doi:10.1510/icvts.2009.212266

INTERACTIVE CARDIOVASCULAR AND THORACIC SURGERY

Interactive CardioVascular and Thoracic Surgery 9 (2009) 797–801

www.icvts.org

Institutional report - Cardiopulmonary bypass

Neutrophil gelatinase-associated lipocalin levels after use of mini-cardiopulmonary bypass system

Fabio Capuano[a,*], Massimo Goracci[a], Remo Luciani[b], Giovanna Gentile[c], Antonino Roscitano[a], Umberto Benedetto[a], Riccardo Sinatra[a]

[a]*Department of Cardiac Surgery, II Faculty of Medicine, University La Sapienza, Sant' Andrea Hospital, Rome, Italy*
[b]*Department of Nefrology, II Faculty of Medicine, University La Sapienza, Sant' Andrea Hospital, Rome, Italy*
[c]*Department of Biochemical Sciences and Laboratory of Advanced Molecular Diagnostics, II Faculty of Medicine, University La Sapienza, Sant' Andrea Hospital, Rome, Italy*

Received 19 May 2009; received in revised form 8 July 2009; accepted 9 July 2009

Abstract

Neutrophil gelatinase-associated lipocalin (NGAL) has been implicated as an early predictive urinary biomarker of ischemic acute kidney injury (AKI). The aim of this study was to compare the effects of miniaturized cardiopulmonary bypass system (MCPB) vs. standard cardiopulmonary bypass system (SCPB) system on kidney tissue in patients undergoing myocardial revascularization using urinary NGAL levels as an early marker for renal injury. Sixty consecutive patients who underwent myocardial revascularization were studied prospectively. An SCPB was used in 30 patients (group A) and MCPB was used in 30 patients (group B). The SCPB group but not the MCPB group showed a significant NGAL concentration increase from preoperative during the 1st postoperative day (169.0±163.6 ng/ml in the SCPB group vs. 94.1±99.4 ng/ml in the MCPB group, $P<0.05$, respectively). Two patients in the SCPB group developed AKI and underwent renal replacement therapy; no patient in MCPB developed AKI. The MCPB system is safe in routine clinical use. Kidney function is better protected during MCPB as demonstrated by NGAL levels. NGAL represents an early biomarker of renal failure in patients undergoing cardiac surgery and the valuation of its concentration can aid in medical decision-making.

Keywords: Coronary artery bypass grafts (CABG); Cardiopulmonary bypass (CPB); Kidney

1. Introduction

Acute kidney injury (AKI) following cardiac surgery remains a frequent and serious complication which is potentially fatal. In 2005, the acute kidney network (AKIN) proposed a working definition of AKI [1]. Recently, several protein markers have emerged as a sensitive and specific biomarkers with a capacity to be used in the detection of early kidney injury and grading of injury severity: neutrophil gelatinase-associated lipocalin (NGAL) has been implicated as an early predictive urinary biomarker of ischemic AKI in pediatric and adult cardiac surgery [2]. The incidence of AKI has been reported to vary between 1 and 10% [3]. The mortality in patients who develop AKI is persistently high despite significant advances in supportive care [4], and mortality also is elevated in patients with mild renal dysfunction (creatinine >1.5 mg/dl) [5]. Treatment of AKI following cardiac surgery requires careful management and in many situations these patients require early venovenous hemodialysis/filtration to correct fluid and electrolyte imbalances [6]. AKI in cardiac surgery is related to different mechanisms including loss of pulsatile flow, diminished renal blood flow, hypothermia and a generalized inflammatory response. Inflammatory response is determined by the blood contact with foreign surface and the activation of the complement [7], and it is generally accepted that standard cardiopulmonary bypass system (SCPB) initiates a whole body inflammatory reaction, which may be responsible for postoperative organ failure particularly renal insufficiency [8]. To reduce deleterious effects of SCPB novel concepts have been developed based on, miniaturized cardiopulmonary bypass system (MCPB) with closed circuits, low priming volumes and optimized perfusion system. In coronary bypass surgery, it has previously shown that the use of MCPB can reduce systemic inflammation compared to SCPB [9] and so attenuate the pathologic effects of SCPB also on kidney tissue. In current clinical practice, AKI is typically diagnosed by measuring serum creatinine concentrations. Unfortunately, serum creatinine is very insensitive to even substantial declines in glomerular filtration rate. Glomerular filtration rate measured by more accurate techniques may be reduced by up to 50% before serum creatinine becomes elevated. Fortunately, recent studies have uncovered a novel early urinary biomarker for ischemic renal injury: NGAL is identified as one of the most strikingly upregulated genes and overexpressed proteins in the kidney

*Corresponding author. Sant' Andrea Hospital, University of Rome 'La Sapienza', Via di Grottarossa 1035, 00189 Rome, Italy. Tel.: +390633775310; fax: +390633775483.
E-mail address: capmd@katamail.com (F. Capuano).

after ischemia [10]. The aim of this study was to compare the effects of MCPB vs. SCPB system on kidney tissue in patients undergoing myocardial revascularization using urinary NGAL levels as an early marker for renal injury.

