Surgical trauma affects the proinflammatory status after cardiac surgery to a higher degree than cardiopulmonary bypass

Roland Prondzinsky, MD,^a Axel Knüpfer, MD,^a Harald Loppnow, PhD,^a Frank Redling, MD,^b Dirk W. Lehmann, MD,^c Ina Stabenow, MD,^a Rochus Witthaut, MD,^a Susanne Unverzagt, PhD,^d Joachim Radke, MD,^c Hans-Reinhard Zerkowski, MD,^b and Karl Werdan, MD^a

Dr Prondzinsky

From the Department of Medicine III,^a Department of Cardiothoracic Surgery,^b Department of Anesthesiology,^c and Operative Intensive Care Medicine und Coordination Centre for Clinical Trials,^d Martin-Luther-University Halle-Wittenberg, Halle (Saale), Germany.

This study was supported by grant BMBF-06 of the German government to H. Loppnow and K. Werdan, and by an unrestricted grant from Guidant Corporation to R. Prondzinsky and K. Werdan.

Received Dec. 1, 2003; revisions received June 7, 2004; accepted for publication July 6, 2004.

Address for reprints: Roland Prondzinsky, MD, Martin-Luther-University Halle-Wittenberg, Department of Internal Medicine III, Ernst-Grube-Str 40, D-06097 Halle (Saale), Germany (E-mail: roland.prontzinsky@medizin.uni-halle.de).

J Thorac Cardiovasc Surg 2005;129:760–6
0022-5223/\$30.00

Copyright © 2005 by The American Association for Thoracic Surgery

doi:10.1016/j.jtcvs.2004.07.052

Objectives: Cytokines contribute to the development of the systemic inflammatory response syndrome or multiple-organ failure frequently observed after cardiopulmonary bypass–supported cardiac surgery. To quantify the contribution of bypass–induced versus trauma–induced inflammatory response after coronary artery bypass grafting, we examined plasma cytokine levels in 120 patients with coronary artery disease who were treated with or without cardiopulmonary bypass–assisted procedures.

Methods: Patients were treated in accordance with one of the following protocols: (1) elective percutaneous coronary intervention without cardiopulmonary bypass ($n = 69$), (2) cardiopulmonary bypass–supported percutaneous coronary intervention (cardiopulmonary bypass–percutaneous coronary intervention; $n = 10$), and (3) cardiopulmonary bypass–supported coronary artery bypass grafting (cardiopulmonary bypass–coronary artery bypass grafting; $n = 41$). Cytokine levels (picograms/milliliter) were measured by enzyme-linked immunosorbent assay from plasma samples obtained at various time points.

Results: Interleukin-6 was measured in blood samples from all 3 patient populations. The maximum interleukin-6 level was 13.6 ± 22.3 pg/mL in the percutaneous coronary intervention group, 170.4 ± 165.4 pg/mL in the cardiopulmonary bypass–percutaneous coronary intervention group, and 640.3 ± 285.7 pg/mL in the cardiopulmonary bypass–coronary artery bypass grafting group. Interleukin-6 levels were significantly different, and the 95% confidence intervals did not overlap. In the cardiopulmonary bypass–percutaneous coronary intervention group, bypass duration correlated well with interleukin-6 production ($r = 0.915$; $P < .001$), whereas these parameters did not correlate in patients who underwent cardiopulmonary bypass–coronary artery bypass grafting ($r = 0.307$; $P = .054$).

Conclusions: These findings support the suggestion that surgical trauma and cardiopulmonary bypass contribute to the inflammatory response after cardiac surgery, although trauma may contribute to a higher degree.

Organ dysfunction after cardiac surgery is mainly attributed to the systemic inflammatory response syndrome (SIRS). Cytokines are released after surgical trauma or when blood is exposed to artificial surfaces during cardiopulmonary bypass (CPB). In addition to other factors, high levels of cytokines may contribute to postoperative complications such as SIRS and multiple organ failure.¹ Cytokine plasma levels peak within hours after

