Administration of brain natriuretic peptide improves cardiac function following operations using extracorporeal circulation in an animal model

Dorothee H. L. BAIL, Volker STEGER, Uli HEINZELMANN, Sandra SCHILLER, Anita I. GEIM, Benjamin BRÜLLMANN and Gerhard ZIEMER
Department of Thoracic, Cardiac and Vascular Surgery, University of Tübingen, Hoppe-Seyler Str. 3, D-72076 Tübingen, Germany

ABSTRACT

The critical phase during cardiosurgical procedures is weaning the diseased heart from the ECC (extracorporeal circulation). Post-ischaemic heart failure sometimes requires the administration of inotropic and/or vasconstrictive agents. The natriuretic peptides influence pre- and afterload through their natriuretic, diuretic and vasodilating actions. To date, there are only a few reports describing the therapeutic effect of BNP (brain natriuretic peptide) administration during cardiosurgical procedures. The aim of the present study was to evaluate the effect of BNP administration following ECC in an animal model. Surgery was performed on 20 pigs using ECC. A 30-min ischaemic episode was simulated. Following de-clamping, BNP was administered to the BNP group (n = 10) by an i.v. (intravenous) bolus at 0.3 µg·kg⁻¹ of body weight·min⁻¹, followed by an infusion at a rate of 0.015 µg·kg⁻¹ of body weight·min⁻¹ for 60 min. The animals in the control group (n = 10) received a saline solution instead of BNP. Haemodynamic and clinical chemistry parameters as well as the amount of catecholamines that were required were measured. All of the animals in the BNP group had a significantly better cardiac output and cardiac index at the end of the experiment. Seven out of 10 animals from the control group required catecholamines, whereas only one animal from the BNP group did. Creatine kinase levels were significantly lower in the BNP group. Systemic vascular resistance was markedly lower in the BNP group. In conclusion, administration of BNP is highly effective in treating post-ischaemic heart failure following ECC. Haemodynamics are greatly improved, and there is almost no need for pharmacological support.

INTRODUCTION

The natriuretic, diuretic and vasodilating effects of the natriuretic peptides lead to a decrease in pre- and afterload, an improvement in myocardial ischaemia by vasodilating the coronary arteries, and an increase in SV (stroke volume), which in turn improves LV (left ventricular) function [1]. Patients with heart failure or LV
Various studies have examined the i.v. (intravenous) administration of BNP/nesiritide [2–4]. All of these studies have demonstrated a distinct improvement in haemodynamic parameters. A dose-dependent reduction in PCWP (pulmonary capillary wedge pressure), RAP (right atrial pressure), PAP (pulmonary arterial pressure), MAP (mean arterial pressure), SVR (systemic vascular resistance) and, as a result, an increase in SV and CI (cardiac index) were observed. Studies of exogenously administered BNP during the stage of ADHF (acute decompensated heart failure) showed a reduction in ventricular filling pressure, which resulted in improved CO (cardiac output) and CI without increasing HR (heart rate) or significantly decreasing MAP [5].

Compared with other inotropic substances, administration of BNP has not yet been associated with severe adverse effects, especially ventricular arrhythmia, as is seen with dobutamine or phosphodiesterase inhibitors [6,7].

Weaning the patient from the ECC (extracorporeal circulation) and the period immediately thereafter is usually the most unstable phase during cardiac surgery. The heart is in a particularly vulnerable situation, since it must resume perfusion of the entire body after a period of ischaemia. Myocardial insufficiency occurs regularly during this phase. The cardiac surgical trauma, induced ischaemic cardiac arrest, disturbance in electrolyte and acid–base balance, haemodilution and ECC itself can lead to myocardial oedema and insufficiency. The administration of i.v. pharmacological support with various combinations of inotropes, vasoconstrictors and vaso-dilators are part of a well-established treatment for stabilizing and, when necessary, increasing CO.

