A-Type and B-Type Natriuretic Peptides in Cardiac Surgical Procedures

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This study was performed to determine the secretion pattern and prognostic value of A-type (ANP) and B-type (BNP) natriuretic peptide in patients undergoing cardiac surgical procedures. We measured ANP and BNP in patients undergoing coronary artery bypass grafting (CABG) with ($n = 28$) or without ($n = 32$) ventricular dysfunction and in patients undergoing mitral ($n = 21$) or aortic ($n = 24$) valve replacement, respectively. Postoperative mortality was recorded up to 730 days after operation. ANP, but not BNP, concentrations were closely associated with volume reloading of the heart after aortic cross-clamp in all patients. The secretion pattern of BNP during surgery was much less uniform. BNP, but not ANP, concentrations correlated with aortic cross-clamp time ($r^2 = 0.32$; $P = 0.006$) and postoperative troponin I concentrations ($r^2 = 0.22$; $P = 0.0009$) in bypass patients, and preoperative BNP increases were associated with a more frequent postoperative (2-yr) mortality in these patients. Markedly increased preoperative BNP concentrations in mitral (3-fold) and aortic (14-fold) valve disease patients did not further increase during cardiopulmonary surgery. The data suggest that ANP is primarily influenced by intravascular volume reloading of the heart after cross-clamp, whereas the secretion of BNP is related to other factors, such as duration of ischemia and long-term left ventricular pressure and/or excessive intravascular volume. BNP, but not ANP, was shown to be a mortality risk predictor in patients undergoing CABG.

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In the human heart, A-type natriuretic peptide (ANP) is primarily produced by atrial myocytes, whereas B-type natriuretic peptide (BNP) is of both atrial and ventricular origin. The physiological effects of these peptides include natriuresis and diuresis, aldosterone antagonism, relaxation of vascular smooth muscle cells, and direct antiproliferative effects on cardiac myocytes counteracting hypertrophy and destruction of sarcomere structure (1,2). Increased plasma concentrations of ANP and BNP are associated with hypertension, myocardial hypertrophy, arrhythmias, renal insufficiency, and cerebral salt wasting (3–8). In myocardial infarction, concentrations of ANP, and especially BNP, were reported as a prognostic risk indicator independent from left ventricular ejection fraction (9–14).

In critically-ill patients, ANP, but not BNP, secretion is independent of the underlying disease, suggesting different pathophysiological implications of the peptides (15). This suggestion is supported by animal experiments showing that ANP- and BNP-null mice display different phenotypes (16–18). It is therefore hypothesized that ANP and BNP play complementary roles in the regulation of cardiovascular homeostasis. However, clinical data supporting this model in humans are rare, and there are conflicting data for patients undergoing coronary artery bypass grafting (CABG) (19,20). In this study, we evaluated the secretion pattern and prognostic implications of pre- and postoperative ANP and BNP concentrations in patients undergoing CABG or aortic or mitral valve replacement. We hypothesized that the secretion pattern and, possibly, the prognostic value might differ for ANP and BNP, respectively, and that there might also be differences dependent on the underlying disease.

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Methods

After approval of the study protocol by the IRB, we examined 105 adult patients undergoing different cardiac surgical procedures after written, informed consent was obtained from patients or their relatives. Patients were randomly selected for the following four groups: coronary artery disease (CAD) with left ventricular ejection fraction >50% ($n = 32$), CAD with left ventricular ejection fraction <50% ($n = 28$), aortic valve disease ($n = 24$), and mitral valve disease ($n = 21$). Exclusion criteria were any preexisting endocrinological diseases, former cardiac or combined surgical procedures, acute myocardial infarction or acute heart failure, and organ transplantation. ANP is stored in atrial myocytes and can immediately be secreted in response to atrial wall changes or hypervolemia. BNP is not stored in ventricular myocytes, and increased ventricular wall tension initiates the production of new BNP, followed by cleavage and secretion. Thus, BNP production and processing likely results in a delay of secretion compared with ANP. We therefore analyzed the plasma of patients for ANP (pg/mL) and BNP (pg/mL) 20 min after the induction of anesthesia, 20 min after the onset of cardiopulmonary bypass (CPB), 10 min after the onset of myocardial reperfusion, 20 min after CPB, at admission to the intensive care unit (ICU), and 6, 12, 24, and 48 h after admission to the ICU. To calculate normal ranges of ANP and BNP, blood samples were taken from 40 healthy volunteers in the recumbent position. We further determined heart rate (bpm), mean arterial blood pressure (mm Hg), cardiac output (L/min), systemic vascular resistance (dynes $\cdot s^{-1} \cdot cm^{-5}$), central venous and pulmonary artery occlusion pressure (mm Hg), and troponin I (ng/mL). After the induction of anesthesia and at admission to the ICU, left ventricular systolic function and afterload were assessed by transesophageal echocardiography by using standard measurements and formulas: fractional shortening (%), fractional area change (%), global left ventricular wall motion, and left ventricular end-systolic wall stress (dynes/cm^2) (21,22). The preoperative morbidity of patients was determined by the modified Cleveland score (23).