termination of CPB and decrease to preoperative levels after 24 hours.² Patients with severely impaired preoperative left ventricular function and complicated postoperative courses after cardiac surgery³ express higher interleukin-6 (IL-6) levels⁴ and higher tumor necrosis factor- α (TNF- α) and TNF receptor (RI and RII) levels.⁵ However, it remains to be shown whether the increased inflammatory response, for which increased plasma IL-6 levels after CPB-supported major cardiac surgery are indicative, is predominantly induced by the operative trauma, including thoracotomy, or results from the activation of blood after contact with the artificial surfaces of the extracorporeal circuit or the mechanical stress exerted by it. In addition to alternative approaches,^{6,7} interest has focused on minimally invasive revascularization strategies with mini-thoracotomies and CPB, or even without CPB, as well as different revascularization techniques (eg, CPB-percutaneous coronary intervention [PCI] or conventional PCI). The latter strategies offer interesting therapeutic perspectives for the vast number of patients who require cardiac revascularization. Such strategies reduce the risk of an escalating postprocedural SIRS.

This study was designed to distinguish the contribution of CPB from that of surgical trauma to the increase of inflammatory mediators after cardiac surgery. Because IL-6 levels were much higher in patients undergoing cardiac surgery supported by CPB than in those patients who underwent bypass-supported PCI, we conclude that both CPB and surgical trauma contribute to the observed inflammatory response. Surgical trauma of conventional surgical procedures, however, is a more potent activator of the inflammatory response after cardiac surgery than CPB.

Patients and Methods

Patients

This prospective study was approved by the local ethics committee and carried out from 1995 to 1997. After giving their written informed consent, 120 patients were included. Coronary artery disease was diagnosed in all patients, for which they were treated. After diagnostic heart catheterization, patients were assigned to 1 of 3 groups according to the clinical criteria outlined in Table 1. The CPB-PCI group included patients who were not eligible for coronary artery bypass grafting and in whom unsupported PCI was expected to present an unacceptable risk. Criteria for CPB-PCI included poor left ventricular function or 50% or more of jeopardized myocardium close to the targeted vessel, following the definitions used by the "National Registry for Supported Angioplasty."⁸

All CPB procedures were performed under standard general anesthesia: midazolam, pancuronium, and fentanyl were used for induction. Anesthesia was maintained by isoflurane inhalation. The activated clotting time (ACT) was maintained at or above 400 seconds by appropriate heparin doses. During CPB, perfusion pressure was maintained at 50 to 70 mm Hg. Open circuits with combined venous and cardiectomy reservoirs were

used in both CPB groups. Each system included a roller pump, hollow-fiber membrane oxygenator with integrated heat exchanger, and arterial blood filter. All circuits were uncoated. The CPB priming solution (1751 mL: 850 mL Thomaeson electrolyte prime, 500 mL hydroxyethyl starch 6%, 250 mL mannitol M15, 50 mL NaHCO₃, 100 mL aprotinin, and 1 mL heparin) contained 5000 IU of heparin. Both CPB groups were treated with the same standard intravenous heparinization regimen: 350 IU/kg body weight before cannulation and ACT check 5 minutes later (aiming for 400 seconds). If the ACT was lower, an extra third of the initial heparin dose was administered. After weaning from CPB, patients were given protamine to neutralize the heparin. Heparin antagonization was identical in both groups.

In patients undergoing CABG, myocardial protection was performed by antegrade infusion of Bretschneider solution. For inotropic support, epinephrine and enoximone were used as first-line drugs. In the CPB-PCI group, arterial (16F) and venous (18F) cannulas were percutaneously placed in the respective femoral vessels. All CPB procedures were performed under normothermic conditions. Unsupported PCI was performed by the Judkins technique through the femoral artery using conventional (7F) guiding catheters and 0.014-inch guide wires. For coronary angioplasty, 2.5- to 3.5-mm balloon catheters were used.

Determination of Cytokine Levels

Blood samples were obtained before the respective intervention as well as 1, 2, 3, 6, 24, 48, 72, 96, and 120 hours after starting each procedure. Samples were centrifuged, and the plasma was stored at -80°C . Cytokine measurements were performed with commercial enzyme-linked immunosorbent assay kits (IL-6 OPTeIA, Pharmingen, Heidelberg, Germany; IL-1ra, IL-8, Biosource, Hamburg, Germany; IL-1 β , IL-6, IL-10, TNF, TNF RI, and RII, Roche Diagnostics GmbH, Mannheim, Germany; sCD14: IBL, Hamburg, Germany; IL-1 α : R&D Systems, Wiesbaden, Germany) in accordance with the manufacturers' recommendations.