Two of the most important adverse effects of adrenaline (epinephrine) and noradrenaline (norepinephrine) are reduced kidney perfusion and tachyphylaxia. In addition, when ventricular function is already impaired pre-operatively, catecholamine susceptibility can be partly diminished due to down-regulation of β-adrenoceptors. Phosphodiesterase inhibitors, which are administered for acute low-output syndrome or acute refractory heart failure, lead to pronounced peripheral vasodilatation. An α1-sympathomimetic, such as noradrenaline, is often needed to counteract these adverse effects. Phosphodiesterase inhibitors also have considerable arrhythmogenic effects and can lead to thrombopenia and hepatotoxicity. Overall, phosphodiesterase inhibitors have many adverse effects.

Comparing the cardiac situation during and immediately following separation from ECC during conventional stages of heart failure is very limited. There are only a few studies that have evaluated the influence of ECC on plasma BNP concentrations. These are, in part, conflicting [8,9]. In addition, there are only a few studies to date on the therapeutic effects of exogenous administration of BNP during cardiac surgery using ECC.

The aim of the present study was to clarify whether the exogenous administration of BNP leads to improvement in haemodynamics during and after cardiac surgical procedures using ECC, and to determine whether BNP administration results in improvement in LV function during the critical phase of cardiac surgery, which is weaning the heart from ECC. The effectiveness of BNP administration was measured in terms of an increase in CO and CI (of at least 10%), a reduction in RAP and a significant decrease in the need for i.v. agents for circulatory support.

**MATERIALS AND METHODS**

**Animals and ECC**

All animal procedures were approved by the local representatives for animal welfare at the University of Tübingen, consistent with the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health (NIH Publication No. 85-23, revised 1996). Twenty young pigs (27 ± 0.9 kg) of both sexes were randomized to two groups. Ten animals received i.v. BNP (BNP group), whereas the ten animals who did not receive BNP comprised the control group.

On the day of surgery, the pigs were pre-medicated with ketamine (Ketaset®; Pharmacia), diazepam, azeporone (Stresnil®; 40 mg/ml; Janssen-Cilag) and atropine applied intramuscularly (dorsal neck muscle). Before induction of anaesthesia, indwelling catheters were placed in two ear veins. Anaesthesia was maintained intravenously with fentanyl (0.0072 mg·kg⁻¹·min⁻¹), flunitrazepam (0.06 mg·kg⁻¹·min⁻¹) and propofol (0.104 mg·kg⁻¹·min⁻¹). Before median sternotomy, fluid-filled catheters were inserted into the common carotid artery and the internal jugular vein to monitor arterial and central venous pressures, to take arterial and venous blood samples and to administer fluids.

All pigs received heparin (300 international units/kg of body weight) for systemic anticoagulation. In addition, all animals received 250 mg of methylprednisolone (Urbason® solubile forte; Aventis Pharma Deutschland) to prevent cross-reactions with the foreign pig blood that was used to prime the ECC.

ECC was initiated by cannulating the ascending aorta (14 French arterial perfusion cannula; Jostra) and the right atrium (32–34 French two-stage venous cannula; Stöckert CAPS). After connection to the ECC, a catheter was also inserted in the left atrial appendage for measuring LAP (left atrial pressure). Cardioplegic arrest was induced by antegrade infusion of ice-cold (4°C) blood cardioplegic solution (Buckberg), accomplishing external cooling with...
instillation of ice-cold saline solution into the pericardium. The heart was left in cardioplegic cardiac arrest for 30 min. The re-warming period to reach a normal body temperature began several minutes before the aortic cross-clamp was removed. The entire duration of aortic cross-clamping was 30 min. After the aortic cross-clamp was removed and defibrillation was performed to convert the heart into a normal rhythm, a reperfusion period (with ECC maintained) of approx. 10 min followed, which was equivalent to one-third of the aortic cross-clamping time. During the subsequent 60 min (after weaning the heart from the ECC), pharmacological support was used when necessary (adrenaline, noradrenaline and/or dopamine) to sustain a minimum MAP of approx. 60 mmHg. At the end of the experiment, animals were killed with an overdose of anaesthesia and intracardial instillation of potassium (60 mval/l).