After surgery, complications (relevant bleeding, severe myocardial ischemia, malignant tachyarrhythmias, low cardiac output syndrome, myocardial infarction, and intraaortic balloon counterpulsation) were monitored and recorded to 14 days and mortality to 730 days after operation. Severe myocardial ischemia was defined as new ST segment changes of >2 mV detected in the 12-lead electrocardiogram (ECG). Moreover, the occurrence of new supraventricular or ventricular arrhythmias was indicative of myocardial ischemia. Transesophageal examination was performed in cases with ECG changes, arrhythmias, or hemodynamic instability (characterized by increased preload pressure, decreased afterload, low cardiac output, mixed venous oxygen saturation, or increased lactate concentrations). Acute low cardiac output syndrome was defined as follows: cardiac index <2.2 L $\cdot min^{-1} \cdot m^{-2}$, systemic vascular resistance >1000 dynes $\cdot s^{-1} \cdot cm^{-5}$, tachycardia (heart rate >120 bpm), oliguria (<2 mL/h), and metabolic acidosis. Diagnosis of myocardial infarction was based on ECG changes (new persistent Q waves and ST segment deviations: 1-mV ST segment increases in ≥2 limb leads and/or 2-mV ST segment increases in ≥2 precordial leads), a typical increase and decrease in serum creatine phosphokinase, and creatine phosphokinase brain isoenzyme activity curves. Bleeding was deemed clinically important if the blood loss was >150 mL/h during the first 3 h after admission to the ICU and if this blood loss did not decrease during the first 6 h after admission or after normalization of serum coagulation variables.

General anesthesia was induced with IV midazolam (0.1 mg/kg), sufentanil (2–5 μg/kg), and pancuronium bromide (0.1 mg/kg) while patients breathed 100% oxygen. After endotracheal intubation, the patients were mechanically ventilated with oxygen and air (fraction of inspired oxygen, 0.5). The ventilation was adjusted to maintain an end-tidal carbon dioxide tension of 35 to 40 mm Hg. A radial arterial catheter and a flow-directed balloon-tipped 7F Edwards® thermodilution pulmonary artery catheter were inserted for routine monitoring of hemodynamic variables. Anesthesia was maintained by body weight-related doses of sufentanil (0.25–0.375 μg $\cdot kg^{-1} \cdot min^{-1}$) and propofol (1.5–3 mg $\cdot kg^{-1} \cdot h^{-1}$). As a standard procedure, all patients received 2 million units of aprotinin (Trasylol; Bayer, Leverkusen, Germany) in the pump priming before CPB and a continuous infusion of 500,000 U of aprotinin during CPB. Anticoagulation was achieved with an IV dose of heparin (Heparin-Natrium; Braun Melsungen, Melsungen, Germany; initial bolus dose of 400 IU/kg, targeting an activated clotting time of ≥440 s) and was monitored by using the activated clotting time. Management of extracorporeal circulation was standardized with pump flows of 2.3 to 2.8 L $\cdot min^{-1} \cdot m^{-2}$, normothermia (36.5°C), and alpha-stat regulation of arterial blood gas values. Cold cardioplegic arrest was induced by using Bretschneider-HTK solution (Custodiol; Köhler, Alsbach, Germany) and topical cooling. In aortic and mitral valve repair procedures, double cannulation was used, and myocardial protection was performed with retrograde blood cardioplegia. After aortic declamping, the lungs were ventilated with 100% oxygen. Subsequently, the fraction of inspired oxygen in air was adjusted to maintain an arterial oxyhemoglobin saturation at >95%. A positive end-expiratory pressure of 5 cm H_2O was applied after CPB. Heparin was neutralized in a standardized manner by the

administration of protamine. Patients were weaned from the extracorporeal circuit by using nitroglycerin (Perlinganit; Schwarz Pharma, Monheim, Germany; 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$) and epinephrine (Suprarenin; Hoechst, Bad Soden, Germany) when mean arterial blood pressure was <60 mm Hg. In the ICU, mechanical ventilation was maintained as just described. Adequate analgesia and sedation were achieved with repetitive doses of piritramide and midazolam according to standard procedures at our institution. Patients' tracheas were extubated 4–8 h after surgery.

ANP and BNP plasma concentrations were measured by radioimmunoassays (Peninsula Laboratories, Belmont, CA) by using polyclonal rabbit immunoglobulin G antisera raised to the following peptides: α-ANP 1-28 (human) and BNP-32 (human). For measurements, 10 mL of venous blood was taken into a chilled syringe, transferred into polypropylene tubes containing edetic acid (3 mmol/L) and aprotinin (500 kIU/mL) at 4°C, and centrifuged at 1600 rpm for 15 min at 4°C. Plasma was stored at −70°C until analysis. Peptides were extracted from 5 mL of plasma (Sep-Pak C-18; Waters Associates, Milford, MA) and eluted with 3 mL of a mixture of 60% acetonitrile, 0.1% trifluoroacetic acid, and 39% distilled water (by volume). All samples were assayed in triplicate and analyzed as a batch to minimize assay variations. Standard curves were constructed with standard human ANP and BNP in radioimmunoassay buffer. The mean recovery of added natriuretic peptides from plasma was 60%–80%, and the lower detection limits as defined by 95% of the upper plateau of the standard curve were 0.1 nmol per tube for ANP and 0.5 nmol per tube for BNP. Cross-reactivity between natriuretic peptides was <0.1%. The intraassay and interassay coefficients of variations were 3.8% and 9.6% for ANP and 6.1% and 7.9% for BNP, respectively.

