 0.01 vs. control and vs. small shunt).

Atrial ANP and BNP mRNA expression. Left atrial ANP mRNA expression was increased in rats with small shunt and increased further in rats with large shunt (Table 3). In the right atrium, ANP mRNA was not specifically induced in any shunt model. BNP mRNA expression in both atria was unchanged in the small-shunt model and was enhanced only in rats with large shunt (Table 3).

DISCUSSION

This study was designed to test the hypothesis that the cardiac BNP gene expression is specifically induced only in states of severe heart failure. Therefore, we analyzed cardiac mRNA at different time points and in different degrees of heart failure. In both ventricles and atria, a specific BNP mRNA induction occurred only in the large-shunt model after 30 days (when cardiac hypertrophy was further increased and pulmonary congestion, elevated end-diastolic pressures, and decreased cardiac contractility were present), indicating overt heart failure. These data suggest that the cardiac BNP mRNA induction is specifically induced in severe heart failure. In contrast, the cardiac ANP mRNA expression is less dependent on the severity of heart failure and is already induced in compensated heart failure, when hypertrophy occurred, but LVEDP was still normal.

Heart failure was created by an infrarenal aortocaval shunt, an established model of volume overload-induced heart failure (14, 20). The use of two different shunt sizes allowed the creation of either compensated...
or overt heart failure. In addition, the large-shunt model was analyzed 3 days after shunt induction, when no overt heart failure was present. Hemodynamic characterization showed only a slight increase in CVP and no increase in LVEDP in the small-shunt model and after 3 days of large shunt. In contrast, the large-shunt model after 30 days demonstrated the typical characteristics of overt heart failure, such as decreased cardiac contractility, elevated LVEDP, and an increased lung weight as an indicator of pulmonary congestion. The large-shunt model after 30 days demonstrated a significantly higher degree of cardiac hypertrophy compared with the small-shunt model or the large shunt after 3 days. Thus our model does not rule out the possibility that a severe degree of cardiac hypertrophy might have been induced by the molecular changes observed.

It has previously been shown that ventricular ANP mRNA was increased in heart failure (23, 32, 40). Ventricular BNP mRNA expression after severe pressure overload was induced faster than ANP mRNA (1). Similarly, after an acute massive myocardial stress induced by experimental myocardial infarction, BNP mRNA was induced within a few hours and was faster than ANP mRNA (18). The fact that BNP mRNA is upregulated very early in response to an adequate stimulus might be due to either two different mechanisms and two peaks of BNP mRNA induction. Alternatively, and supported by our data, BNP mRNA induction might require a stronger stimulus than necessary for induction of the ANP mRNA expression.

When plasma concentrations were compared, BNP has been shown to be induced earlier than ANP in states of acute, severe heart failure, giving rise to the concept of BNP as an emergency hormone (16, 21). Our data demonstrate a dissociation between increased BNP plasma concentrations and unchanged ventricular BNP mRNA expression in the compensated heart.

Table 2. ANP and BNP plasma concentrations

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<th>Control 30 Days</th>
<th>Small Shunt 30 Days</th>
<th>Large Shunt 30 Days</th>
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</thead>
<tbody>
<tr>
<td>ANP, pM</td>
<td>117.9 ± 31.0</td>
<td>346.3 ± 62.3*</td>
<td>932.3 ± 106.3*†</td>
</tr>
<tr>
<td>BNP, pM</td>
<td>6.3 ± 0.5</td>
<td>28.9 ± 2.6*</td>
<td>49.7 ± 7.5*§</td>
</tr>
</tbody>
</table>

Data are means ± SE. ANP, atrial natriuretic peptide; BNP, brain natriuretic peptide. ANP and BNP plasma concentrations are shown for controls and rats with small and large shunt. *P < 0.01 vs. control, †P < 0.01 vs. small shunt, §P < 0.05 vs. small shunt.
failure models. It was recently reported that α-adrenergic stimulation of cardiomyocytes increased the half-life of BNP mRNA up to fivefold via activation of mitogen-activated protein kinase and protein kinase C (19). Although not investigated in this study, an increased BNP mRNA stability in cardiomyocytes might have led to increased BNP plasma concentrations in the small-shunt model without enhancing the transcription rate. A different translation rate could be an alternate explanation for the observed discrepancy between increased BNP plasma concentrations and unaffected mRNA expression.

In this study, we compared the mRNA expression of both peptides in different degrees of heart failure. In compensated heart failure, either induced by a small aortocaval shunt or by a large shunt with only 3 days duration, left and right ventricular ANP mRNA expressions were elevated, indicating that already a slightly impaired ventricular function was a powerful stimulus for ANP mRNA induction. In overt heart failure, no further induction of ANP mRNA occurred. Although it was not the aim of this study to investigate the reason for the lack of further induction of ventricular ANP mRNA, our data are compatible with an autoregulatory negative feedback mechanism of ANP on its own gene expression, similarly to an autoregulatory mechanism that has been described for the regulation of ANP release (27).

In contrast to ANP, left and right ventricular BNP mRNA expression was not induced in compensated heart failure, indicating that stronger stimuli, like elevated end-diastolic pressure or enhanced ventricular wall stress, might be required. In overt heart failure, ventricular BNP mRNA was significantly increased, suggesting a different regulation of ventricular BNP mRNA in severe heart failure. These data are in agreement with a previous study in pacing-induced heart failure describing no change in left ventricular BNP mRNA in early left ventricular dysfunction and an increase in overt heart failure (24). No ANP mRNA was measured in that report. Therefore, to the best of our knowledge, this is the first report describing the specific induction of ventricular BNP, in contrast to ANP, in severe heart failure.