**Administration of BNP**

Various studies [5,10] have favoured a single BNP bolus application as a loading dose with subsequent continual administration in a lower dose over a defined period of time. In view of this, we prepared the following protocol on the basis of information in the literature.

The BNP solution was prepared by dissolving the calculated amount of porcine BNP-32 (BNP-32 trifluoroacetate salt reconstituted in sterile water for injection; Bachem) in 5% dextrose (50 ml). In the BNP group (n = 10 pigs), BNP was administered as an i.v. bolus (0.3 µg/kg of body weight) through a central venous cannula immediately after releasing the aortic cross-clamp, followed by an infusion at a rate of 0.015 µg·kg⁻¹·min⁻¹ of body weight·min⁻¹ for 60 min [5]. In the control group (n = 10 pigs), 50 ml of 0.9% saline was injected instead of BNP.

**Determination of haemodynamic parameters**

CO was measured following sternotomy, pericardiotomy and preparation of the large vessels using a Transonic® perivascular ultrasonic volume flow sensor (Transonic Systems) placed directly on the ascending aorta just above the aortic root. In addition, CO was measured at regular intervals until the end of the experiment. RAP, MAP and LAP were measured continually during the entire experiment with a catheter. CI was calculated from CO and BSA (body surface area) (CI = CO/BSA). SVR was calculated from MAP, RAP and CO values.

**Determination of metabolic and biochemical parameters**

While the haemodynamic parameters were being recorded, the metabolic status (including lactate) was evaluated by analysing arterial blood gas samples. Levels of CK (creatine kinase), a sensitive and specific marker of myocardial damage, were measured once before ECC and then at regular intervals using the ADVIA chemistry systems® method (Bayer), together with human probes, in the laboratory at the University of Tübingen.

**Determination of plasma BNP concentrations**

Blood samples for plasma BNP were collected in chilled plastic tubes containing EDTA, placed immediately on ice, centrifuged within 20 min at 4°C, and stored at −70°C until assayed. Plasma levels of BNP were determined after extraction with a conventional available RIA kit for porcine BNP (Peninsula Laboratories). The minimal detectable amount of the assay was 1 pg/tube. The intra- and inter-assay coefficient of variation was 8.5 and 10.5% respectively.

**Measurement times**

Measurements of the haemodynamic and clinical chemistry parameters took place at the following time intervals: pre-operatively following induction of anaesthesia and after sternotomy (pre-op); after beginning ECC (ECC start); after de-clamping the aorta (i.v. BNP bolus) (AXCL open); immediately after ending ECC (ECC end); and at 15 min intervals up to 60 min after ending ECC (15 min–60 min).

**Additional parameters**

The amount of i.v. vasoactive agents required (dopamine, adrenaline and/or noradrenaline) to maintain an adequate perfusion pressure during ECC and the amount of fluids administered were recorded. Colloid and crystalloid fluids were given intravenously when MAP levels fell below 60 mmHg in combination with a low cardiac filling pressure. In the case of increased LV filling pressure or high SVR, inotropic (adrenaline and/or dopamine) and/or vasoconstrictive agents (noradrenaline) were administered.

**Statistics**

All analyses were performed with SPSS 12.0 software. All results are means ± S.E.M. The number of test animals was calculated in collaboration with the Institute for Medical Biometrics at the University of Tübingen. One-way ANOVA (with Levene’s test for inhomogenous variances) was used to calculate the significance of BNP-induced haemodynamic changes between the two groups for normally distributed data (as determined using Shapiro–Wilk test). Non-parametric tests (Mann–Whitney U test) were used for non-normally distributed data. Fisher’s exact test was used to calculate an exact probability value for the relationship between dichotomous variables. P values < 0.05 indicate statistical significance.
Table 1  Haemodynamic parameters before and after BNP administration