Plasma concentrations of cardiac troponin I were measured by using a commercially available one-step colorimetric immunoassay based on the "sandwich" principle (Dimension® RxL; Dade Behring, Marburg, Germany). After sampling, the plasma was stored at −70°C until analysis. For analysis, samples were incubated with chromium oxide particles coated with a monoclonal antibody specific for the cardiac troponin I molecule and a conjugate reagent (alkaline phosphate)-labeled monoclonal antibody specific for cardiac troponin I to form a particle/cardiac troponin I/conjugate sandwich. Unbound conjugates were removed by magnetic separation and washing. The particle/cardiac troponin I/conjugate sandwiches were then transferred to the cuvette, where the sandwich bond triggered an amplification cascade that finally converted 3,5-dichloro-2-hydroxybenzenesulfonic acid and 4-aminoantipyrine to a colored product that absorbs at 510 nm. The color change was directly measured proportional to the concentration of cardiac troponin I present in the patient sample. The intraassay and interassay coefficients of variations were 3.2% and 4.7%, respectively. The cross-reactivity of the assay with human skeletal muscle troponin I, cardiac troponin T, and cardiac troponin C was 0.04%, 0.34%, and 0.00%, respectively. The sensitivity was 0.04 ng/mL.

Nominal scale variables were described by using relative and absolute frequencies, and the Chi-Square test was used to assess differences among groups. Fisher's Exact test was used if matched cells were rare (expected frequencies <5). Interval or rational scaled variables were described as mean ± SD. Paired Student's *t*-tests or repeated-measures Analysis of Variance was used to compare groups (SPSS Version 10.0; SPSS Inc., Chicago, IL). In the Analysis of Variance, we calculated between- and within-group differences. Between-subjects factors were analyzed by simple contrasts; polynomial contrasts were used to analyze within-subject factors. Differences of natriuretic peptide concentrations among groups were detectable (power = 80%; $\alpha = 0.05$; $\delta = 0.6$) if they amounted to 0.75-fold of the SD. The described power required a minimum of 20 patients per group. The predictive value of BNP concentrations and other relevant variables for outcome in patients with CAD was calculated with Cox regression analysis. Covariates were added by likelihood forward selection. Covariation between variables was assessed with Pearson correlation analyses. $P < 0.05$ was considered statistically significant.

Results

All patients were separated successfully from CPB and remained in the ICU for 24 h. In all patients, cardioplegia induced a prompt temperature decrease in both atria and ventricles, and none of the patients had mechanical action or fibrillations during cross-clamp. Moreover, none of the patients had a stroke. Patients with CAD received one internal mammary artery bypass onto the left anterior descending artery. The number of venous grafts was not significantly different between patients with left ventricular ejection fraction <50% and >50%. Three of the 28 patients with left ventricular ejection fraction <50% experienced severe myocardial ischemia, and one had a postoperative myocardial infarction. None of the patients with aortic or mitral valve disease had additional CAD (as documented by angiography). Patients' underlying diseases, characteristics, demographic data, preoperative morbidity, and left ventricular ejection fraction; use of epinephrine during the weaning period from CPB and intensive care therapy; incidence of postoperative complications; and postoperative mortality are summarized

in Tables 1 and 2 for each group. In all patients, heart rate and cardiac output increased and systemic vascular resistance decreased after CPB. Mean arterial blood pressure, central venous pressure, and pulmonary artery occlusion pressure did not change within groups. These hemodynamic variables did not significantly differ among groups during the study period. Global systolic function was significantly reduced in patients with CAD and preexisting impaired left ventricular function compared with the other groups after the induction of anesthesia and at admission to the ICU ($P < 0.05$). In patients with mitral valve disease, the left ventricular end-systolic wall stress was increased compared with other patients ($P < 0.05$) (Table 3).

The mean concentration of ANP in healthy volunteers was 26.8 ± 9.7 pg/mL. In all patients, baseline values of ANP were slightly increased compared with controls ($P < 0.05$). This increase was more pronounced in patients with mitral valve disease ($P < 0.05$). In all groups, ANP concentrations increased to the highest values during reperfusion after aortic cross-clamp and decreased thereafter ($P < 0.05$). This secretion pattern was less pronounced in patients with CAD and normal left ventricular function compared with those with CAD and impaired left ventricular function or with aortic or mitral valve disease. Moreover, there was no effect for ANP between groups in the analysis of variance comparing patients with CAD and patients with mitral or aortic valve disease (Fig. 1).

