Natriuretic peptides and endothelin-1 in patients undergoing coronary artery bypass grafting

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Abstract. Off-pump coronary artery bypass grafting (CABG) is an alternative to conventional CABG using cardiopulmonary bypass. Off-pump technique reduces the complications of CABG performed with extracorporeal circulatory assistance (Lancey et al. 2000; Mack et al. 2004a,b). The object of this study was to compare peri- and postoperative time courses of vasoactive peptides – atrial natriuretic poptide (ANP), brain natriuretic poptide (BNP) and endothelin-1 (ET-1) in off-pump *versus* on-pump CABG.

22 patients, who underwent on-pump (group A, $n = 11$) or off-pump CABG (group B, $n = 11$) were studied. The peri- and postoperative time courses of plasma ANP and BNP were similar in both groups. A statistically significant difference between ET-1 plasma level 2 h after surgery in the group A and ET-1 plasma level 2 h after surgery in the group B (2.46 ± 1.14 pg/ml/Ht *versus* 0.74 ± 0.09 pg/ml/Ht, $p < 0.0001$) was found.

Different CABG techniques were not associated with significant changes in peri- and postoperative plasma ANP and BNP. By contrast, plasma ET-1 significantly rose in the group A 2 h after surgery, indicating endothelial damage.

Key words: Cardiopulmonary bypass — On-pump CABG — Off-pump CABG — Atrial natriuretic peptide — Brain natriuretic peptide — Endothelin-1

Introduction

Coronary artery bypass grafting (CABG) is one of the most effective therapeutic solutions for ischemic heart disease. The advance of cardiopulmonary bypass (CPB) and myocardial protection techniques has made this procedure safe and effective for revascularization of diseased coronary vessels. In contrast to the bloodless and motionless operative field in conventional (on-pump) CABG, off-pump (on beating heart) technique eliminates CPB to accomplish CABG (Masuda et al. 2002; Puskas et al. 2003). Off-pump CABG is considered to be less invasive compared with conventional CABG. Coronary anastomoses are performed during temporary coronary occlusion (Wan et al. 1999; Czerny et al. 2000; Wildhirt et al. 2000; Okubo et al. 2003).

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The heart secrets two different natriuretic peptides, atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) – homeostatic hormones, which seem to have almost exclusively beneficial physiological properties including balanced vasodilation, natriuresis, diuresis, and inhibition of both the sympathetic nervous system and the renin-angiotensin-aldosterone axis (Bonow 1996; Stein and Levin 1998; De Lemos and Morrow 2002). Endothelin-1 (ET-1) secreted by vascular endothelial cells exerts potent vasoconstrictory effects upon vascular smooth muscle cells (Kruse et al. 1997; Miyauchi and Masaki 1999; Kedzierski and Yanagisawa 2001). This study was conducted to investigate peri- and postoperative serial changes of vasoactive peptides – ANP, BNP and ET-1, thus assessing the impact of CABG technique on the heart in both the off-pump CABG and the conventional CABG patients.

Materials and Methods

Eleven patients (2 women) undergoing conventional (on-pump) CABG (group A) with moderate systemic hypothermia (core temperature 33–34°C) and eleven patients (1 woman) undergoing off-pump CABG (group B) with Octopus stabilizing device for coronary stabilization were enrolled in this study. Written informed consent was obtained from all patients. Each study patient received identical anaesthetic premedication and identical anaesthesia. Surgical access to the heart was through a standard median sternotomy in all cases.

The left ventricular ejection fraction (LVEF) was evaluated by echocardiography using Simpson´s biplane method. Blood samples were obtained from the central venous line after induction of anaesthesia, at the end of surgery, 2, 4, 6 and 18 h postoperatively. Immediately after the blood collection for natriuretic peptides determination, blood samples were transferred into ice-chilled tubes containing potassium salt of ethylendiaminetetraacetic acid (EDTA) and aprotinin, then centrifuged at 4°C and stored at –20°C until analysis. Into tubes containing EDTA, the additional blood was drawn for ET-1 determination; within 30 min after collection, plasma was separated by centrifugation and frozen below –20°C until analysis.

Plasma natriuretic peptides were measured directly with a highly sensitive and specific immunoradiometric assay using a commercially available kit (Shionogi, Japan). Solid phase ELISA was used to determine plasma concentrations of ET-1 (R&D Systems Inc., USA). Aforementioned ELISA is designed to measure ET-1 in extracted EDTA plasma. The measured values of vasoactive peptides were adjusted to the standard Ht (hematocrit) value (0.40). The Kolmogorov–Smirnov test was used to test variables for normality. For group comparisons of numeric variables, the Mann–Whitney rank sum test (U test) and the Student´s paired *t*-test were used. All data are expressed as mean ± SEM (standard error of the mean). In all analyses, the probability value $p < 0.05$ was considered statistically significant.