Statistical Analysis

Statistical analysis was performed by using SPSS (SPSS Inc, Chicago, Ill) for descriptive statistics and analysis of variance. Changes of IL-6 serum levels were prospectively defined as the end points of the study. The relationship between the IL-6 level on the first day posttreatment and the type of management protocol was assessed in 69 patients who underwent PCI, in 10 patients after CPB-PCI, and in 41 patients after CABG (Table 1). The analysis focused on the 2- to 24-hour time period to avoid an observational bias caused by missing data of earlier or later time points. The statistical analysis included analysis of variance, risk score ranging, Pearson's correlation, multiple Sidak adjusted comparisons for global probability, and the Dunnett C test for unequal variances.

To avoid systematic errors when calculating maxima, the baseline value (preprocedure sample) was subtracted from the level reached at each subsequent sampling time. The peak value was then determined as indicated in formula 1:

Formula 1:

TABLE 1. Patient data: Clinical, angiographic, and procedural characteristics

	PCI	CPB-PCI	CPB-CABG
No. of patients	69	10	41
Demographic data			
Age (y)	58.8 ± 9.0	58.0 ± 7.3	63.7 ± 8.9
Sex (male/female)	53/17	7/1	36/5
Preprocedural data			
Coronary artery disease (1/2/3 vessel disease)	21/22/21 (5)*	2/3/5	1/13/27
Previous angioplasty	28	2	3
Previous CABG	1	6	0
Heart failure (NYHA)	2.20 ± 0.88	2.67 ± 0.71	2.34 ± 0.76
Angina pectoris (CCS)	1.87 ± 0.7	2.67 ± 1.1	2.51 ± 0.8
Diabetes	24/44 (1)*	5/5	12/29
Ejection fraction (%)	63.1 ± 13.0 (2)*	45.0 ± 19.4	57.1 ± 17.6 (1)*
APACHE-II (preprocedural)	5.0 ± 1.9 (4)*	11.8 ± 2.3 (4)*	5.8 ± 2.3
Risk score	1.29 ± 0.78 (5,* 1†)	1.90 ± 0.67	1.62 ± 0.79 (1)*
Medication‡			
Acetylsalicylic acid	66/3	70 (3)*	37/4
Ticlopidine	15/48 (6)*	4/2 (4)*	0/41
Clopidogrel	0/64 (5)*	0/7 (3)*	0/41
Abciximab	1/63 (5)*	0/7 (3)*	0/41
Tirofiban	0/64 (5)*	0/7 (3)*	0/41
Eptifibatide	0/64 (5)*	0/7 (3)*	0/41
Procedural data			
Systemic heparinization§			
Preoperational	69/0	10/0	41/0
1. Postprocedural day	14/55	7/3	38/3
2. Postprocedural day	3/66	2/8	18/23
3. Postprocedural day	10/59	1/5 (4)*	11/30
CPB duration (min)	—	82.9 ± 31.0	56.3 ± 30.2
CPB mean flow (L/min)	—	2.35 ± 0.4	4.60 ± 0.4
Stents	11	6	—

PCI, Percutaneous coronary intervention; CPB, cardiopulmonary bypass; CABG, coronary artery bypass grafting; NYHA, New York Heart Association; CCS, Canadian Cardiovascular Society.

*Number of patients with missing data.

†Treatment day of missing data.

‡Yes/no.

§Intravenous/subcutaneous.

$$\begin{aligned} \text{Max}_{\text{IL-6}} = & \text{Max (IL-6/2 hours - baseline IL-6;} \\ & \text{IL-6/3 hours - baseline IL-6;} \\ & \text{IL-6/6 hours - baseline IL-6;} \\ & \text{or IL-6/24 hours - baseline IL-6)} \end{aligned}$$

Analysis of variance requires that the IL-6 level increase is normally distributed with comparable variances among the 3 treatment groups. However, the data were not normally distributed, but showed a steep left-sided slope. Therefore, a sensitivity analysis investigating the influence of the steep left-sided slope and different variances was performed. The analysis showed that neither resulted in the loss of significance of the differences in IL-6 production among the 3 treatment groups.