2. Patients and methods

Sixty consecutive patients referred to the hospital because of cardiac symptoms between January 2007 and November 2008 were studied prospectively. To obtain a homogeneous group of cases, several exclusion criteria were adopted: combined surgical procedures other than coronary artery bypass grafting (CABG) operations, redo CABG, emergencies, terminal renal insufficiency with dialysis, and left ventricular ejection fraction <45%. An SCPB was used in 30 patients (group A) and MCPB was used in 30 patients (group B). The decision whether or not to use SCPB or MCPB dependent mainly on the availability of the system and on the surgeon's preference, preoperative data were collected during the patient's admission as a part of routine clinical practice on the variables shown in Table 1. Heart disease was diagnosed by preoperative valuation (echocardiographic and angiographic study) and indication for CABG was made in accordance with the international guidelines [11]. The Institutional Review Board approved the study, and all patients gave written informed consent.

2.1. Cardiopulmonary bypass (CPB)

All the procedures were performed through a standard median sternotomy. CPB was installed with an arterial cannula in the distal ascending aorta and a two-stage venous cannula inserted through the right atrium. In Group A, SCPB system was used (Caps; Stöckert Instruments, Munich, Germany); this system consisted of a membrane coated oxygenator with a cardiotomy reservoir, a standard roller pump, heater-cooler device, and arterial filter. All lines were treated with Carmeda (Carmeda AB, Upplands Väsby, Sweden); the priming volume amounted to 1500 ml and mean tubing length was longer than 2 m. In group B, performer with Medtronic Resting Heart circuit (Medtronic, Inc, Minneapolis, Minn) was used; this MCPB is a closed circuit (containing an active air-removal device) and consists of a centrifugal pump, heat exchanger, a membrane oxygenator and an integrated venous bubble trap; total length of the circuit was <1 m. Because of the shorter tubing length, the circuit was near the patients. Also in group B, all lines were treated with Carmeda (Carmeda AB, Upplands Väsby, Sweden). Cardiotomy reservoir and the conventional suction device were eliminated. The intrapericardial blood was sucked in using only a cell salvage device. Crystalloid priming volume, in group B, was approximately 400–900 ml. In both groups, during aortic cross-clamping, myocardial protection was achieved by hyperkalemic cold blood intermittent antegrade cardioplegia, delivered every 15 min. Myocardial revascularization was obtained by suturing the left internal mammary artery as first-choice arterial conduit on the left anterior descending coronary artery and using the right internal mammary artery and segments of saphenous vein in other vessels. Both groups underwent surgery in normothermia.

Table 1
Baseline characteristics of study participants

Characteristics	Group A (*n*: 30)	Group B (*n*: 30)	*P*-value*
Demographic profile			
Age, years (mean±S.D.)	66.0±7.9	66.6±8.1	ns
Male, *n* (%)	15 (50%)	15 (50%)	ns
Medical history			
Hypertension, *n* (%)	19 (63.3%)	18 (60%)	ns
Chronic obstructive pulmonary disease, *n* (%)	1 (3.3%)	2 (6.6%)	ns
Unstable angina pectoris, *n* (%)	4 (13.3%)	5 (16.6%)	ns
Stable angina pectoris, *n* (%)	26 (86.6%)	25 (83.3%)	ns
NYHA class			
1, *n* (%)	9 (30%)	9 (30%)	ns
2, *n* (%)	9 (30%)	7 (23.3%)	ns
3, *n* (%)	2 (6.6%)	4 (13.3%)	ns
Diabetes mellitus, *n* (%)	6 (20%)	6 (20%)	ns
EuroSCORE			
0–2, *n* (%)	6 (20%)	6 (20%)	ns
3–5, *n* (%)	12 (40%)	14 (46.6%)	ns
>6, *n* (%)	12 (40%)	10 (33.3%)	ns
Angiographic findings			
Angiographic stenosis >75%			
LM, *n* (%)	5 (16.6%)	7 (23.3%)	ns
Single-vessel disease, *n* (%)	4 (13.3%)	2 (6.6%)	ns
Double-vessel disease, *n* (%)	12 (40%)	10 (33.3%)	ns
Triple-vessel disease, *n* (%)	9 (30%)	11 (36.6%)	ns

*$P<0.05$ is significant.
NYHA, New York Heart Association; LM, left main; S.D., standard deviation; ns, not significant.