Table 1. General characteristics of patients

	Group A	Group B	*p*
Number (*n*)	11 (2 female)	11 (1 female)	
Age (years)	59.4 ± 2.73 (43–70)	53.8 ± 1.98 (44–65)	n.s.
NYHA II (*n*)	5	5	
NYHA III (*n*)	6	6	
History of MI	5	6	
Hypertension	8	8	
Insulin-dependent diabetes mellitus	1	1	
Preoperative *β*-blocker therapy	11	10	
Postoperative inotropic support	1	1	
CPB time (min)	84.3 ± 6.87 (48–120)		
Aortic cross-clamp time (min)	56.0 ± 3.52 (38–68)		
Total ventilation time (h)	8.9 ± 0.46	11.0 ± 1.23	n.s.
Number of grafts/pt (*n*)	2.64 ± 0.15	1.09 ± 0.09	$p < 0.001$

Data are mean ± SEM; group A, on-pump CABG; group B, off-pump CABG; NYHA, New York Heart Association functional class of heart failure; MI, myocardial infarction; CPB, cardiopulmonary bypass; n.s., not significant; $p < 0.05$.

Table 2. Preoperative and postoperative left ventricular ejection fraction (LVEF) in coronary artery bypass grafting (CABG) patients

	Preoperative LVEF (%)	Postoperative LVEF (%)	*p*
Group A	57.7 ± 1.04	59.8 ± 1.02	n.s.
Group B	54.5 ± 3.33	53.2 ± 2.72	n.s.

Data are mean ± SEM; group A, on-pump CABG; group B, off-pump CABG; n.s., not significant; $p < 0.05$.

Results

The baseline clinical and demographic features of both study groups are described in Table 1. The distribution of age, gender, NYHA class (New York Heart Association functional class of heart failure), history of myocardial infarction, insulin-dependent diabetes mellitus, arterial hypertension and medication was comparable (*β*-blockers preoperatively, inotropic support postoperatively). The mean number of grafts *per* patient performed in the group B was significantly less than in the group A. Total ventilation time did not differ significantly between both study groups.

There was no statistically significant difference between the preoperative and the postoperative mean value of LVEF in both study groups (Table 2).

Peri- and postoperative changes of plasma ANP in the groups A and B were almost identical (Figure 1). Plasma values of ANP peaked at the end of surgery (ANP2) with a significant difference in comparison with the ANP1 value after induction of anaesthesia (ANP1 *vs*. ANP2) in the group A (28.89 ± 5.63 pg/ml/Ht *vs*. 108.52 ± 34.54 pg/ml/Ht, $p < 0.05$), and in the group B (36.04 ± 6.65 pg/ml/Ht *vs*. 134.08 ± 32.93 pg/ml/Ht, $p < 0.001$). Nevertheless, there was

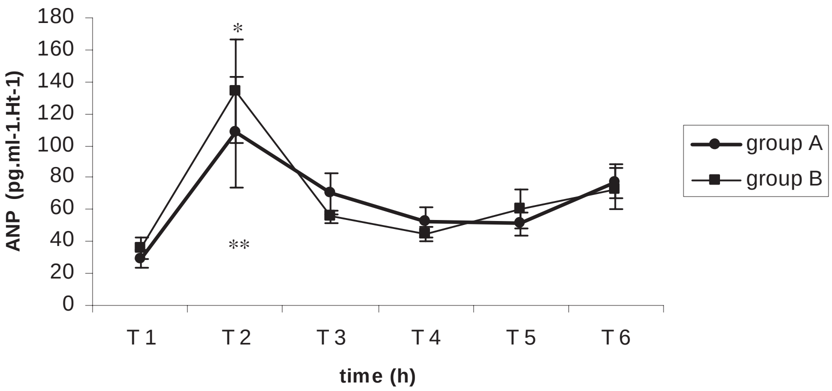

Figure 1. Peri- and postoperative time course (mean ± SEM) of plasma atrial natriuretic peptide (ANP) after induction of anaesthesia (T1), at the end of surgery (T2), 2 h (T3), 4 h (T4), 6 h (T5) and 18 h (T6) postoperatively. Difference with T1: * $p < 0.05$; ** $p < 0.001$; group A, on-pump CABG; group B, off-pump CABG.