The mean control value of BNP was 15.9 ± 9.6 pg/mL. BNP concentrations were also increased in all patients at baseline. However, this increase was 6.8-fold larger in patients with aortic valve disease compared with patients with CAD ($P < 0.05$). Moreover, the secretion pattern of BNP in coronary artery patients was completely different from that in patients with aortic or mitral valve disease (Fig. 2). In patients with CAD, BNP concentrations that were only mildly increased under baseline conditions and increased 6 h after admission to the ICU, reaching a maximum 24 h after surgery. By contrast, baseline BNP concentrations in patients with aortic or mitral valve disease were approximately 14-fold and 3-fold increased, respectively, and remained unchanged during the entire observation period ($P < 0.05$).

In patients with CAD, the largest BNP concentrations obtained 24 h after surgery correlated with the duration of aortic cross-clamp ($r = 0.57$; $r^2 = 0.32$; $P = 0.006$; $n = 60$), CPB time ($r = 0.53$; $r^2 = 0.28$; $P = 0.003$; $n = 60$), and postoperative troponin I concentrations ($r = 0.47$; $r^2 = 0.22$; $P = 0.009$; $n = 60$). Such correlations were not found in patients undergoing aortic or mitral valve replacement ($P > 0.05$). The largest ANP concentrations obtained during the reperfusion time, by contrast, did not correlate with aortic cross-clamp ($r = 0.127$; $r^2 = 0.02$; $P = 0.405$; $n = 60$) or CPB ($r = 0.13$; $r^2 = 0.017$; $P = 0.85$; $n = 60$) time in all groups. No significant correlation was detected between pre- and postoperative variables of left ventricular systolic and end-systolic meridional wall stress and the concentrations of ANP and BNP at any time point ($P > 0.05$).

Ten of the 60 patients with CAD died during the observation period of 730 days after coronary revascularization. Before surgery, BNP, but not ANP, concentrations were significantly larger in nonsurvivors (65.0 ± 17.1 pg/mL; $n = 10$) compared with survivors (28.8 ± 9.0 pg/mL; $n = 50$) ($P < 0.05$). This difference in BNP concentrations for survivors and nonsurvivors was not detectable after CABG ($P < 0.05$). In patients who died, troponin I concentrations were significantly increased before surgery (survivors, 0.2 ± 1.1 ng/mL; nonsurvivors, 3.5 ± 3.2 ng/mL; $P < 0.05$) and increased 12 h after admission to the ICU (survivors, 5.7 ± 2.1 ng/mL; nonsurvivors, 18.8 ± 5.6 ng/mL; $P < 0.05$). Before and after the surgical procedure, the left ventricular wall motion index was higher in nonsurvivors compared with survivors, indicating more global left ventricular dysfunction in nonsurvivors ($P < 0.05$). Figure 3 shows the values of BNP and ANP and the left ventricular wall motion index in survivors and nonsurvivors before and after surgery and shows the troponin I concentrations of these patients after CABG. Other postoperative echocardiographic variables of left ventricular systolic function did not differ between survivors and nonsurvivors ($P > 0.05$).

Twelve patients had preexisting BNP concentrations of >80 pg/mL, and 48 patients had concentrations of <80 pg/mL. The mortality in patients with BNP concentrations more than 80 pg/mL (4 of 12) was 2.7-fold higher than in patients with BNP concentrations less than 80 p/mL (6 of 48) ($P = 0.03$). Significant prognostic values for long-term outcome after CABG were found for preoperative BNP concentrations ($P = 0.008$), the extent of postoperative regional wall motion abnormalities ($P = 0.006$), and cross-clamp time ($P = 0.044$). No significant prognostic value could be calculated for preoperative left ventricular ejection fraction, Cleveland score, and postoperative troponin I concentrations (Table 4).

Discussion

This study describes for the first time the secretion pattern of ANP and BNP during and after different cardiac surgical procedures. Natriuretic peptides are thought to play an important role in the defense against excess salt and water retention (1). The peptides act through the bloodstream to relax vascular smooth muscle or stimulate diuresis and natriuresis, through an autocrine pathway to block excessive cardiac hypertrophy and destruction, or through paracrine mechanisms to inhibit fibroblast proliferation (17,24–26).

Table 1. Patients' Underlying Diseases and Surgical Procedures

Group	Underlying disease	Surgical procedure
Coronary artery disease, EF >50% (n = 32)	One-vessel disease (n = 3) Two-vessel disease (n = 6) Three-vessel disease (n = 23)	Coronary artery bypass grafting
Coronary artery disease, EF <50% (n = 28)	One-vessel disease (n = 2) Two-vessel disease (n = 5) Three-vessel disease (n = 21)	Coronary artery bypass grafting
Aortic valve disease (n = 24)	Predominant stenosis (n = 13) Predominant insufficiency (n = 11)	Valve replacement (n = 24)
Mitral valve disease (n = 21)	Predominant stenosis (n = 3) Predominant insufficiency (n = 18)	Valve replacement (n = 17) Valve reconstruction (n = 4)

EF = left ventricular ejection fraction.

