Postoperative plasma levels of NTproBNP do not reflect a short-lasting low-cardiac output state after coronary artery bypass surgery

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Abstract

Introduction: The N-terminal-prohormone of the B-type-natriuretic-peptide (NTproBNP) is an accepted marker of acute heart failure in medical patients. It is not known if the plasma levels of this peptide may also be useful to detect a low-cardiac-output-syndrome (LCOS) in postoperative cardiac surgery patients.
Materials and methods: A posthoc analysis of a prospective, randomized trial investigating the effects of different inotropes on metabolism and renal function in patients presenting with a LCOS upon ICU-admission in comparison with a group of patients not needing inotropes after coronary artery bypass grafting (CABG) surgery was performed. LCOS was defined as a cardiac index (CI) < 2.2 l/min/m^2 despite optimization of filling pressures and mean arterial pressure. 18 patients fulfilled the LCOS-criteria (LCOS-group) and underwent 14h treatment with adrenaline or milrinone aimed to achieve a CI > 3.0 l/min/m^2, 20 patients served as controls (CON-group). Plasma levels of NTproBNP and hemodynamics were determined at 0, 2, 6, 10, 14, and 48 hours after ICU-admission.
Results: Baseline NTproBNP levels in the LCOS- and the CON group were 462 ± 404 pg/ml and 296 ± 259 pg/ml, and increased to 2411 ± 1592 pg/ml and 2321 ± 1375 pg/ml respectively, at t=48h. No significant between-group differences in NTproBNP were observed. CI in the LCOS-group was 1.9 ± 0.2 l/min/m^2 at t0, increased to 2.9 ± 0.5 l/min/m^2 at t2, and was maintained at 3.0 to 3.4 l/min/m2 thereafter. Cardiac index in the CON-group was 3.1±0.4 l/min/m^2 at t0 ($p<0.001$ vs. LCOS) and increased to 3.8 ± 1.0 l/min/m^2 ($p=0.019$) during the treatment period.
Conclusions: Postoperative plasma levels of NTproBNP do not discriminate between patients with a short-lasting LCOS or a normal myocardial function. This questions the usefulness of determining plasma NTproBNP levels for guiding hemodynamic treatment in the immediate postoperative period after CABG surgery.
Clinical trials registration: ClinicalTrials.gov NCT00446017

Introduction

B-type-natriuretic-peptides (BNP) are increasingly used as humoral markers for the detection of acute heart failure and for the monitoring of treatment in medical patients with myocardial dysfunction [1]. Recent studies have shown that preoperative and immediate postoperative levels of BNP are predictive of outcome in patients after cardiac [2,3] and vascular surgery [4].

It is a matter of debate if BNP levels may also be helpful for guiding hemodynamic treatment in the postoperative period after cardiac surgery. Mekontso-Dessap and coworkers have shown that the plasma levels of this hormone are not useful for the determination of fluid responsiveness in this context [5]. No

data are available, whether plasma levels of BNP may be helpful for the assessment of myocardial function and the detection of a low-cardiac-output syndrome (LCOS) after cardiac surgery.

We have recently analyzed the effects of different inotropes on renal function and metabolism in patients with myocardial dysfunction after coronary-artery-bypass-grafting (CABG) [6]. Using the database of this study (AMORI-trial: ClinicalTrials.gov NCT0044 6017), the present posthoc analysis was performed to determine if plasma levels of the N-terminal prohormone of BNP (NTproBNP) may help to discriminate between patients presenting with a postoperative low-cardiac output syndrome (LCOS) or normal cardiocirculatory function.

Materials and methods

The AMORI project (ClinicalTrials.gov NCT0044 6017) is a prospective, randomized, controlled pilot study investigating the effects of adrenaline and milrinone on renal function, inflammation and metabolism in patients with myocardial dysfunction after CABG. The study protocol and the results regarding renal function and metabolism have been described in detail previously [6].

Following approval by the local ethical committee and preoperative written consent, 18 patients presenting with a LCOS immediately after ICU-admission were treated for 14h with inotropes (adrenaline: n = 7; milrinone: n = 11) to achieve and maintain a cardiac index (CI) > 3.0 l/min/m^2. 20 patients without the need of inotropes to reach a CI > 3.0 l/min/m^2 served as controls (CON). LCOS was defined as a CI < 2.2 l/min/m^2 [7] despite a central venous pressure of 12 to 15 mmHg, a diastolic pulmonary artery occlusion pressure of 15 to 18 mmHg, and a mean arterial blood pressure of 65 to 90 mmHg that had been titrated with noradrenaline or sodium-nitroprusside, respectively.