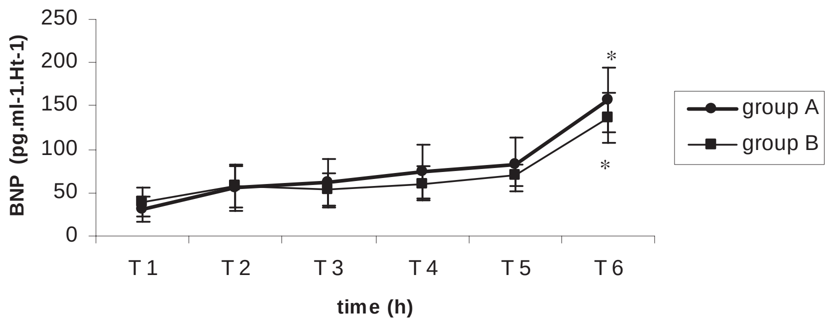

Figure 2. Peri- and postoperative time course (mean ± SEM) of plasma brain natriuretic peptide (BNP) after induction of anaesthesia (T1), at the end of surgery (T2), 2 h (T3), 4 h (T4), 6 h (T5) and 18 h (T6) postoperatively. Difference with T1: * $p < 0.05$; group A, on-pump CABG; group B, off-pump CABG.

no statistically significant change in *Δ*ANP2-ANP1 between both study groups (Table 3).

Next, no statistically significant intergroup differences regarding serial BNP measurements were noted (Figure 2).

Table 3. *Δ* intergroup difference in coronary artery bypass grafting (CABG) patients

	Group A	Group B	*p*
*Δ*ANP2-ANP1 (pg/ml/Ht)	79.6 ± 34.3	8.0 ± 33.5	n.s.
*Δ*BNP6-BNP1 (pg/ml/Ht)	125.2 ± 24.5	97.0 ± 20.5	n.s.
Δ(ET-1 3)-(ET-1 1) (pg/ml/Ht)	1.7 ± 1.2	–.0 ± 0.9	n.s.

Values are mean ± SEM; group A, on-pump CABG; group B, off-pump CABG; Ht, hematocrit; n.s., not significant; $p < 0.05$.

Levels of plasma BNP after induction of anaesthesia (BNP1) rose gradually and reached the maximum 18 h after surgery (BNP6). There was a significant change (BNP1 *vs*. BNP6) in the group A (31.93 ± 14.48 pg/ml/Ht *vs*.157.10 ± 36.48 pg/ml/Ht, $p < 0.05$), and in the group B (39.89 ± 16.21 pg/ml/Ht *vs*. 135.91 ± 28.83 pg/ml/Ht, $p < 0.05$). No statistically significant intergroup difference in *Δ*BNP6-BNP1 was found (Table 3).

ET-1 in plasma showed another time course as compared to ANP and BNP. Plasma ET-1 levels after induction of anaesthesia (ET-1 1) in the group B were higher than in the group A, but they did not differ significantly. By contrast, the value of ET-1 two hours postoperatively (ET-1 3) in the group A was significantly higher than in the group B – 2.46 ± 1.14 pg/ml/Ht *vs*. 0.74 ± 0.09 pg/ml/Ht, $p < 0.0001$ (Figure 3). However, no significant intergroup difference in *Δ*(ET-1 3)-(ET-1 1) was observed (Table 3).

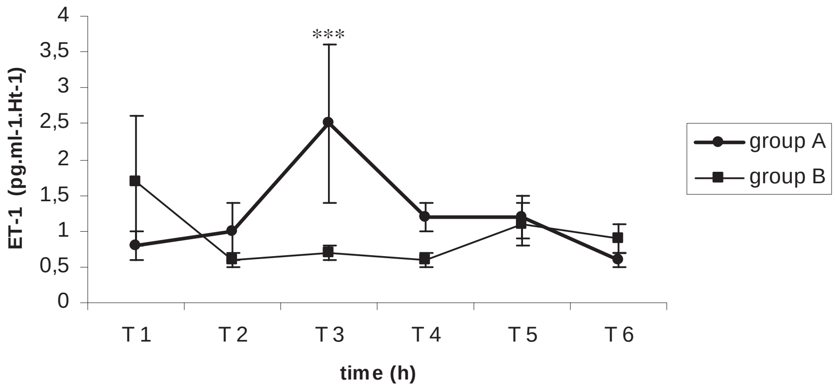

Figure 3. Peri- and postoperative time course (mean ± SEM) of plasma endothelin-1 (ET-1) after induction of anaesthesia (T1), at the end of surgery (T2), 2 h (T3), 4 h (T4), 6 h (T5) and 18 h (T6) postoperatively. Difference between group A and group B: *** $p < 0.0001$; group A, on-pump CABG; group B:, off-pump CABG.

Discussion

The use of beating heart *versus* conventional cardioplegic cardiac arrest strategies for myocardial revascularization is being intensively discussed at present. Off-pump CABG is considered to be less invasive compared with conventional CABG using CPB and cardioplegic arrest. The published data by Lockowandt et al. (2000) do not support this opinion. They demonstrated, that coronary bypass surgery performed on the beating heart may not be superior in preventing cardiac ischemia and endothelial disturbance, compared with conventional bypass surgery. Also Johansson-Synnergren et al. (2004) reported that off-pump CABG did not affect significantly endothelial function.