Table 2. Demographic Data of Patients

Variable	Coronary artery disease, EF >50% (n = 32)	Coronary artery disease, EF <50% (n = 28)	Aortic valve disease (n = 24)	Mitral valve disease (n = 21)
Age (yr)	65 ± 9	63 ± 9	66 ± 10	59 ± 9
Height (cm)	172 ± 8	169 ± 9	172 ± 10	166 ± 10
Weight (kg)	76.1 ± 10.3	72.4 ± 14.5	77.3 ± 13.9	70.2 ± 14.4
Sex (F/M)	7/25	5/23	6/18	9/12
Body surface area (m^2)	1.9 ± 0.2	1.8 ± 0.2	1.9 ± 0.2	1.8 ± 0.2
Baseline ANP concentration (pg/mL)	44 ± 18	52 ± 27	59 ± 24	102 ± 34
Baseline BNP concentration (pg/mL)	30 ± 11	28 ± 10	205 ± 74	43 ± 9
Patients with hypertension (%)	7/25 (21.9)	16/12 (57.1)	15/9 (62.5)	2/19 (9.5)
Cleveland score[a]	2 ± 1	12 ± 2	7 ± 2	14 ± 4
Left ventricular ejection fraction (%)	65 ± 10	36 ± 8	60 ± 7	44 ± 11
Cross-clamp time (min)	40 ± 10	45 ± 16	62 ± 15	51 ± 14
Cardiopulmonary bypass time (min)	60 ± 14	75 ± 25	92 ± 20	81 ± 19
Use of epinephrine				
Weaning period (%)	3/29 (9.4)	10/18 (35.7)	7/17 (29.1)	5/16 (23.8)
Intensive care unit (%)	1/31 (3.1)	7/21 (25.0)	3/21 (12.5)	3/18 (14.3)
No. of venous grafts	1.7 ± 0.3	2.1 ± 0.6	NA	NA
Mechanical ventilation (h)	11 ± 4	20 ± 9	14 ± 7	14 ± 9
Intensive care therapy >24 h (%)	1/31 (3.1)	4/24 (14.3)	2/22 (8.3)	1/20 (4.7)
Postoperative complications (%)				
Bleeding	ND	1/27 (3.6)	ND	ND
Severe myocardial ischemia	ND	3/25 (10.7)	ND	ND
Intraaortic counterpulsation	ND	6/22 (21.4)	ND	1/20 (4.7)
Malignant tachyarrhythmias	ND	5/23 (17.8)	ND	1/20 (4.7)
Myocardial infarction	ND	1/27 (3.57)	ND	ND
Postoperative CPK-MB (U/L)	17 ± 11	28 ± 14	26 ± 12	23 ± 12
Nonsurvivors (%)[b]	2/30 (6.3)	8/20 (25.6)	1/23 (4.1)	2/19 (8.3)

Data are mean ± SD unless otherwise noted.
ND = not detectable; NA = not applicable; CPK-MB = creatine phosphokinase (brain and cardiac muscle isoenzyme); EF = left ventricular ejection fraction; ANP = A-type natriuretic peptide; BNP = B-type natriuretic peptide.
[a] The modified Cleveland score estimates patients' preoperative comorbidity; the highest value is 32 points, indicating a very severe risk.
[b] Mortality was recorded to 730 days after surgery.

One important and novel finding of this investigation is that only the secretion of ANP was consistently related to reloading of the heart after cross-clamp in all cardiac surgery patients independently of the underlying disease. The largest concentrations of ANP were found during reperfusion after aortic cross-clamping. In this period, the heart is reloaded with volume after cardiac arrest. Moreover, the timely secretion pattern of ANP was very similar in all patient groups. Thus, the main trigger of ANP secretion in our patients was most likely volume reloading. A larger peak secretion of ANP was observed in patients with primarily altered left ventricular function or preexisting congestive heart failure because of mitral or aortic valve dysfunction. These groups had a larger percentage of patients needing initial inotropic support, which may

Table 3. Patients' Left Ventricular Systolic Function Before and After Surgery

Variable	Reference values	Coronary artery disease, EF >50%		Coronary artery disease EF <50%		Aortic valve disease		Mitral valve disease	
		Before	After	Before	After	Before	After	Before	After
Systolic function									
Fractional area change (%)	~50%	56 ± 13	58 ± 11	32 ± 12*	36 ± 9*	60 ± 12	63 ± 12	37 ± 10†	41 ± 8†
Fractional shortening (%)	40–50%	39 ± 11	44 ± 16	26 ± 11*	28 ± 14*	42 ± 15	44 ± 15	28 ± 11†	32 ± 9†
Left ventricular ejection time (ms)	~300	291 ± 42	271 ± 48	289 ± 65	262 ± 49	301 ± 65	280 ± 46	277 ± 42	260 ± 52
Global left ventricular wall motion[a]	0	0.5 ± 0.2	0.4 ± 0.3	1.8 ± 0.3*	1.6 ± 0.3*	1.0 ± 0.6	1.1 ± 0.6	1.0 ± 0.6	1.1 ± 0.6
Left ventricular end-systolic wall stress (dynes/cm^2)[b]	80–90	62 ± 16	64 ± 15	66 ± 21	57 ± 26	47 ± 28	48 ± 22	86 ± 12†	97 ± 16†

Data are mean ± SD. EF = left ventricular ejection fraction.