Values are means ± S.E.M. i.v. BNP administration started after re-opening the aortic cross-clamp with a bolus loading dose and continuous infusion until 60 min after the end of ECC (end of trial). *P < 0.039 and †P < 0.0027 compared with the control group.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group</th>
<th>Measurement point</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP (mmHg)</td>
<td>Pre-operative</td>
<td>BNP</td>
</tr>
<tr>
<td></td>
<td>70.4 ± 5.3</td>
<td>58.5 ± 5.4</td>
</tr>
<tr>
<td>CO (litres/min)</td>
<td>2.66 ± 0.15</td>
<td>2.55 ± 0.28</td>
</tr>
<tr>
<td>CI (litres·m⁻¹·min⁻¹)</td>
<td>3.21 ± 0.5</td>
<td>2.74 ± 0.2</td>
</tr>
<tr>
<td>RAP (mmHg)</td>
<td>8.5 ± 1.0</td>
<td>6.8 ± 0.9</td>
</tr>
<tr>
<td>LAP (mmHg)</td>
<td>5.3 ± 0.8</td>
<td>4.9 ± 1.0</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>88.1 ± 4.1</td>
<td>88.5 ± 3.1</td>
</tr>
<tr>
<td>SVR (dyn·s⁻¹·cm⁻⁵)</td>
<td>1757.5 ± 142</td>
<td>1683.7 ± 131</td>
</tr>
</tbody>
</table>

Figure 1  Effect of BNP administration on CO
Administration of BNP led to a significant increase (P < 0.039) in CO at 60 min after the end of ECC compared with the control group (see Table 1).

Figure 2  Effect of BNP administration on CI
CI in the BNP group was significantly higher (P < 0.0027) than in the control group at 60 min after the end of ECC, and was markedly higher than the initial values within the BNP group (see Table 1).

RESULTS

CO, CI and catecholamines
Prior to ECC, no difference in CO or CI was observed in either group. After ending ECC, there was still no difference between the two groups. However, at 15 min after ending ECC until the end of the experiment (60 min), animals in the BNP group had significantly higher CO (P < 0.039) and CI (P < 0.0027) compared with those in the control group (Table 1, Figure 1 and Figure 2).

On average, animals in the BNP group had a 41% (960 ml/min) higher CO at the end of the experiment (after 60 min of independent cardiac activity) than the animals in the control group. The CO in the control group was slightly lower (approx. 9%) at the end of the experiment compared with the pre-operative value. In
Table 2  Differences in haemodynamic parameters and CK levels at the end of the experiment compared with at the beginning

Values are means ± S.E.M. Differences (Δ) were calculated by subtracting the values at 60 min after the end of ECC from the pre-operative values for each parameter. P values indicate significant differences compared with the control group. NS, not significant.

<table>
<thead>
<tr>
<th>Difference</th>
<th>Parameter</th>
<th>Group</th>
<th>BNP</th>
<th>Control</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔCO (litre/min)</td>
<td>0.62 ± 0.2</td>
<td>−0.22 ± 0.3</td>
<td>P &lt; 0.035</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ΔCl (litre ⋅ min⁻¹ ⋅ m⁻²)</td>
<td>0.74 ± 0.2</td>
<td>−0.27 ± 0.3</td>
<td>P &lt; 0.019</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ΔMAP (mmHg)</td>
<td>−4.5 ± 6.6</td>
<td>0 ± 5.3</td>
<td>NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ΔSVR (dyn ⋅ s⁻¹ ⋅ cm⁻²)</td>
<td>−352 ± 245</td>
<td>263 ± 133</td>
<td>P &lt; 0.04</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ΔLAP (mmHg)</td>
<td>1.4 ± 1.0</td>
<td>2.4 ± 1.2</td>
<td>NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ΔHR (beats/min)</td>
<td>9 ± 9</td>
<td>27 ± 12</td>
<td>NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ΔCK (units/l)</td>
<td>223 ± 100</td>
<td>1224 ± 221</td>
<td>P &lt; 0.0049</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

the BNP group, CO was higher at the end of the experiment compared with the pre-operative value. ΔCO (difference in the value at the end of the experiment minus the preoperative value) in the BNP group was significantly higher (P < 0.035) compared with the control group (Table 2).