A basal increase of the IL-6 level can be the result of various preclinical parameters. The conditions described by the preprocedural APACHE-II score or the parameters of the risk score described next (formula 2), including diabetes (DM), ejection frac-

tion (EF), and severity of coronary artery disease (CAD; all 3 presented in Table 1), may be of major importance for the preprocedural IL-6 plasma level. Thus, the latter 3 variables were included in the risk score. The sum of the risk score can range from 0 (risk not increased) to 3 (very high risk). For the analysis of variance, the baseline conditions were treated as covariates.

Formula 2:

$$\text{risk score} = \text{sum_DM} + \text{sum_EF} + \text{sum_CAD}$$

$$\text{sum_DM} = \begin{cases} 1 & \text{if diabetic} \\ 0 & \text{if not diabetic} \end{cases}$$

$$\text{sum_EF} = \begin{cases} 1 & \text{if EF} < 50 \\ \frac{70}{20} - \frac{1}{20} \text{EF} & \text{if } 50 \leq \text{EF} \leq 70 \\ 0 & \text{if EF} > 70 \end{cases}$$

Figure 1. Increased levels of various cytokines in cardiopulmonary bypass (CPB)-supported patients undergoing percutaneous coronary intervention (PCI) (CPB-PCI). Plasma levels of 3 high-risk patients undergoing CPB-PCI (marked by 3 different symbols) of interleukin (IL)-6, soluble CD14 (sCD14), tumor necrosis factor (TNF) receptors type 1 (RI) and type 2 (RII), IL-1 receptor antagonist (IL-1ra), and IL-10 were measured in blood samples obtained at various time points. The cytokine levels are given in percent; the 100% reference values for the various cytokines were as follows: IL-6, 70 pg/mL; sCD14, 8000 pg/mL; TNF RI, 5000 pg/mL; TNF RII, 12,000 pg/mL; IL-1ra, 20,000 pg/mL; IL-10, 700 pg/mL). Note the broken scale in the IL-1ra graph.

$$\text{sum_CAD} = \begin{cases} 1 & \text{if CAD} = 3 \\ 0.5 & \text{if CAD} = 2 \\ 0 & \text{if CAD} = 1 \end{cases}$$

Both factors (APACHE-II score and risk score) were taken into account because both reflect the patients' overall pretreatment condition. The factors were not correlated with each other (Pearson correlation: $r = 0.167$; $P = .073$).

Differences between treatment modalities and their relationship to IL-6 release were assessed by variance analysis. The model took the influence of the treatment method on IL-6 increase into account. Pretreatment risk (risk score according to formula 2) and preprocedure APACHE-II score were considered to be covariates. Differences between the treatment methods were also evaluated by using multiple Sidak adjusted comparisons for a global probability of an error of 5%. Furthermore, the influence of the different variances and the steep left-sided slope were investigated by additional analyses of variance.

Results

High-Risk CPB-Supported Patients Undergoing Percutaneous Coronary Intervention Express Elevated Levels of Various Cytokines

To study the role of cytokines in the inflammatory response to cardiac surgery supported by CPB, we first investigated the expression of various cytokines in 3 selected high-risk patients undergoing CPB-PCI. Cytokine levels were determined in samples taken at various time points: before surgery (0), immediately after starting the procedure, and up to 120 hours postoperatively. Among the cytokines tested, IL-1 α and IL-1 β were not detectable, and neither IL-8 nor TNF was elevated throughout the investigational period

(data not shown). Plasma levels of IL-6, IL-1 receptor antagonist (IL-1ra), IL-10, soluble TNF receptor types 1 and 2, and soluble CD14 were elevated (Figure 1). Because the role of TNF receptors and sCD14 is still controversial, and IL-1ra and IL-10 levels showed marked variations between patients, we used IL-6 as an accepted marker for the inflammatory response in the subsequent investigation.