[a] Global left ventricular wall motion was assessed from following views: midesophageal four-chamber view (three septal and three lateral segments), midesophageal two-chamber view (three anterior and three inferior segments), midesopheageal long axis (two anteroseptal and two posterior segments), and transgastric short axis (six segments at the mid level). Estimation of wall motion was performed by the same investigator and scored as follows: 0, normal wall motion, 1, hypokinesia; 2, akinesia; and 3, dyskinesia.

[b] Left ventricular end-systolic wall stress was derived from the basic Laplace relationship according a previously described formula (23, 24).

* $P < 0.05$, patients with coronary artery disease without (EF >50%) versus with (EF <50%) left ventricular dysfunction; † $P < 0.05$, patients with aortic versus mitral valve disease.

also have contributed as a secretion stimulus. Although there are no available data about the influence of atrial cannulation on ANP concentrations, the possibility that the double cannulation for valve surgery may be responsible for the larger peak concentrations of ANP in these patients induced by muscle injury cannot be dismissed. Moreover, ANP secretion could be stimulated by interleukin-1, endothelins, or other mechanisms. A further finding is the increase in basal concentrations of ANP in all patients. Because ANP is a defense against volume overload and hypertension, the most likely explanation for this finding is that a relevant percentage of patients has preexisting hypertension (1,18). None of the healthy volunteers, by contrast, had hypertension.

The secretion pattern of BNP was completely different and greatly varied among the patient groups. In patients with CAD, BNP concentrations increased 6 hours after admission to the ICU, peaked after 24 hours, and decreased thereafter. A subgroup of patients with reduced ejection fraction had larger peak concentrations; however, the time course of secretion was identical. Thus, the secretion of BNP did not parallel reperfusion after aortic cross-clamping. This observation does not necessarily exclude a role of BNP in volume regulation. BNP, in contrast to atrial natriuretic peptide, is not stored in intracellular vesicles, which may explain a delay in secretion. However, the late onset >24 hours after reperfusion makes a key role of this natriuretic peptide in volume regulation less likely. We were interested to find that BNP, but not ANP, concentrations closely correlated with the duration of myocardial ischemia induced by aortic cross-clamp in patients with CAD. Myocardial ischemia may be a key inductor of BNP secretion in these patients. Thus, the duration of cross-clamp represents a potential confounder for inhomogeneous BNP release after myocardial revascularization. Moreover, only BNP was a mortality risk predictor. In aggregate, these data suggest that the secretion stimuli and the physiological roles of these two natriuretic peptides are different.

It has been shown that BNP is a more powerful predictor of left ventricular function after myocardial infarction than ANP. Richards et al. (13) proposed that the increase in BNP in patients with CAD may also reflect the extent of myocardial ischemia. Our data strongly support this concept and suggest that ischemia is the main secretion stimulus for BNP during cardiac surgery. In accordance with this concept, in patients with aortic and mitral valve disease (in whom CAD had been excluded by angiography), BNP concentrations were not influenced by the surgical procedure and the following intensive care therapy. In addition, we found no relationship between BNP concentration and aortic cross-clamp time in this subgroup of patients.

In contrast, the basal concentration of BNP in aortic and in mitral valve patients was markedly increased. The reason for this increase is not clear. Chronic mechanisms, such as long-term left ventricular volume overload and increased wall tension after left ventricular hypertrophy or increased left ventricular end-diastolic pressure, may be responsible. This possibility is further supported by the larger plasma concentrations in patients with aortic valve dysfunction (14-fold increase) compared with patients with mitral valve disease (3-fold increase).

The most likely explanation for our observations and previous reports on ANP- and BNP-null mice and guanylyl cyclase A-null mice is that these peptides