The CI in the BNP group was 60% higher than in the control group at the end of the experiment. The CI in the BNP group at the end of the experiment was increased by 23% compared with the pre-operative value. ΔCI in the BNP group was significantly higher (P < 0.019) compared with the control group (Table 2).

From the beginning of the experiment, during ECC and after re-opening of the aortic cross-clamp, a number of animals in both groups needed i.v. catecholamines (dopamine, noradrenaline and/or adrenaline) in order to maintain an adequate perfusion pressure during ECC (Figure 3 and Table 3). Seven out of ten (70%) animals in the control group needed pharmacological support after ending ECC until the end of the experiment. Only three (30%) animals from the BNP group required pharmacological support after ending ECC until the end of the experiment, although at a lower dose than in the control animals. Animals in the BNP group required significantly less catecholamines (P < 0.001) than those in the control group during the entire phase of independent cardiac action after ending ECC (Figure 3 and Table 3).

MAP

MAP did not differ significantly throughout the entire experiment in either group (Table 1); however, 70% of the animals in the control group required catecholamines after ending ECC to sustain a minimum MAP of 60 mmHg. ΔMAP was not significantly different between the groups (Table 2).

SVR

SVR did not vary between groups at the beginning of the experiment; however, clear differences were already observed at 15 min after ending ECC. The animals in the BNP group had markedly lower SVR values until the end of the experiment, although the values were not significantly different (Table 1 and Figure 4). The median SVR in the control group was not significantly higher at the end of the experiment compared with pre-operatively. ΔSVR was significantly lower (P < 0.04) in the BNP group compared with the control group (Table 2).

CK

There was no difference in CK levels between the two groups at the beginning of the experiment until the start of ECC. During ECC, CK levels increased in both groups and remained elevated in the control group (Figure 5). Animals in the BNP group had significantly lower CK values after opening the aortic cross-clamp until the end of the experiment compared with the control group (Table 3). ΔCK levels were significantly lower (P < 0.0049) in the BNP group compared with the control group (Table 2).

![Figure 3](image-url)  Number of animals requiring catecholamine administration after ECC

The number of animals in the control group who required catecholamines to treat post-ischaemic heart failure after ECC was significantly higher (P < 0.001) than in the BNP group (see Table 3).
Table 3 CK and lactate levels, and frequency of catecholamines, before and after BNP administration

Values are means ± S.E.M. i.v. BNP administration started after re-opening the aortic cross-clamp with a bolus loading dose and continuous infusion until 60 min after the end of ECC (end of trial). *P < 0.018, †P < 0.013 and ‡P < 0.001 (as determined by Fisher’s exact test) compared with the control group.

<table>
<thead>
<tr>
<th>Measurement point</th>
<th>Parameter</th>
<th>Group</th>
<th>Group</th>
<th>Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Parameter</td>
<td>BNP</td>
<td>Control</td>
<td>BNP</td>
</tr>
<tr>
<td></td>
<td>CK (units/l)</td>
<td>1015 ± 455</td>
<td>1191 ± 924</td>
<td>1407 ± 306*</td>
</tr>
<tr>
<td></td>
<td>Lactate (mmol/l)</td>
<td>2.29 ± 1.6</td>
<td>2.92 ± 1.8</td>
<td>5.71 ± 2.8</td>
</tr>
<tr>
<td></td>
<td>Catecholamines (n)</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
</tbody>
</table>

Figure 4 Effect of BNP administration on SVR

Mean SVR was markedly lower (from 15 min after ending ECC to the end of procedure) in the BNP group.

Figure 5 Effect of BNP administration on CK levels

For the time period after re-opening the aortic cross-clamp to the end of the procedure, mean CK was significantly lower (P < 0.018 and P < 0.013 respectively) in the BNP group compared with the control group (see Table 3). U, units.

RAP

RAP did not vary between the groups at the beginning of the experiment. At 15 min after ending ECC, RAP in the BNP group was significantly lower than in the control group (8.0 ± 0.8 compared with 10.5 ± 0.8 mmHg respectively; P < 0.04). However, there were no other significant differences in RAP between the groups at any time throughout the experiment (Tables 1 and 2).