The diffuse inflammatory response elicited by CPB has been invoked to explain the small but finite incidence of serious injury in multiple organ systems, causing numerous postoperative complications and prolonging hospital stay (Wan et al. 1997; Puskas et al. 2003; Mack et al. 2004a,b; Ward and Kelly 2004; Rastan et al. 2006). CPB, aortic crossclamping, and cardioplegia entail global myocardial ischemia during the crossclamp interval. Although effective cardioplegia reduces this risk, myocardial injury may still occur. Off-pump surgery results in equal early hemodynamics despite a significantly lower release of cTnI (cardiac troponin I) and CK (creatine kinase), suggesting a reduced myocardial cell damage as compared to on-pump CABG (Thielmann et al. 2005). Fewer grafts tend to be performed with off-pump CABG than with on-pump CABG. Hemodilution and hemolysis are direct consequences of CPB and may produce significant coagulopathy, necessitating transfusion of blood products (Masuda et al. 2002; Puskas et al. 2003; Sellke et al. 2005). Natriuretic peptides play an important role in the regulation of cardiovascular homeostasis and fluid volume. They express broad and disparate effects in cardiovascular, renal and endocrine homeostasis, including natriuresis, diuresis, vasodilation, and inhibition of the renin-angiotensin system, sympathetic outflow, and vascular smooth muscle and endothelial proliferation (Stein and Levin 1998; Mair 2002). ET-1 is a peptide with 21 amino acid residues, released from endothelium. It is the most potent endogenous vasoconstrictor, which is involved in the regulation of arterial blood pressure and cardiac output (Wan et al. 1997).

Our study has not proven significant differences of ANP and BNP throughout the peri- and postoperative period between the conventional CABG group and the off-pump CABG group. There was no difference in number of patients treated with β-blockers preoperatively in both study groups and the same number of patients in groups A and B received inotropic postoperative support.

A statistically significant change in plasma ANP in both groups of patients was noticed at the end of surgery (ANP1 *vs.* ANP2). Next, in the groups A and B the last observed values of BNP were significantly higher than the first ones (BNP1 *vs.* BNP6). 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 (Berendes et al. 2004). We suppose, that differences between the two cardiac peptide systems with regard to intracellular storage, synthesis and secretion mechanisms may be responsible for a different time course between ANP and BNP secretion after cardiac surgery. A similar time course of ANP and BNP as in our on-pump group was presented by Berendes et al. (2004). Elevated BNP and proBNP concentrations do not necessarily reflect heart failure, but may also result from cardiac ischemia (Goetze et al. 2003). The data from Mair et al. (1997) clearly suggest, that myocardial ischaemia and reperfusion is a stimulus for BNP release in humans. They provide further evidence for the fact, that ischaemia itself is a stimulus for the enhanced ANP release observed during myocardial ischaemia (Mair et al. 1997).

The increase of plasma BNP in the off-pump group may be also attributed to an ischemic myocardial injury triggered by the short period of regional ischemia during the procedure.

We suppose, that the levels of ANP and BNP increased postoperatively in both groups of patients, since the following events – general anaesthesia, sternotomy, cardiac herniation, stabilizer compression, regional blood flow blockage and reperfusion injury – caused a great degree of stress. We found out that different CABG techniques were not associated with significant changes in peri- and postoperative plasma ANP and BNP between these groups. Our findings are in agreement with the results published by Masuda et al. (2002).

Interestingly, despite identical anaesthetic premedication and identical anaesthesia ET-1 plasma level after induction of anaesthesia in the off-pump group was higher than ET-1 plasma level after induction of anaesthesia in the on-pump group, but without a significant difference. On the other hand, a significantly higher ET-1 in plasma 2 h after surgery in the group A than in the group B was observed. CABG with the use of CPB in comparison to off-pump CABG surgery is associated with a significantly more expressed endothelial response in the immediate postoperative period. Oxidative stress and endothelial damage are major events during CABG (Carlucci et al. 2002).

Coronary artery bypass operations are associated with increased circulating levels of the powerful vasoconstrictor ET-1. The mechanism involved is not related to a decreased pulmonary clearance of ET-1 from the systemic circulation, but rather to an increased endothelin release by the lungs (Mathieu et al. 2001). According to data published by Dorman et al. (2004), increased ET in the postoperative period may contribute to a more complex recovery from coronary artery bypass surgery in patients undergoing CPB.

We suppose, that difference in postoperative ET-1 between CABG with and without CPB reflects a more pronounced production and secretion of ET-1 predominantly by lungs as a response to the lung endothelial injury resulting from CPB in more invasive on-pump CABG.

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