2.2. NGAL

NGAL belongs to the lipocalin family of proteins. NGAL was originally isolated from the supernatant of activated human neutrophils, but it is also expressed at a low level in other human tissues including the kidney, prostate and epithelia of the respiratory and alimentary tracts [12, 13]. Because of its small molecular size and resistance to degradation, NGAL is readily excreted and detected in the urine. Raised plasma levels of NGAL were found to be strongly correlated with decreased renal function in patients with renal damage due to systemic vasculitis [14]. The results for renal ischemia-reperfusion injury were subsequently confirmed and extended to nephro-toxic agents [2]. It has been suggested that urinary NGAL levels may serve as an early marker for ischemic renal injury in patients after CPB [10].

2.3. NGAL analysis by ELISA

To detect NGAL concentrations, we used an ELISA procedure; this procedure was performed in micro-wells coated with a monoclonal antibody against human NGAL. Bound NGAL was detected with a horseradish peroxidase-conjugated monoclonal antibody and the assay was developed by incubation with a color-forming substrate.

2.4. Statistical analysis

Data are presented as mean values±their first S.D. A Mann–Whitney *U*-test and χ^2-test were used for comparison between groups of continuous and nominal variables, respectively. A $P<0.05$ was considered significant.

Table 2
Operative characteristics of study participants

Characteristics	Group A (*n*: 30)	Group B (*n*: 30)	*P*-value*
Mean bypass time, min (mean±S.D.)	109±32	111±26	ns
Aortic cross-clamp time, min (mean±S.D.)	82±29	84±17	ns
Number of grafts/patient (mean±S.D.)	2.8±0.8	2.9±0.6	ns
IABP, *n* (%)	1 (3.3%)	0	ns
Left internal mammary artery, *n* (%)	30 (100%)	30 (100%)	ns
Right internal mammary artery, *n* (%)	1 (3.3%)	1 (3.3%)	ns

*$P<0.05$ is significant.
IABP, intraortic balloon pump; S.D., standard deviation; ns, not significant.

3. Results

All patients tolerated the surgical procedure and survived without significant complications related to the study. In patients undergoing surgery with MCPB system, neither intraoperative perfusion accidents nor the need to switch to SCPB were reported. Average age was 66.0±7.9 years in Group A vs. 66.6±8.1 years in Group B (*P*: ns). Operative characteristics of the study population are presented in Table 2. All patients were similar regard to intraoperative characteristics. In regards to postoperative outcomes of the study population (Table 3), significant differences appear in relation to duration of ventilation, shorter in Group B (8.7±3.3 h in Group A vs. 6.4±1.6 h in Group B, $P<0.01$), and to bleeding, lesser in Group B (530±321 ml/12 h in Group A vs. 373±218 ml/12 h in Group B, $P<0.01$). Only one perioperative acute myocardial infarction was detected in Group A. There was a trend observed toward shorter intensive care unit stay and hospital stay in Group B, without reaching statistical significance. In-hospital mortality was 0% for both groups.

3.1. Renal function

To detect renal injury, urine and blood was sampled for NGAL and creatinine measurements at three time points: preoperatively (T1), 24 (T2) and 72 h postoperatively (T3). Preoperative NGAL urine concentration did not differ between patients undergoing MCPB or SCPB. The SCPB group but not the MCPB group showed a significant NGAL concentration increase from preoperative during the 1st postoperative day (169.0±163.6 ng/ml in SCPB group vs. 94.1±99.4 ng/ml in MCPB group, $P<0.05$, respectively).

Table 3
Postoperative outcomes of study participants

Characteristics	Group A (*n*: 30)	Group B (*n*: 30)	*P*-value*
Duration of ventilation, h	8.7±3.3	6.4±1.6	<0.01
Bleeding, ml/12 h	530±321	373±218	<0.01
Transfusion of EC, No. of patients	12	5	<0.01
New path. Q-waves, *n* (%)	1 (3.3%)	0	ns
Intensive care unit stay, days (mean±S.D.)	2.6±1.7	2.1±0.9	ns
Hospital stay, days (mean±S.D.)	6.6±2.2	5.8±1.1	ns
Acute renal failure, *n* (%)	2 (6.6%)	0	ns
Death in hospital, *n* (%)	0	0	ns

*$P<0.05$ is significant.
EC, erythrocyte concentrate; ns, not significant; S.D., standard deviation.

