Original Article

Proinflammatory Mediator Response in Coronary Bypass Surgery Using a Centrifugal or a Roller Pump

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ABSTRACT

Major surgery, trauma, and infection induce a proinflammatory mediator response which, if excessive, may cause tissue injury. The response was measured during elective coronary bypass surgery when a centrifugal pump or a roller pump, differing in their basic working principles, was used for extracorporeal circulation (ECC). Eight patients were perfused with a centrifugal pump and eight patients with a roller pump during ECC. Plasma interleukin-1_β (IL-1_β), IL-2, IL-6, tumor necrosis factor$_\alpha$ (TNF_α), group II phospholipase A_2, (PLA_2), endotoxin, fibronectin and serum C-reactive protein (CRP) concentrations were measured. The operation increased plasma IL-6, group II PLA_2, and serum CRP concentration and decreased plasma fibronectin concentrations. IL-1_β and TNF_α concentrations did not change. IL-2 ocurred only occasionally, and endotoxin did not occur in any patient. No differences were seen between the group using a centrifugal pump and the group using the roller pump. Cardiac surgery with a perfusion time of less than two hours thus caused a proinflammatory mediator response which was similar whether a centrifugal or a roller pump was used for ECC.

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INTRODUCTION

During extracorporeal circulation (ECC), blood is susceptible to a certain degree of mechanical trauma, which may depend on the choice between a centrifugal and a roller pump (1). The gentle action of a centrifugal pump is expected to minimize damage to blood cells and thus mitigate changes in the proinflammatory mediator response. The use of ECC is also associated with intestinal hypoperfusion, which may cause intestinal ischemia and increased intestinal permeability and, further, result in the release of endotoxin into the blood circulation (2). These responses combined with contact with foreign surfaces and with the effects of major surgery cause release of inflammatory mediators (3). The present study started with the hypothesis that differences emerge in the responses of proinflammatory mediators depending on whether a centrifugal pump or a roller one is used during cardiac surgery. Interleukin-1_β (IL-1_β), IL-2, IL-6, tumor necrosis factor$_\alpha$ (TNF$_\alpha$) and group II phospholipase A_2 (PLA_2) concentrations were measured.

Table 1: Background data of the patients, means (SD) or median values [range]. No statistically significant differences between the groups.

	Centrifugal pump		Roller pump	
No. of patients	8		8	
Male/female	8/0		7/1	
Age (years)	56	(3.1)	57	(8.5)
Weight (kg)	89.8	(7.3)	84.4	(14.7)
Height (cm)	178	(4.8)	173	(7.5)
NYHA class	3	[2-4]	2	[2-3]
Ejection fraction (%)	67	[51-86]	73	[51-84]
No. of grafts	3	[3-3]	2.5	[2-4]
Duration of:				
- operation (min)	260	(19.0)	248	(21.9)
- perfusion (min)	104	(9.7)	99	(19.1)
Blood transfusion (units of blood)	4	[3-6]	6	[4-8]

MATERIALS AND METHODS

Sixteen patients admitted for elective coronary artery bypass surgery were included in the study (Table 1). Patients with a history of malignant, hematological or endocrinological disease or receiving drugs with an immunosuppressive effect were excluded. The study was approved by the Ethical Committee of the Turku University Medical Faculty and Turku University Central Hospital. Informed consent was obtained from each patient.

The patients were randomly allocated to two groups: centrifugal pump group and roller pump group. Moreover, the persons processing the blood samples were blinded to the group assignment of the patients. In the centrifugal pump group seven patients had for continuous medication beta-blockers; six patients, isosorbide nitrates; and one patient, captopril. In the roller pump group, eight patients had beta-blockers and six patients had isosorbide nitrates. These medications were continued until the operation. As preanesthetic medication the evening before the operation the patients received 5-10 mg of lorazepam perorally and 60-90 minutes before the operation scopolamine 6 µg/kg body weight (b.w.) and morphine 0.2 mg/kg b.w. intramuscularly. The operations were performed under high dose fentanyl anesthesia (100 µg/kg b. w.) supplemented with lorazepam and pancuronium and using mechanical ventilation with 40% oxygen in air. Bypass was performed under moderate (28°C) systemic hypothermia. Anticoagulation was induced with heparin (initial dose 3 mg/kg b.w.). Activated clotting time was maintained over 400 seconds throughout bypass. Cardioplegic arrest was achieved with 1000 ml of 4°C St Thomas's solution and local cooling was obtained by ice-slush in the pericardial cradle. No corticosteroids were used. Invasive central hemodynamics with the use of a Swan Ganz catheter and radial artery cannula, electrocardiogram, pulse oximetry and end-tidal CO_2 were monitored during and after the operation. No remarkable hemodynamic instability occurred in any of the patients. After operation, the patients were ventilated in normocapnia until the first postoperative morning and then extubated. No operative or other complications were seen.