Plasma samples for determination of NTproBNP were taken at 0, 2, 6, 10, 14, and 48 hours after ICU-admission. NTproBNP was determined by an electrochemiluminescence immunoassay (Elecsys-proBNP-sandwich-immunoassay; Roche Diagnostics, Basel, Switzerland). The mean intraassay variance was 4.3% (range: 2.7 to 5.9%) for plasma samples with a concentration between 65 to 23413 pg*ml^{-1}, interassay variance was 3.2%. The lower detection limit was 5 pg*ml^{-1}.

Statistical analyses

Data are given as mean ± standard deviation. Following Kolmogoronov-Smirnov test for normal distribution, between group differences were analyzed by unpaired Student's t-test or ANOVA followed by posthoc Fisher's PLSD, as appropiate. Intraindividual changes were analyzed by paired Student's t-test with Bonferoni-adjustment. Correlation analyses were performed by Spearman's rank correlation test. A p-value < 0.05 was considered significant.

Results

Groups were not significantly different regarding demographics, preoperative left ventricular ejection fraction, duration of surgery, cardiopulmonary bypass, and aortic cross clamp times (table1).

NTproBNP levels at t0 and throughout the observation period were not significantly different between groups (figure 1). In the CON-group, NTproBNP increased continuously from t0 to t48. In the LCOS-group, a minor but significant decrease (p = 0.005) from t0 to2 was observed. Thereafter, NTproBNP levels increased comparably to the CON-group.

CI in the LCOS-group was 1.9 ± 0.2 l/min/m^2 at baseline (t0), increased to 2.9 ± 0.5 l/min/m^2 at t2, and was maintained at 3.0 to 3.4 l/min/m^2 thereafter. Cardiac index in the CON-group was 3.1 ± 0.4 l/min/m^2 at t0 (p < 0.001 vs. LCOS) and increased to 3.8 ± 1.0 l/min/m^2 (p = 0.019) during the treatment period.

The LCOS-group was treated with 1.2 ± 0.5 mg adrenaline, 21.6 ± 7.7 mg milrinone, and 0.7 ± 1.1 mg

Table 1. Demographic and procedure related variables

	LCOS N = 18	**CON N = 20**
Age [years]	68 ± 9	63 ± 9
Height [cm]	174 ± 7	176 ± 7
Weight [kg]	86 ± 15	85 ± 13
Ejection-fraction [%]	57 ± 19	61 ± 16
Creatinine [mol/l]	97 ± 26	84 ± 17
Diabetics	n = 6	n = 4
operation time [min]	221 ± 32	211 ± 41
CPB time [min]	89 ± 22	80 ± 19
ACC time [min]	61 ± 16	59 ± 17

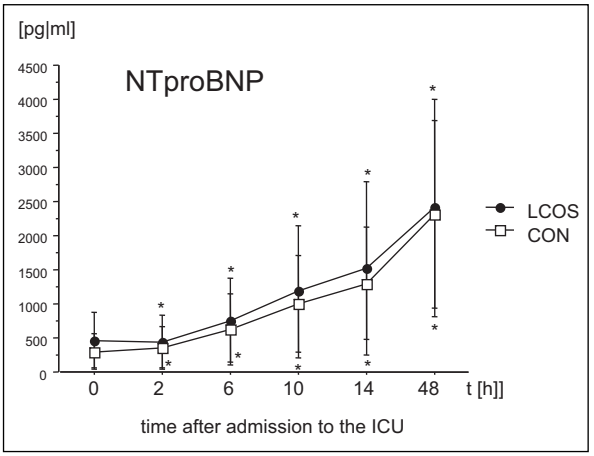

*Figure 1. Time course of plasma levels of N-terminal pro B-type natriuretic peptide (NTproBNP) in patients with a low-cardiac-output syndrome (LCOS) after CABG surgery treated with adrenaline or milrinone (n = 18), and in control patients (n = 20) not needing inotropic support. Data are given as mean ± standard deviation. *: significant difference in comparison with baseline levels (t0); Student's t-test for paired observations with Bonferoni-correction. ANOVA with posthoc Fisher's PLSD revealed no significant between-group differences.*

nordadrenaline. The noradrenaline use in the CON-group was 0.2 ± 0.4 mg and tended to be lower than in the LCOS-group (p = 0.065). No differences between groups were observed in the amount of crystalloid (LCOS: 1140 ± 260 ml; CON: 1054 ± 266 ml) and colloidal fluids (LCOS: 1932 ± 576 ml; CON: 1625 ± 666 ml) during the treatment period of 14h.