Plasma BNP concentrations

Pre-operatively, BNP concentrations were equally low in the control and BNP groups (Table 4). After connecting to the ECC, plasma BNP concentrations increased significantly in both groups. In the control group, BNP plasma concentrations declined after the aortic cross-clamp was removed; however, BNP concentrations were still higher at the subsequent measurement points than those pre-operatively. In BNP-treated animals, BNP was administered after removing the aortic cross-clamp. BNP was given as a single bolus (0.3 µg/kg of body weight), followed by continuous infusion for 1 h (0.015 µg·kg⁻¹·min⁻¹). The highest BNP concentration in plasma was measured immediately after bolus application, and plasma BNP values in the treated animals remained constantly high until the end of the experiment (Table 4).
Plasma BNP concentrations over the time course of the experiment

<table>
<thead>
<tr>
<th>Group</th>
<th>Pre-op</th>
<th>ECC start</th>
<th>AXCL open</th>
<th>Reperfusion</th>
<th>ECC end</th>
<th>15 min</th>
<th>30 min</th>
<th>45 min</th>
<th>60 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>BNP group</td>
<td>9.8 ± 1.1</td>
<td>268.6 ± 62.1</td>
<td>363.5 ± 90.2</td>
<td>340.3 ± 84.5</td>
<td>267.7 ± 92.2</td>
<td>332.2 ± 69.5</td>
<td>374.2 ± 1.2</td>
<td>315.3 ± 4.0</td>
<td>367.2 ± 67.3</td>
</tr>
<tr>
<td>P value</td>
<td>—</td>
<td>P &lt; 0.004</td>
<td>P &lt; 0.01</td>
<td>P &lt; 0.005</td>
<td>P &lt; 0.03</td>
<td>P &lt; 0.001</td>
<td>P &lt; 0.0005</td>
<td>P &lt; 0.001</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td>Control group</td>
<td>9.0 ± 1.2</td>
<td>270.8 ± 89.9</td>
<td>98.0 ± 28.2</td>
<td>63.0 ± 9.3</td>
<td>131.8 ± 49.6</td>
<td>63.2 ± 11.3</td>
<td>42.8 ± 5.9</td>
<td>36.9 ± 4.8</td>
<td>39.3 ± 19.6</td>
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<tr>
<td>P value</td>
<td>—</td>
<td>P &lt; 0.004</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
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<td>NS</td>
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</tbody>
</table>

Lactate, LAP and HR

There was no difference in mean lactate values between the groups at the beginning of the experiment. During ECC, lactate was increased in both groups. At 60 min after ECC, lactate values decreased slightly in the BNP group (Table 3). LAP was lower (approx. 5 mmHg) before ECC in both groups and increased to 10 mmHg after ending ECC until the end of the experiment (Tables 1 and 2). Mean HR at the end of the experiment was slightly lower in the BNP group compared with the control group, but this was not statistically significant (Tables 1 and 2).

Fluid administration and urine output

Total fluid intake in the BNP group was approximately twice that of the control group (1580 ± 149 compared with 518 ± 268 ml respectively; P < 0.003). In addition, total urine output was markedly higher in the BNP group compared with the control group (407 ± 151 compared with 235 ± 81 ml respectively; P < 0.021).

DISCUSSION

The present study shows the impressive haemodynamic effects of intravenously administered BNP during surgical procedures using ECC. The results demonstrate an outstanding improvement in CO and CI along with a decrease in SVR, almost without the need for inotropic support.

The results of present study are consistent with other reports of patients [5,10a,10b] who received BNP for either chronic decompensated heart failure or ADHF. There are, however, only a very limited number of studies to date evaluating the effects of BNP after operations using ECC [11,12]. The induced myocardial ischaemia and 'post-ischaemic heart failure' caused by multiple factors can be only partially compared with other studies. Hayashida et al. [13] studied patients undergoing cardiac surgery who received ANP (atrial natriuretic peptide) perioperatively. Nine patients with mitral valve disease received ANP over 6 h at a rate of 0.05 μg · kg⁻¹ of body weight · min⁻¹ after beginning ECC. The haemodynamic effect was seen in the form of a decrease in pre- and after-load, a decrease in PCWP, RAP and SVR, and a significant increase in CI. At the same time, there were no adverse effects, i.e. hypotension, arrhythmias or allergic reactions, to exogenous ANP.