Interleukin-6 Levels in High-Risk, CPB-Supported Patients Undergoing Percutaneous Coronary Intervention Are Lower than in Bypass-Supported Patients Undergoing CABG

To investigate to what extent CPB contributes to the inflammatory response after cardiac surgery, we compared the release of IL-6 during and after conventional PCI, CPB-PCI, and CPB-CABG. Patients undergoing PCI produced only very low levels of IL-6 during the whole time course of the investigation. In these patients, the IL-6 mean peak plasma level ($\text{Max}_{\text{IL-6}}$) (Figure 2) defined between 2 and 24 hours was 13.6 ± 22.3 pg/mL. In contrast, patients undergoing CPB-PCI produced more IL-6 (170.4 ± 165.4 pg/mL). Patients undergoing CPB-CABG experienced CPB under conditions qualitatively comparable with those of patients undergoing CPB-percutaneous transluminal coronary angioplasty, but instead of PCI, patients undergoing CPB-CABG were subjected to conventional major cardiac surgery. In these patients, the $\text{Max}_{\text{IL-6}}$ was 640.3 ± 285.7 pg/mL.

IL-6 levels may be influenced by various baseline conditions reflected by the pretreatment APACHE-II and risk

Figure 2. IL-6 plasma levels in patients undergoing PCI, CPB-PCI, or CPB-CABG are significantly different. Plasma was taken from patients of the 3 groups at various time points after the surgical procedure was started. IL-6 was measured by enzyme-linked immunosorbent assay. The preoperative level was subtracted, maximal IL-6 release ($\text{Max}_{\text{IL-6}}$) in the 2- to 24-hour period was determined, and a box plot analysis was performed. The circle in the box reflects the mean ($\text{Max}_{\text{IL-6}}$: PCI 13.6 ± 22.3 pg/mL; CPB-PCI, 170.4 ± 165.4 pg/mL; CPB-CABG, 640.3 ± 285.7 pg/mL) of the data, and the dotted line reflects the median. The lines above and below the box provide the 75th and 25th percentiles, respectively. The whiskers above and below show the 90th and the 10th percentiles, respectively. The *P* values obtained by Sidak conformation are presented. Ninety-five percent confidence intervals were -28.0 and 55.2 for PCI; 61.1 and 279.6 for CPB-PCI; and 586.4 and 694.1 for CPB-CABG.

score. In the CPB-PCI group, both scores were unfavorable compared with PCI and CPB-CABG (Table 1) and were therefore entered as covariates. Variance analysis revealed that 75% of the IL-6 level changes result from a combination of the specific type of treatment, the APACHE-II, and the risk score. Analysis of variance also showed that the increase of the IL-6 level was significantly related to the particular type of treatment ($P < .001$), whereas the initial conditions did not have a significant impact (APACHE-II, $P = .274$; risk score, $P = .164$). All differences between the 3 treatment groups were validated by pairwise multiple comparison (Sidak correction, Dunnett C test for unequal variances; P values $< .026$). The differences between treatment groups were significant (compare Figure 2). The lack of overlap between the confidence intervals, presented in the legend to Figure 2, supports the suggestion that these differences are significant. The differences are not affected by logarithmic transformation of the data or by adding the covariates. On the other hand, different baseline conditions

Figure 3. Correlation between CPB duration and $\text{Max}_{\text{IL-6}}$ is lower in the CPB-CABG group than in the CPB-PCI group. The IL-6 release of each individual patient was measured in the 2- to 24-hour time period. $\text{Max}_{\text{IL-6}}$ was determined for this period (Figure 2), and the data were correlated to the duration of the CPB. The correlation of the CPB-PCI (filled circles) was $r = 0.915$ ($P < .001$), and the correlation of the CPB-CABG (open circles) was $r = 0.307$ ($r = 0.054$). The outlier (filled triangle) was removed from the CPB-PCI calculation, because outlier analysis showed that the value was out of the 3S area.

present in the groups investigated in this study may disguise the influence of the type of treatment, although the treatment may have a significant impact. The impact of the baseline data interferes with the level of significance, the influence of the type of procedure, and the role of CPB on IL-6 release. However, the influence of the initial conditions, reflected by the pretreatment risk score and the APACHE-II score, on IL-6 release remained insignificant.