Correlation analyses of the relationship between NTproBNP levels, hemodynamics at t0, surgical, and demographic data revealed no correlation between the plasma levels of this peptide and cardiac index, stroke volume index, mean arterial pressure, central venous, systolic, and mean pulmonary arterial pressure as well as duration of CPB and aortic crossclamp time. Minor correlations were observed between NTproBNP and diastolic pulmonary artery pressure (Spearman's rho = 0.37; p = 0.03) and mixed venous oxygen saturation (Spearman's rho = -0.36; p = 0.03). There was a close correlation between baseline NTproBNP levels and preoperative left ventricular ejection fraction (t0: Spearman's rho = -0.89; p < 0.0001). Correlation analyses did not reveal any relationship between changes in hemodynamics, volume therapy, and the course of NTproBNP levels throughout the observation period.

Table 2. Time course of hemodynamic variables

		t0	**t2**	**t6**	**t10**	**t14**
CI [l/min/m^2]	LCOS CON	1.9 ± 0.2 * 3.3 ± 0.4	2.9 ± 0.5 § 3.1 ± 0.4	3.0 ± 0.5 § 3.4 ± 0.6 §	3.4 ± 0.6 § 3.5 ± 0.8 §	3.4 ± 0.5 3.8 ± 1.0 §
SvO_2 [%]	LCOS CON	64.5 ± 7.2 * 74.1 ± 5.5	70.9 ± 6.8 § 73.5 ± 5.0	67.3 ± 6.4 71.9 ± 4.5	69.1 ± 7.9 § 71.2 ± 6.6	66.4 ± 5.7 71.5 ± 5.2
MAP [mmHg]	LCOS CON	79 ± 11 83 ± 8	78 ± 12 70 ± 8	78 ± 8 82 ± 11	80 ± 10 82 ± 8.0	79 ± 9 79 ± 9
HR [bpm]	LCOS CON	94 ± 11 95 ± 8	94 ± 11 96 ± 5	98 ± 13 98 ± 6	98 ± 11 98 ± 7	99 ± 9 98 ± 6 *
PAPM [mmHg]	LCOS CON	26 ± 6 23 ± 4	26 ± 5 25 ± 5	25 ± 6 23 ± 5	24 ± 5 21 ± 6	22 ± 4 21 ± 8
CVP [mmHg]	LCOS CON	15 ± 4 12 ± 4	14 ± 4 12 ± 4	13 ± 4 11 ± 4	12 ± 4 * 10 ± 4	11 ± 4* 10 ± 4

Time course of hemodynamics in patients presenting with low-cardiac output syndrome (LCOS: cardiac index (CI) < 2.2l/min/m^2 despite optimization of mean arterial pressure and filling pressures) upon ICU-admission treated with adrenaline or milrinone, and of control patients (CON) not needing inotropic after coronary artery bypass grafting with cardiopulmonary bypass. SvO_2: mixed venous oxygen saturation; MAP: mean arterial blood pressure; HR: heart rate; PAPM: mean pulmonary artery pressure; CVP: central venous pressure. §: Significant difference (p<0.05) in comparison with baseline (t0). *: Significant difference (p<0.05) in comparison with the control group.

Discussion

The role of B-type natriuretic peptides for the detection of myocardial dysfunction in patients after cardiac surgery remains to be determined. In healthy individuals, BNP is produced predominantly by the atria. This changes during left ventricular dysfunction when the peptide is increasingly produced also by myoendocrinic cells of the ventricle. During the maturation process of the active peptide BNP, the N-terminal prohormone NTproBNP is cleaved in equimolar amounts [1]. Evidence is accumulating that the sensitivity of NTproBNP for the detection of heart failure is higher than the sensitivity of BNP [8].

In line with results from other groups [9] our data show that the levels of NTproBNP in patients after on-pump CABG increase tremendously during the first postoperative hours. The mechanisms mediating this increase are not clear. In healthy individuals with low NTproBNP levels, acute volume loading induces a delayed increase in NTproBNP levels up to more than 200% of baseline [10]. It is presently unknown, if patients with heart failure (and increased NTproBNP levels) show a comparable response.

The effects of surgical manipulation on postoperative plasma levels of NTproBNP have not been studied in detail. Berendes and coworkers have analyzed the course of A- and B-type natriuretic peptides in various groups of cardiac surgery patients and observed a moderate correlation between duration of cardiopulmonary bypass and aortic crossclamping and the postoperative increase in BNP in CABG patients, suggesting that myocardial ischemia during aortic crossclamping and CPB may be an important stimulus for BNP secretion [8]. However, in patients undergoing aortic or mitral valve surgery, no postoperative increase in BNP levels was observed. The latter finding is in contrast with the hypothesis that a postoperative increase in BNP secretion is mediated primarily by ischemia during CPB and suggests that additional factors may play a relevant role.