The haemodynamic effects of BNP in the present study are consistent with studies on BNP in decompensated heart failure [14–16]. BNP led to a 28% improvement in CI [17] and, in other studies, to an increase of 400 ml/m² [5,14] in patients with severe heart failure. In the present study, BNP resulted in a significant improvement in CI (60% or 1490 ml/m²) and CO (41% or 960 ml/min) compared with the control group.

The administration of BNP led to a rapid vasodilative effect, which resulted in a reduction in pre- and after-load and a decrease in SVR [18]. At the same time, BNP led to an increase in SV and CO output. We found a reduction in SVR in the BNP group, which is consistent with findings from several other studies [5,19].

In the control group, increased cardiac filling pressure and decreased CO and CI resulted in the need for catecholamines and a reduction in fluid administration. In the BNP group, the cardiac filling pressure was low. The urine output in the BNP group was significantly higher, which resulted in a higher volume of fluid administration. The greater need for fluids in the BNP group can be explained by the low filling pressure and by the fact that the GFR (glomerular filtration rate) was higher in these animals who did not have pre-existing cardiac disease. Jensen et al. [20] observed a higher GFR in patients with congestive heart failure after treatment with BNP. The sympatho-inhibitive effect of BNP reduces renal vasoconstriction, and this reduction, combined with an overall improvement in CO, results in enhanced renal perfusion. In the kidney, blood flow and filtration are increased with concomitant natriuresis and diuresis after treatment with BNP [21].

The administration of BNP did not lead to a relevant decrease in MAP (caused by vasodilation of arteries and veins), which is consistent with recent studies [14,19].

The animals in the control group required various catecholamines, sometimes in combination (i.e. adrenaline, noradrenaline and dopamine) to treat myocardial
contractile dysfunction caused by post-ischaemic heart failure. In contrast, animals in the BNP group needed almost no inotropic support. Only one animal required noradrenaline at the end of the experiment, and this was at a concentration approx. 7 times lower than the animals in the control group. Hayashida et al. [14] found that patients in both groups (placebo and ANP) needed approximately the same amount of catecholamines post-operatively. In this study [14], both groups of patients had severe cardiac disease. In contrast, neither group in our present study had cardiac disease. This could account for the difference in results between these studies.

BNP is produced primarily in the left ventricle, and compensatory secretion of BNP is greater than ANP in congestive heart failure. Although the effects of ANP are very similar to BNP, ANP has a lesser effect in patients with congestive heart failure [22] and has a shorter elimination time (1–3 min). BNP is used worldwide as recombinant human BNP/nesiritide following FDA (Federal Drug Administration) approval in 2001.

BNP/nesiritide has coronary vasodilative effects on both coronary artery conductance and resistance. When administered, coronary artery blood flow is increased, coronary resistance is decreased and myocardial oxygen uptake is decreased [23]. BNP leads to direct vasodilation of coronary vessels [24] and also improves reperfusion of induced myocardial ischaemia after ECC. CK, an indicator of ischaemic myocardial damage, was significantly lower in the BNP group than in the control group, which could be indicative of a positive influence of exogenous BNP on myocardial function, particularly after ischaemia [23,25]. A further indication of haemodynamic improvement in the BNP group was the lower lactate values after ending ECC, which showed that the administration of BNP led to a significant improvement in post-ischaemic heart failure after ECC. Further studies are needed to evaluate the effects of BNP in patients with pre-existing heart failure/impaired cardiac function.

BNP lowers pre- and after-load without reflex tachycardia [26], and also reduces the release of endogenous catecholamines by the autonomic nervous system [16]. We did not observe reflex tachycardia following the administration of BNP. Reflex tachycardia can cause an increase in myocardial oxygen consumption, as well as an increase in venous pooling and a decrease in vascular tone. None of the animals had a significant change in HR while receiving BNP. HR was even slightly lower in the BNP group.