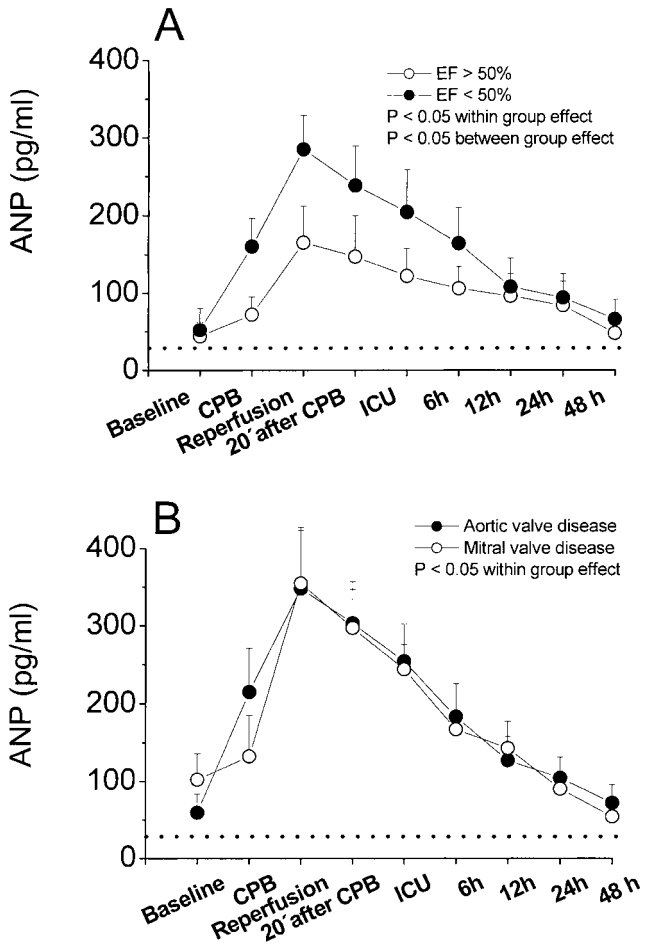

Figure 1. Time course of A-type natriuretic peptide concentrations during and after coronary artery bypass grafting with and without left ventricular dysfunction (A) and aortic and mitral valve replacement (B). Mean values of healthy volunteers are indicated by the dotted lines. Data are mean ± SD. ANP = A-type natriuretic peptide; CPB = cardiopulmonary bypass; ICU = intensive care unit; EF = left ventricular ejection fraction.

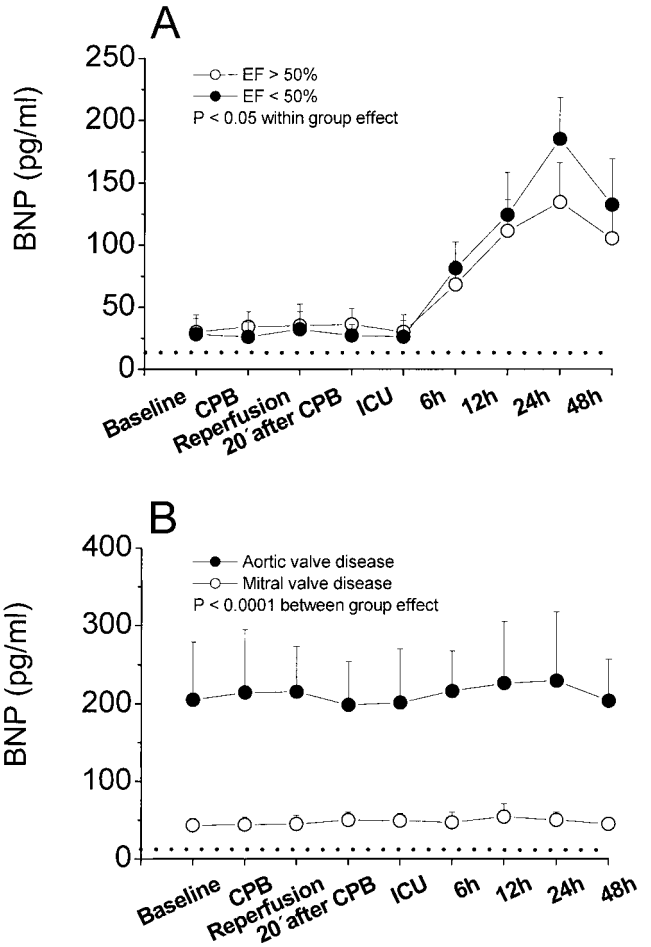

Figure 2. Time course of B-type natriuretic peptide concentrations during and after coronary artery bypass grafting with and without left ventricular dysfunction (A) and aortic and mitral valve replacement (B). Mean values of healthy volunteers are indicated by the dotted lines. Data are mean ± SD. BNP = B-type natriuretic peptide; CPB = cardiopulmonary bypass; ICU = intensive care unit; EF = left ventricular ejection fraction.

play complementary roles in the regulation of cardiovascular homeostasis. ANP is likely to regulate blood pressure and water-electrolyte balance, whereas BNP may function as a ventricular local regulator to protect the heart from damage and fibrosis. However, both ANP and BNP act through the guanylyl cyclase A receptor, and the secretion of both peptides is thought to be triggered by similar mechanisms (2). There are several possible explanations for this apparent discrepancy. ANP and BNP display a different distribution pattern in the heart. ANP is stored in granules within the cardiac atrial myocytes, and atrial stretch causes an immediate release of the granules, enabling very rapid endocrine and local effects. BNP, in contrast, is more widespread in atrial and ventricular tissue. BNP is not stored in granules, and its secretion is rather constitutive. Moreover, BNP may also have an autocrine-paracrine role to modulate left ventricular and coronary vascular function, to abbreviate contractile function, and to accelerate isovolumic relaxation mediated by its second messenger guanosine 3',5'-cyclic monophosphate (27).