The data indicated a higher contribution of the surgical trauma to elevated IL-6 levels in patients undergoing CPB-CABG, compared with the effects of CPB. This suggestion is further supported by the observation that, compared with the CPB-CABG group, CPB duration is significantly higher (Mann-Whitney *U* test: $P = .004$; Table 1) in patients undergoing CPB-PCI and by analyzing the correlation of the bypass duration to maximal IL-6 levels. The latter analysis showed a correlation in the CPB-PCI group ($r = 0.915$, $P < .001$), whereas the correlation was low in the CPB-CABG group ($r = 0.307$) and not significant ($P = .054$), indicating that IL-6 levels depend more on CPB duration in patients undergoing CPB-PCI compared with CPB-CABG (Figure 3). On the other hand, there was no detectable correlation between mean flow rates ($r = 0.067$) or peak flow rates ($r = 0.164$) and the maximal IL-6 levels in patients undergoing CPB-CABG or CPB-PCI ($r = 0.454$ or 0.425 , respectively).

Discussion

Cytokines are important modulators of immune functions, infectious processes, and the inflammatory response.⁹ Recent interest has focused on the role of cytokines in cardiac surgery, particularly CPB-supported surgery. In comparison with other heart diseases, little is known about cytokine release in patients who develop postoperative complications after cardiac surgery.¹⁰ So far, it has not been possible to distinguish between the role of surgical trauma versus CPB on cytokine production after cardiac surgery. We provide evidence that in patients undergoing CPB-CABG, the surgical procedure itself is a more potent activator of the proinflammatory response than CPB.

Elevated levels of cytokines have been observed in patients who underwent CPB-supported surgery.¹¹⁻¹³ Severe inflammatory response to CPB-supported cardiac surgery is thought to be mediated by cytokines involved in the regulation of inflammation, such as IL-6 or TNF. However, the role and expression of cytokines in high-risk patients with cardiac disease who undergo PCI supported by normothermic CPB are not well understood. Thus, we first investigated the expression of important proinflammatory and anti-inflammatory cytokines in 3 selected high-risk patients undergoing CPB-PCI. Among the cytokines tested, plasma levels of TNF, IL-1 α , IL-1 β , and IL-8 were not above baseline in these patients. Likewise, our previous reports regarding TNF expression after cardiac surgery have shown that postoperative TNF levels are not increased in patients with low APACHE-II scores.⁵ This is consistent with the present results, because the APACHE-II score of patients investigated here was below 19. We have also reported⁵ that patients with APACHE-II scores greater than 24 expressed considerably elevated TNF levels, and that TNF and TNF receptor levels could be used to predict adverse outcome. On the other hand, data regarding TNF during cardiac surgery are conflicting,¹⁴ with TNF- α reported to be present in chronic heart failure and cachexia,^{15,16} as well as during and after CPB, paralleled by elevated levels of endotoxin.¹⁷ The role of IL-1 in cardiovascular diseases has not been investigated in great detail.^{18,19} However, IL-1 is present in the plasma of patients with myocarditis,²⁰ but not in those with myocardial infarction²¹ or chronic heart failure.²² From the various cytokines tested, we chose IL-6 as a marker of the inflammatory response in all 3 patient groups. Increased IL-6 levels have been proposed as a prognostic proinflammatory marker, for example, in heart failure²³ and after cardiac surgery with CPB support.²⁴ Our data show that the maximal IL-6 levels observed during the first postoperative 24 hours were significantly higher in patients undergoing CPB-CABG compared with PCI and CPB-PCI. These results are consistent with recent publications showing that procedures without CPB support ("off-pump procedures") minimized surgical trauma, other than the CPB-

PCI techniques used in this work, and decreased the severity of the postoperative SIRS.²⁵⁻²⁸

Our data extend the mentioned literature findings by providing evidence that in patients undergoing CPB-CABG, trauma contributes more potently to IL-6 release than extracorporeal circulation. This conclusion is supported by 2 lines of evidence. First, we show that the maximum IL-6 release in patients undergoing CPB-PCI is much lower than in patients undergoing CPB-CABG. In patients undergoing CPB-PCI, most of the IL-6 release is probably induced by CPB, because only very small amounts of IL-6 are detectable in patients undergoing PCI without CPB. Assuming a comparable effect of CPB in patients undergoing CPB-CABG or CPB-PCI, trauma must be the major IL-6 inducer in patients undergoing CPB-CABG: After correction for the IL-6 level observed in patients undergoing PCI (13.6 pg/mL), the contribution of the CPB (156.8 pg/mL), as determined in patients undergoing CPB-PCI, counts for only one quarter of the IL-6 (626.7 pg/mL) measured in patients undergoing CPB-CABG. The remaining 75% of the IL-6 ($626.7 - 156.8 = 469.9$ pg/mL) may be caused by the trauma and additional factors. Second, the present data show a statistically significant correlation ($P < .001$) of CPB duration and IL-6 release ($r = 0.915$) in patients undergoing CPB-PCI. However, in patients undergoing CPB-CABG, the correlation between bypass duration and IL-6 peak levels is low ($r = 0.307$) and not significant ($P = .054$). It remained insignificant ($P = .095$), even if the outlier was included in the calculation of the correlation.