Cardiopulmonary Bypass

A heart-lung machine with a hollow fibre oxygenator[a], cardiotomy reservoir/venous reservoir and customized polyvinylchloride tubing including arterial line leukocyte nondepleting filter[b] was primed with 2000 ml of a crystalloid solution and 100 ml of 15% mannitol. A Biomedicus BP-80 centrifugal pump with bioconsole 540[c] or a Stöckert roller pump[d] with a 70cm silicone tubing was used. The nonpulsatile flow rate was 2.4 l/min/min^2 body surface area, lowered to 1.7 l/min/min^2 body surface area during hypothermia.

Blood Samples

Plasma IL-1_β, IL-2, IL-6, TNF$_\alpha$, group II PLA_2 and endotoxin concentrations were measured in blood samples drawn from the radial artery before induction of anesthesia, at the end of

a Dideco D 703 Compactflo System; Dideco S.p.A., Mirandola, Italy
b Micro 20A, Dideco
c Biomedicus Inc, Minneapolis, MN
d Sorin Biomedical, Irvine, CA

the operation and on the first postoperative morning. In addition, serum C-reactive protein (CRP) and plasma fibronectin concentrations were measured before induction of anesthesia and on the first postoperative morning. Processing of the blood samples was started immediately.

Cytokine Assays

The concentrations of IL-1_β, IL-2, IL-6 and TNF_α were measured from plasma samples centrifuged immediately after separation and stored at -70°C for not more than two months. A sandwich-type ELISA immunoassay[e] was used for measurement of cytokines. The sensitivities of the assays were 0.3 ng/l, 10 ng/l, 0.35 ng/l and 7.5 ng/l for IL-1_β, IL-2, IL-6 and TNF_α, respectively. According to measurement of cytokine levels in 20 healthy persons with the assays, all IL-1_β concentrations were below 3.9 ng/l, IL-2 concentrations below 10ng/l, IL-6 concentrations below 3.1 ng/l, and TNF_α concentrations below 15 ng/l. The intra-assay precision for all these assays was below 15% at the lowest standard level.

Phospholipase A_2 Assay

The plasma concentrations of group II PLA_2 were measured by a time-resolved fluoroimmunoassay, involving a polyclonal rabbit antibody raised against recombinant human group II PLA_2 (4). The upper limit of reference for PLA_2 interval is 10.8 mg/l.

Endotoxin Assay

Gram-negative lipopolysaccharide (endotoxin, LPS) levels in plasma were measured from samples drawn into endotoxin-free vacutainer tubes[f] by the chromogenic Limulus amebocyte lysate (CLAL) assay using a microtiter modification of the test (5) and Coatest[R]-Endotoxine kits[g]. The sensitivity of the assay was 5 ng/l.

CRP and Fibronectin Assays

Samples for measurement of CRP and fibronectin concentrations were stored at -20°C and measured simultaneously using a Hitachi 705 Automatic Analyzer[h]. Serum CRP concentrations were measured by an immunoturbidimetric assay with CRP antiserum[i] and a CRP standard[j].

Plasma fibronectin concentrations were determined by a modified immunoturbidimetric assay according to the endpoint method using the Fibronectin Kit[k](6). For improved sensitivity, 4% polyethylene glycol phosphate buffer (w/v) was used instead of the 3% polyethylene glycol phosphate buffer (w/v) of the kit. The precision of the method at a fibronectin level of 295 mg/l was 1.8% (CV).

Statistical Analyses

The repeated measures analysis of variance (ANOVA) with two within factors (pump and time) was used in the overall analysis. Logarithmic transformation was used for normalization of the distribution of data. When no differences between the groups were observed or when the interaction between the groups and time was not statistically significant but a significant time-effect appeared, the Student's t-test with Bonferroni correction was used of pooled values to identify the points of differences within the groups. Background data are shown as mean values (standard deviation, SD) or median values (range) and follow-up data as median values (25% and 75% quartiles) due to their distribution.

RESULTS

No overall differences were observed in any of the values between the group using a centrifugal pump and that using a roller pump for ECC (Table 2). Instead, several values showed time-

e Quantikine Supersensitive, R&D Systems, Minneapolis, MN
f KabiTube•ET, Kabi Diagnostica, Molndahl, Sweden
g Chromogenix Ab, Mölndahl, Sweden
h Hitachi, Tokyo, Japan
i Kallestad Laboratories, Chaster, MN
j Orion Diagnostica, Espoo, Finland
k Boehringer, Mannheim, Germany

Table 2: Plasma interleukin-1_β (IL-1_β), interleukin-6 (IL-6), tumor necrosis factor$_\alpha$ (TNF_α), group II phospholipase A_2, (PLA_2) and fibronectin, and serum C-reactive protein (CRP) concentrations. Median values and [25% and 75% quartiles]. No statistically significant differences between the groups. P-values refer to statistical significance of pooled values at the end of operation or on the first postoperative day compared to those before anesthesia.