BNP, but not ANP, was shown to be a mortality risk predictor in our patients with CAD. Patients who died within the first 2 years had significantly larger concentrations of BNP before surgery. It has previously been shown that BNP is a hormonal predictor of death in patients with CAD, especially in those with myocardial infarction (11,12). Our data show that preoperative BNP may also provide independent information for risk prediction in patients undergoing CABG and support previous findings that BNP concentrations of 80 pg/mL in patients with CAD predict a worse long-term outcome (12). However, our findings suggest further that the measurement of preoperative,

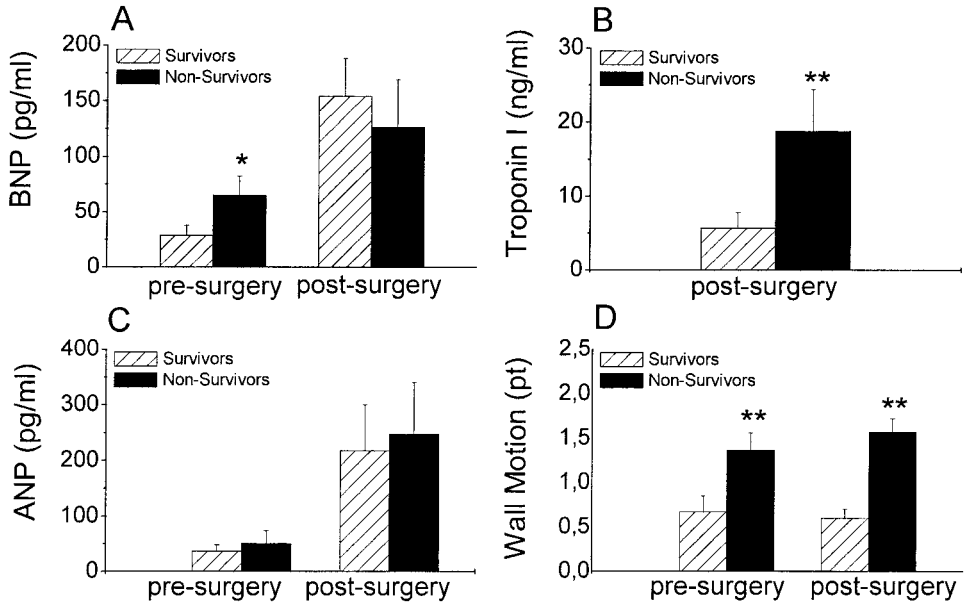

Figure 3. Pre- and postoperative values of B-type natriuretic peptide (A), postoperative troponin I values (B), pre- and postoperative values of A-type natriuretic peptide (C), and left ventricular wall motion abnormalities (D) in patients who survived (n = 50) and died (n = 10) during the first 730 days after coronary artery bypass grafting. Postoperative values of natriuretic peptides and cardiac troponin I were determined 12 h after surgery. Data are mean ± SD. *$P < 0.05$; **$P < 0.001$. ANP = A-type natriuretic peptide; BNP = B-type natriuretic peptide.

Table 4. Prognostic Value of Preoperative BNP Concentrations and Confounding Variables in Patients with Coronary Artery Disease

Variable	B	Wald index	P value
Preoperative BNP concentrations	0.058	6.954	0.008
Duration of intraoperative myocardial ischemia	−0.145	4.057	0.044
Cleveland score	0.378	2.427	0.119
Postoperative troponin I	−0.005	0.054	0.995
Preoperative left ventricular ejection fraction	0.024	0.447	0.504
Postoperative wall motion abnormalities	4.342	7.702	0.006

Cox regression analysis; Wald index indicates the significance of the calculated coefficient (B).
BNP = B-type natriuretic peptide.

but not of intra- or postoperative, BNP allows prediction of long-term outcome in patients undergoing CABG. Interpretation of troponin I concentrations reveals a similar problem. Although postoperative cardiac troponin I concentrations were larger in patients who died during the following 2 years after coronary artery grafting, no predictive value could be calculated for this variable. Moreover, for postoperative cardiac troponin I, a cutoff value for relevant myocardial ischemia could not be defined. Thus, perioperative myocardial ischemia was detected by relevant ST segment changes and echocardiographic detection of new regional wall motion abnormalities and was only supported by measured troponin I concentrations.

Two limitations of our study are the relatively small sample size and the inhomogeneity of subgroups. However, we measured ANP and BNP plasma concentrations at several time points during and after the surgical procedures, demonstrated a differential secretion pattern for the peptides, and showed that BNP, but likely not ANP, concentrations are dependent on the underlying disease.

In conclusion, ANP and BNP show a differential secretion pattern in cardiac surgery patients. ANP seems to be primarily associated with volume reloading of the heart after cross-clamp. The secretion of BNP, in contrast, is related to other factors, such as ischemia or increased myocardial wall tension. Preoperative BNP, but not postoperative BNP, concentrations are helpful for the prediction of long-term outcome after CABG.

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