The data derived from the present analysis show that the immediate postoperative NTproBNP levels as well as the postoperative course up to 48h do not differ between patients with a LCOS and patients with a normal cardiocirculatory performance. Only minor correlations between diastolic pulmonary arterial pressure, mixed venous oxygen saturation, and NTproBNP levels at baseline were observed. However, NTproBNP levels were closely related to the preoperative left ventricular ejection fraction, emphasizing the well established association between chronic left ventricular dysfunction and the plasma concentration of this peptide [1].

Our findings differ from observations in patients with septic shock and acute lung injury. Witthaut and coworkers observed an inverse correlation between plasma BNP levels and cardiac index in patients with septic shock in comparison with healthy controls [11]. Comparably, Jefic et al. found an inverse correlation between plasma BNP and NTproBNP levels and cardiac index in patients with hypoxic respiratory failure [12].

In line with the observations in medical patients [13], the initiation of inotropic treatment in the LCOS group was followed by a slight, albeit significant decrease in NTproBNP levels. This effect, however, induced only a short delay until NTproBNP began to rise again, comparably to the control group. Ultimately, the use of inotropes did not lead to a permanent decrease in NTproBNP levels in the LCOS group. This suggests that the effects of inotropes on the B-type natriuretic peptide system indeed differ between medical and postoperative cardiac surgery patients.

Limitations

First, the present analysis is based on a pilot study. Consequently, the conclusions are based on a small sample size and might be different in a larger set of patients. However, based on the between group difference and standard deviations at t0, at least 100 patients per group would be necessary to achieve significance with a power of 80%.

A second limitation is the fact that the LCOS was not so severe that aortic counterpulsation had to be initiated and was effectively treated within 2 hours. Thus, the present data do not rule out that a more severe and prolonged low output state would have differently influenced plasma levels of NTproBNP.

Additionally, the use of NTproBNP instead of BNP may have altered our results. The half life time of the active hormone is much shorter than the half life time of the prohormone. Consequently, minor changes in BNP secretion may be more easily detected by measuring the active hormone.

A major limitation is, that we did not measure preoperative NTproBNP levels. This however was not possible since a large number of patients (n = 251) were monitored and only a minimal subset of these pa-

tients presented with a LCOS upon ICU-admission [6].

Conclusions

In conclusion, the data derived from the present analysis suggest that postoperative NTproBNP levels do not allow to detect a short-lasting postoperative low-cardiac output state in patients in the immediate postoperative period after CABG surgery. Nonetheless, postoperative NTproBNP levels were closely related to preoperative left ventricular ejection fraction and may thus be used to estimate the severity of preoperative myocardial dysfunction for risk stratification.

Key messages

- The plasma concentration of the N-terminal prohormone of the B-type natriuretic peptide (NTproBNP) is an accepted humoral marker for the determination of acute heart failure in medical patients.
- The present study shows that immediate postoperative NTproBNP levels in patients after cardiac surgery do not discriminate between patients presenting with a short-lasting low cardiac output syndrome after cardiac surgery and patients not needing inotropes. This questions the usefulness of determining plasma NTproBNP levels for guiding hemodynamic treatment in the immediate postoperative period after CABG surgery.
- Postoperative NTproBNP levels were closely related to preoperative left ventricular ejection fraction and may thus be used to estimate the severity of preoperative myocardial dysfunction for risk stratification.

Abbreviations

ACC = aortic crossclamp
CABG = coronary artery bypass grafting;
CI = cardiac index;
CON = control;
CPB = cardiopulmonary bypass;
CVP = central venous pressure;
HR = heart rate;
ICU = intensive care unit;
LCOS = low cardiac output syndrome;
MAP = mean arterial blood pressure;
NTproBNP = N-terminal prohormone of B-type natriuretic peptide
PAPM = mean pulmonary arterial pressure
SvO_2 = mixed venous oxygen saturation.

Competing interests

The authors M. Heringlake and F. Eberhardt have received scientific support in the form of analytical assays by Roche Diagnostics, Germany, a manufacturer of a commercially available NTproBNP assay. The other authors declare they have no competing interests.

Authors contributions

MH, HH, and JS participated in the design of the study, performed the statistical analyses and were responsible for drafting the manuscript. MW and JG performed the data acquisition, calculations, and were involved in drafting the manuscript. LD, TH, MB, MM, and FB participated in coordinating the study, in the interpretation of data, and revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

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