Even though the specific induction of cardiac BNP mRNA during the transition from compensated to overt heart failure has not been compared previously with the induction of cardiac ANP mRNA, our results are in agreement with reports on the regulation of plasma concentrations of ANP and BNP. Previous reports described ANP and BNP plasma concentrations as a useful marker of impaired ventricular function (37, 41). BNP plasma concentrations have been suggested as an indicator of poor prognosis after myocardial infarction (4, 29, 31), but the prognostic usefulness remains to be

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**Table 3.** Right ventricular and atrial ANP and BNP mRNA expression

<table>
<thead>
<tr>
<th></th>
<th>Control 30 Days</th>
<th>Small Shunt 30 Days</th>
<th>Large Shunt 30 Days</th>
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<tbody>
<tr>
<td>Right ventricle, AU</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ANP/GAPDH mRNA</td>
<td>0.5 ± 0.1</td>
<td>0.8 ± 0.1†</td>
<td>0.9 ± 0.1†</td>
</tr>
<tr>
<td>BNP/GAPDH mRNA</td>
<td>0.5 ± 0.1</td>
<td>0.9 ± 0.2</td>
<td>1.2 ± 0.1*</td>
</tr>
<tr>
<td>Left atrium, AU</td>
<td></td>
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</tr>
<tr>
<td>ANP/GAPDH mRNA</td>
<td>1.6 ± 0.2</td>
<td>3.3 ± 0.2*</td>
<td>4.3 ± 0.3§</td>
</tr>
<tr>
<td>BNP/GAPDH mRNA</td>
<td>2.4 ± 0.2</td>
<td>2.6 ± 0.2</td>
<td>3.3 ± 0.3‡</td>
</tr>
<tr>
<td>Right atrium, AU</td>
<td></td>
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</tr>
<tr>
<td>ANP/GAPDH mRNA</td>
<td>1.9 ± 0.2</td>
<td>2.6 ± 0.3</td>
<td>1.9 ± 0.2</td>
</tr>
<tr>
<td>BNP/GAPDH mRNA</td>
<td>2.1 ± 0.4</td>
<td>2.8 ± 0.4</td>
<td>4.0 ± 0.5†</td>
</tr>
</tbody>
</table>

Data are means ± SE. GAPDH, glyceraldehyde-3-phosphate dehydrogenase. Right ventricular and atrial ANP and BNP mRNA expression (normalized to GAPDH mRNA) are shown for controls and rats with small and large shunt 30 days after surgery in arbitrary units (AU). *P < 0.01 and †P < 0.05 vs. control; §P < 0.05 vs. small shunt.
heart failure. These results suggest that cardiac BNP mRNA expression was elevated specifically in overt heart failure, whereas ANP was proposed to be more specifically released in response to atrial overload (43). The specific cardiac recruitment of BNP in overt heart failure, which is described in the present study, might contribute to the superiority of BNP plasma concentrations as a prognostic and diagnostic marker in heart failure compared with ANP.

In vitro studies in neonatal ventricular cardiomyocytes indicated that ANP and BNP gene expressions are regulated by distinct mechanisms (28). In studies with isolated hearts, the induction of BNP mRNA was faster (28), responded more to stretch (25), and was inducible to a greater degree after stimulation with endothelin (8) compared with ANP. In the present study, ventricular BNP expression was selectively induced in overt heart failure, indicating that a stronger stimulus was required for induction of BNP mRNA than for ANP mRNA. Ventricular stretch or excessive hypertrophy might be a possible candidate for the specific induction of BNP mRNA in overt heart failure animals. Other regulatory mechanisms, like neurohormonal interactions (endothelin, angiotensin II) or local hypoxia due to diminished coronary flow, are alternative mechanisms for the induction of cardiac BNP mRNA in overt heart failure. Previous reports proposed the role of BNP as a fast, emergency hormone because of its rapid activation compared with ANP (18). The present study demonstrates that cardiac BNP mRNA was induced only in overt heart failure, suggesting a possible protective function of BNP in severe heart failure. Although not tested in this study, the ventricular synthesis of BNP might be a late compensatory mechanism in severe cardiac failure, and its biological effects might delay further decompensation. The biological profile of BNP with its natriuretic and vasodilating properties is compatible with the idea that the observed cardiac BNP gene expression might be a consequence rather than the cause of severe heart failure. However, BNP mRNA induction and elevation of BNP plasma concentrations did not successfully lead to an improvement of severe heart failure, nor did it prevent its occurrence. Therefore, BNP might not be an efficient compensatory hormone. This alternate hypothesis would limit the importance of BNP in severe heart failure to a marker of this disease state. The analysis of the functional importance of BNP, which was not the aim of the present study, warrants further investigation.

In conclusion, ventricular ANP mRNA expression was induced already in compensated heart failure, whereas the hemodynamic deterioration occurring in overt heart failure did not lead to any further induction of ventricular ANP mRNA. In contrast, cardiac BNP mRNA expression was elevated specifically in overt heart failure. These results suggest that cardiac BNP mRNA expression might be a more specific marker of overt heart failure compared with ANP.

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REFERENCES