	Before anesthesia	End of operation	First postoperative day
IL-1_β (ng/l)			
Centrifugal pump	1.0 [0-2.5]	1.0 [0-3.5]	3.5 [0-6.0]
Roller pump	0.0 [0-2.0]	0.0 [0-1.3]	0.0 [0-2.0]
IL-6 (ng/l)		p<0.05	p<0.001
Centrifugal pump	4.5 [2.0-7.0]	32.5 [23.0-40.3]	118.0 [75.8-160.8]
Roller pump	3.5 [1.0-4.0]	42.0 [37.5-98.8]	54.5 [50.0-89.0]
TNF_α (ng/l)			
Centrifugal pump	14.5 [8.3-15.8]	19.0 [13.8-24.8]	11.5 [10.0-20.0]
Roller pump	8.5 [4.0-14.0]	11.0 [8.8-14.5]	13.0 [7.5-18.0]
Group II PLA_2 (mg/l)			p<0.001
Centrifugal pump	5.6 [4.6-7.4]	6.9 [4.2-8.7]	34.0 [21.3-55.0]
Roller pump	4.6 [2.3-6.2]	7.7 [2.7-12.2]	29.6 [15.1-50.5]
Fibronectin (mg/l)			p<0.001
Centrifugal pump	364 [299-426]		178 [173-199]
Roller pump	368 [354-471]		201 [189-225]
CRP (mg/l)			p<0.001
Centrifugal pump	<10		80.5 [74.5-88.5]
Roller pump	<10		73.5 [67.8-92.3]

Table 3: Leukocyte, neutrophil, lymphocyte and platelet count, hematocrit and serum alumin concentration before anesthesia and on the first postoperative day. Mean values (SD). No statistically significant differences between the groups. P-values refer to statistical significance of pooled values on the first postoperative day compared to those before anesthesia.

	Before anesthesia	First postoperative day	
Leukocytes (x10^9/l)			p<0.05
Centrifugal pump	7.6 (1.9)	9.0 (2.8)	
Roller pump	7.9 (2.2)	11.8 (3.7)	
Neutrophils (x10^9/l)			p<0.01
Centrifugal pump	4.6 (1.3)	6.8 (2.8)	
Roller pump	5.4 (1.7)	9.4 (3.6)	
Lymphocytes (x10^9/l)			p<0.05
Centrifugal pump	1.9 (0.7)	1.2 (0.4)	
Roller pump	1.6 (0.5)	1.3 (0.7)	
Platelets (x10^9/l)			p<0.001
Centrifugal pump	194 (32)	111 (13)	
Roller pump	189 (63)	110 (32)	
Hematocrit			p<0.001
Centrifugal pump	0.40 (0.03)	0.31 (0.01)	
Roller pump	0.39 (0.03)	0.34 (0.03)	
Serum albumin (g/l)			p<0.001
Centrifugal pump	37.7 (1.7)	19.4 (1.5)	
Roller pump	36.3 (3.1)	19.6 (3.9)	

related changes.

Blood IL-6 concentrations were increased ten-fold at the end of the operation and further increased on the first postoperative morning (Table 2). By contrast, no changes were observed in IL-1_β or TNF_α concentrations. IL-2 was in most patients below the detection limit of the method.

Plasma group II PLA_2 concentrations were increased six-fold on the first postoperative morning (Table 2). Similarly, CRP concentrations were increased, whereas plasma fibronectin concentrations were decreased on the first postoperative day from preoperative values. No endotoxin was detected in any blood samples.

No differences were observed in the leukocyte, neutrophil, lymphocyte or platelet counts, hematocrit or serum albumin concentration between the groups, but time-related changes were observed (Table 3).

Serum free hemoglobin concentration at the end of surgery was in the centrifugal pump group 55 [50 - 180] mg/l (median [25% and 75% quartiles]) and in the roller pump group 80 [68 - 125] mg/l (n.s.).

DISCUSSION

The new findings of this study were that the plasma group II PLA_2 concentrations increased by the first postoperative morning after open-heart surgery and that the responses of the measured proinflammatory mediators were similar whether a centrifugal pump or a roller pump was used during open-heart surgery. The study confirmed also some earlier findings about IL-1_β, IL-6, TNF_α and CRP responses during and after open-heart surgery (7-9).