During the 3rd postoperative day, NGAL urine concentration was not significantly different from preoperative in both groups (Fig. 1). Two patients in the SCPB group developed AKI (according to AKIN criteria stage 3) and underwent renal replacement therapy with continuous veno-venous hemofiltration; diagnosis of AKI with serum creatinine was only possible three days after operation; on the contrary NGAL concentration, in those patients, raised during the 1st postoperative day (T2) (Fig. 2a,b). No one patient in MCPB developed AKI. There was a trend toward better creatinine concentrations and clearance of creatinine in Group B, without reaching statistical significance (Fig. 3a,b).

3.2. Limitations of the study

The limitations of our study on renal function after MCPB are due to the relatively small number of patients in each group. Moreover, this is a prospective non-randomized study, which limits the power of our conclusions. Only studies on a much larger scale will provide adequate statistical power to assess the assumed benefits of a MCPB system in terms of renal protection during cardiac surgery.

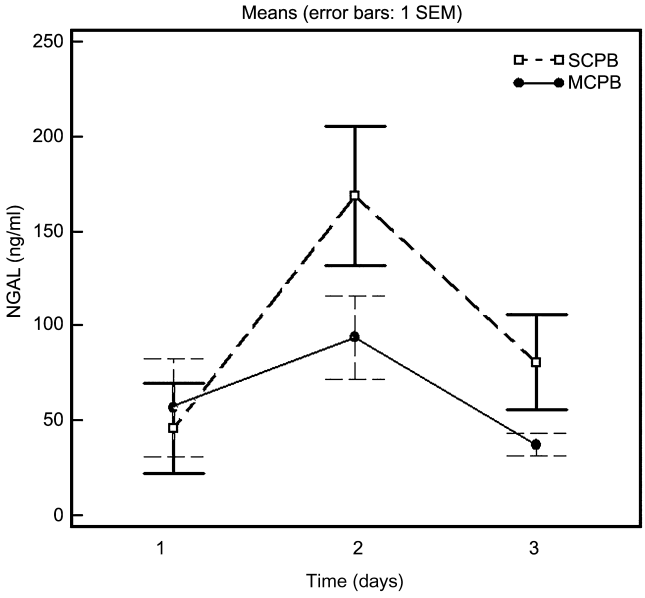

Fig. 1. NGAL urine concentration in the study population at three time points. MCPB, miniaturized cardiopulmonary bypass system; SCPB, standard cardiopulmonary bypass system; NGAL, neutrophil gelatinase-associated lipocalin.

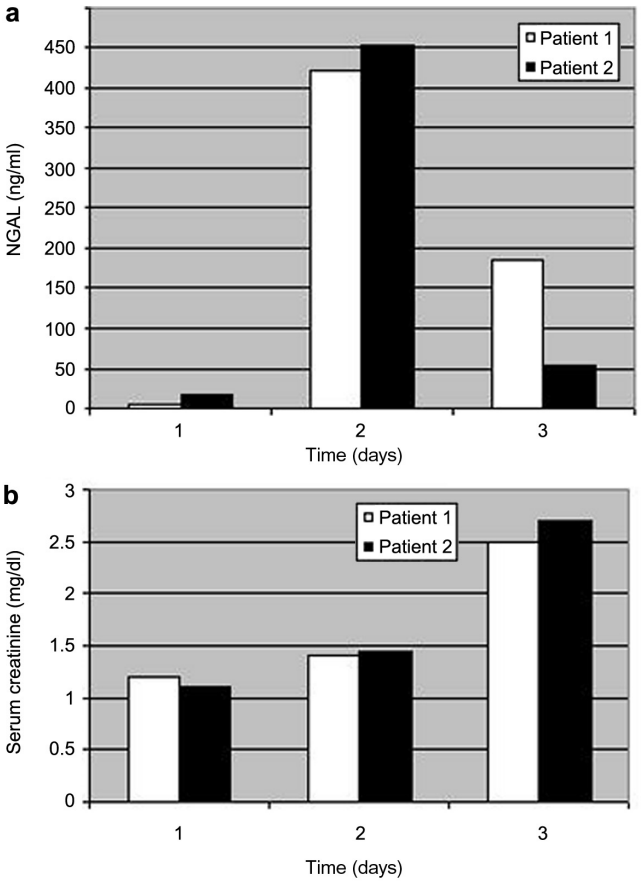

Fig. 2. Biologic data of patients with acute kidney injury: NGAL urine concentration (a) and serum creatinine concentration (b). NGAL, neutrophil gelatinase-associated lipocalin.