Almost all studies report a significant decrease in RAP after exogenous BNP administration [5]. We, however, could not confirm this. Only at one measurement point (15 min after ending ECC) was RAP significantly lower in the BNP-treated group, which was in our view due to bolus administration of the peptide. After declamping the aorta, animals in the BNP group received a bolus dosage 20 times higher than the subsequent infusion rate. The time span from the bolus until 15 min after the end of ECC was 25 min. The onset of action of BNP following i.v. bolus administration is usually observed within 15–20 min.

The effect of BNP is similar to nitroglycerine, although the reduction of PCWP is greater [27–29]. LAP values, which correspond to PCWP, remained unchanged following BNP administration; however, animals in both groups did not have heart disease and, therefore, did not have elevated PCWP/LAP values pre-operatively.

The observed increase in CO and CI is due entirely to afterload reduction secondary to vasodilation [20]. The positive haemodynamic effects of BNP do not cause an increase in oxygen consumption as it is not dependent on the andrenergic receptor system [14]. No severe adverse effects have been reported yet, in contrast with other drugs used to treat heart failure or low-output syndrome [30]. The improvement in haemodynamics is not caused by a secondary increase in intracellular cAMP and calcium, as is the case with positive inotropic substances (e.g. dobutamine). Therefore arrhythmias were not seen during BNP administration. A major advantage of BNP over phosphodiesterase inhibitors is the shorter half-life, which makes it easier to control. The other adverse effects associated with phosphodiesterase inhibitors, such as arrhythmia, hepatotoxicity and peripheral vasodilation, do not occur with BNP. Peripheral vasodilation caused by phosphodiesterase inhibitors must often be counteracted with noradrenaline, which causes decreased kidney and intestinal perfusion.

Sackner-Bernstein et al. [31] have shown impaired renal function after nesiritide treatment; however, this study should be considered carefully in respect to our data because it is a meta-analysis of studies involving patients with ADHF. The disease pattern of ADHF may involve many factors that could result in elevated serum creatinine levels, rather than an effect of BNP therapy itself. In addition, the surgical procedure involving ECC may affect renal function itself. Furthermore, the analysis was based on the unavailability of primary study data. We believe that, in our present study, 60 min is too short to determine any change in renal function. In fact, in our present study, as in others [32,33], diuresis was clearly improved in BNP-treated animals.

One limitation of the present study was that the animals did not have heart disease or heart failure before surgery, as represented by the low BNP concentration pre-operatively. Nevertheless, in both groups, BNP concentration rose significantly after the ECC was connected. The results of the control group clearly show that procedures using ECC, which cause ischaemia, result in a significant increase in plasma BNP and in a decline in myocardial function and the need for catecholamines post-operatively. On the contrary, in BNP-treated pigs, BNP levels rose after bolus injection of BNP and stayed
constantly high thereafter until the end of the experiment. Following bolus administration and initiation of a continuous infusion, 60% of the steady-state haemodynamic response is observed within 15 min and 95% with 1 h [34].

BNP demonstrates excellent effects, especially in the case of severely impaired myocardial function. Further studies are needed involving hearts with pre-existing heart disease. These patients are often difficult to wean from ECC and need high doses of pharmacological support. Post-ischaemic heart failure is one of the main reasons for a greater demand of catecholamines and for a decline in myocardial contractile function following cardiac surgery. Therefore a further limitation of the present study is the relatively short duration of ischaemia, namely 30 min. Even so, animals in the control group had an increase in plasma BNP and a decline in contractile function even though they received inotropic support (adrenaline).

**Conclusions**

The present study shows BNP to be a highly potent and readily available agent that offers significant advantages, especially in cardiac surgery. When planning this experiment, we expected an increase in CO and CI of at least 10% and a considerable decrease in vasoactive agents for circulatory support. These expectations were greatly exceeded.

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