Group II PLA_2 measured in this study is an important mediator of inflammation, cleaving phospholipid substances to yield biologically active products such as prostaglandins, thromboxanes, leukotrienes and platelet activating factor, but its precise role and its cellular source are unknown (10). By contrast, group I PLA_2 is secreted by pancreatic acinar cells and the best-characterized biological role of this group I PLA_2 is digestion of the phospholipid component of dietary fat (11). Increased levels of group II PLA_2 have been found during major surgery, trauma and infections (12, 13). Similarly, increased levels of group II PLA_2 were observed in this study. No endotoxin was detected in any of our blood samples, suggesting that surgical trauma per se increases group II PLA_2 concentrations. Moreover, our finding that IL-6 concentrations increased earlier than those of group II PLA_2 supports the concept that IL-6 is involved in the regulation of group II PLA_2 synthesis and secretion (14).

The increase in IL-6 concentrations seen in this study after surgery is a well-known phenomenon (8, 9). IL-6 is a key mediator of the acute-phase response with extensive biological activities. Recently, IL-6 has been shown to impair cardiac function (15), IL-2 and TNF_α have negative inotropic effects in isolated hamster papillary muscle preparations (16) and IL-1_β and TNF_α cause relaxation of vessel walls through induction of nitric oxide synthase in smooth muscle (17). However, no changes occurred in our study in TNF_α or IL-1_β concentrations, and we could measure IL-2 only at times. Increased TNF_α concentrations have been reported in patients during the ischemic and reperfusion periods of ECC (8,18), but in one study TNF_α concentrations still remained elevated on the first postoperative day after coronary artery bypass surgery (19). As these cytokines, especially TNF_α, are secreted in pulses and their half-life is short in the blood circulation, we may have missed the peaks.

On the other hand, in spite of frequent sampling, Mazer and co-workers found no changes in IL-1_β plasma concentrations during or after cardiopulmonary bypass (20), and other studies have reported similar findings (7,9,15,21). In one study, intracellular monocyte IL-1_β concentrations or activities were not increased during or immediately after bypass. However, intracellular monocyte IL-1 activity increased 24 hrs after ECC, but no TNF_α occurred in monocyte lysates or plasma (22). Cytokine response to open-heart surgery is greater after normothermic

than after hypothermic bypass (23), but lack of TNF_α response in our study is not explained by body temperature since patients in the study of Jansen and co-workers with increased TNF_α values had like our patients hypothermic ECC (19).

The absence of increased TNF_α or $IL\text{-}1_\beta$ concentrations in our study is compatible with our finding of the absence of endotoxin in any blood samples. Endotoxin is a potent activator of the inflammatory response and stimulates macrophages to synthesize and release cytokines. In earlier studies, high serum endotoxin levels have been observed in the blood circulation (24) and in samples from the ECC circuit, pulmonary artery and cardiac suction lines in patients undergoing cardiopulmonary bypass (25). The chromogenic Limulus assay is very sensitive, but, on the other hand, trace amounts of contaminating endotoxin can cause false positive reactions. This was carefully avoided in the present study, and no endotoxemia was detected in our patients.

Entrapment of endotoxin in fibrin clots does not explain the absence of endotoxin in our study, because citrated plasma was used instead of serum to avoid this problem. The mean perfusion time in some earlier studies was longer than in our study (24,25), and intraoperative contamination by fluids, extracorporeal circuit and other material may have affected the results of these studies. In some recent studies, serum endotoxin values above normal range have been observed during aortic cross-clamp and perfusion (8), during prolonged ECC (26) or in some cases at the end of ECC, 3 hours thereafter and even on the first postoperative morning (27) as well as in hepatic and mixed venous blood until one hour after termination of ECC (7). Therefore, we cannot definitely exclude the possibility that our patients had elevated endotoxin levels for a short period during ECC and peaks of TNF_α and $IL\text{-}1_\beta$ in their blood circulation which went undetected without any clinical effects.

Earlier in vitro studies with human or animal blood have shown that platelets are better preserved and leukocytosis, hemolysis as well as complement activation show lower levels (1,28) when a centrifugal pump is used instead of a roller one, especially at long perfusion times (29). Wheeldon and coworkers found also in their clinical study lower C_{3a} levels and higher platelet count when a centrifugal pump was used instead of a roller pump (30). However, most clinical studies show no differences in plasma free hemoglobin concentration, hematocrit or platelet count (31) or in clinical outcome data (32,33) when these two types of pumps are used during cardiac surgery. Also, our clinical study did not show differences in the concentrations of proinflammatory mediators or in the leukocyte, neutrophil or lymphocyte counts or in the extent of hemolysis when a centrifugal or a roller pump was used in elective coronary bypass surgery. Even if the number of patients in this study was low, none of the tests showed any differences between the groups making the likelihood of a false negative result in the proinflammatory mediator response less likely. Thus a general modifying effect of either pump alone is unlikely when the patients have stable hemodynamics and their mean perfusion time is short as was the case in our patients. Experimental studies show differences in hemolysis and complement activation first after a perfusion time of 8-16 hours (29). It is, therefore, possible that differences might appear during longer extracorporeal circulation, e.g. in patients treated for respiratory failure which was not tested in this study.

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