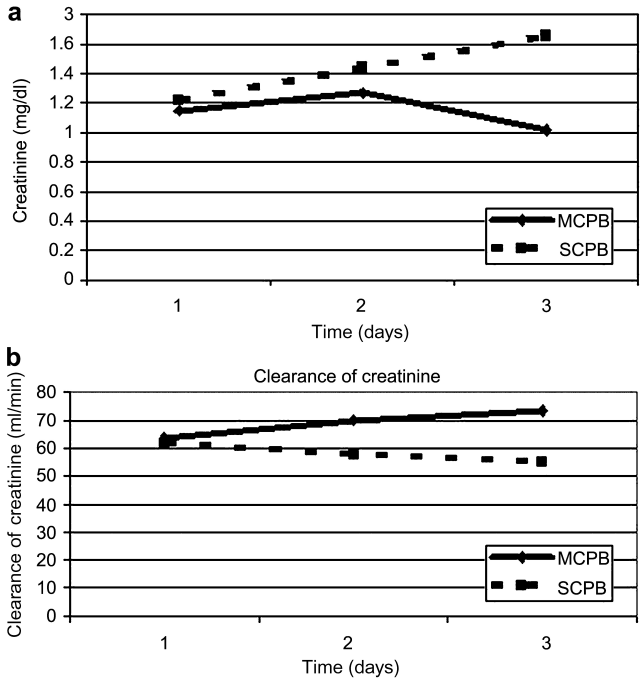

Fig. 3. Creatinine concentrations (a) and clearance of creatinine (b) in the study population. MCPB, miniaturized cardiopulmonary bypass system; SCPB, standard cardiopulmonary bypass system.

4. Discussion

CPB remains a major factor in systemic inflammatory response syndrome apparition; this syndrome is a multifactorial process, which is mainly initiated by blood contact with foreign surfaces. AKI represents a very important and potentially devastating disorder after cardiac surgery [10], and this is the consequence of whole body inflammatory reaction due to CPB. In an attempt to attenuate the pathologic effects of CPB, MCPB systems have been developed to attenuate these disadvantages. The MCPB system may be considered as a simplification of traditional SCPB and may, therefore, represent an attractive compromise between SCPB and coronary artery bypass grafting on a beating heart; Mazzei et al. confirmed that beating heart and MCPB should be considered equivalent tools with respect to reduction of postoperative morbidity [15]. In our study, we prospectively enrolled 60 patients who underwent isolated elective CABG because of coronary artery disease; these patients were operated on with SCPB or MCPB system. The main purpose of our study was to compare the effects of MCPB vs. SCPB system on kidney tissue in patients undergoing myocardial revascularization using urinary NGAL levels as an early marker for renal injury. Our data indicated that in coronary surgery the MCPB system is associated with a lesser amount of transfusions: 12 (40%) patients transfused in Group A vs. 5 (16.6%) patients in Group B; $P<0.01$; 15 units of erythrocyte concentrate was used in Group A vs. 5 units of erythrocyte concentrate in Group B; $P<0.01$. Moreover, we observed lesser postoperative bleeding in Group B that was consistent with other published studies; we observed also shorter duration of ventilation in patients operated on with MCPB system. Regarding kidney function, we tested the hypothesis that the use of a MCPB system has a protective effect on renal function using urinary NGAL levels. Devarajan concluded that NGAL can be considered an emerging troponin for kidney injury [16]. Our study shows that significantly lower urine NGAL levels, especially at 24 (T2) h postoperatively, were observed when MCPB system was used; two patients in SCPB group developed AKI (stage 3) with need of dialysis, and diagnosis of AKI by serum creatinine was only possible three days postoperatively; while the NGAL concentration, in those patients, was raised on the 1st postoperative day (T2). In summary, the MCPB system is safe in routine clinical use and should be considered a safe and efficacious alternative to the use of a SCPB system in all revascularization cases. Kidney function is better protected during MCPB like demonstrated by NGAL levels. NGAL represents an early biomarker of renal failure in patients undergoing cardiac surgery and the valuation of its concentration can aid in medical decision-making.

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