Conclusions from these results may be limited because of the relatively small patient numbers in the CPB-PCI group. Nevertheless, we believe that the weak correlation between IL-6 release and CPB duration in patients undergoing CPB-CABG (in comparison with CPB-PCI patients) indicates trauma (vs extracorporeal circulation) as a cause of higher and more variable IL-6 release.

With respect to the statistical analysis, the small number of patients in the CPB-PCI group presents a particular problem, especially because of the nonrandomized character of the study. For ethical and legal reasons, however, randomization would not have been acceptable at any time.

In addition, inclusion of a CPB-PCI patient group was a unique chance from a historical perspective, because this treatment strategy is no longer indicated or has only rare indications. In view of the markedly improved options provided by catheter interventions, including clearly safer and less-complicated stent insertion and the use of GP-IIb/IIIa antagonists supplemented by intraaortic balloon pumping, CPB-PCI can no longer be justified today.

Current data²⁹ are inconclusive as to which patient group derives the most benefit from off-pump coronary revascularization. Reduced inflammatory response, that is, initial benefit of avoiding CPB, has to be weighed against de-

creased 3-month graft patency rates. Conceivably, the benefit will be highest in elderly patients in whom preoperative comorbidities are more frequent and who are subsequently expected to have a higher perioperative risk of organ failure.

In summary, the present data show that both CPB and the surgical procedure itself strongly contribute to the induction of IL-6 release during cardiac surgery. However, the contribution of trauma, compared with CPB, is much higher in CPB-assisted cardiac surgery.

References

- Wan S, LeClerc J-L, Vincent J-L. Inflammatory response to cardiopulmonary bypass: mechanisms involved and possible therapeutic strategies. *Chest*. 1997;112:676-92.
- Steinberg JB, Kapelanski DP, Olson JD, Weiler JM. Cytokine and complement levels in patients undergoing cardiopulmonary bypass. *J Thorac Cardiovasc Surg*. 1993;106:1008-16.
- Pilz G, Kääb S, Kreuzer E, Werdan K. Evaluation of definitions and parameters for sepsis assessment in patients after cardiac surgery. *Infection*. 1994;22:8-17.
- Fujiwara T, Seo N, Murayama T, Hiratao S, Kawahito K, Kawakami M. Transient rise in serum cytokines during coronary artery bypass graft surgery. *Eur Cytokine Netw*. 1997;8:61-6.
- Pilz G, Fraunberger P, Appel R, Kreuzer E, Werdan K, Walli A, et al. Early prediction of outcome in score-identified, postcardiac surgical patients at high risk for sepsis, using soluble tumor necrosis factor receptor p55 concentrations. *Crit Care Med*. 1996;24:596-600.
- Menasche P. The inflammatory response to cardiopulmonary bypass and its impact on postoperative myocardial function. *Curr Opin Cardiol*. 1995;10:597-604.
- Pilz G, Appel R, Kreuzer E, Werdan K. Comparison of early IgM-enriched immunoglobulin vs. polyvalent IgG administration in score-identified postcardiac surgical patients at high risk for sepsis. *Chest*. 1997;111:419-26.
- Tommaso CL, Vogel RA. National registry for supported angioplasty: results and follow-up of three years of supported and standby supported angioplasty in high-risk patients. *Cardiology*. 1994;84:238-44.
- Levy JH, Tanaka KA. Inflammatory response to cardiopulmonary bypass. *Ann Thorac Surg*. 2003;75:15-20.
- Werdan K. The activated immune system in congestive heart failure—from drowsy to the cytokine paradigm. *J Intern Med*. 1998;243:87-92.
- Khobar KSA, ElBarbary MA, Khouqeer F, Devol E, Al-Gain S, Al-Halees Z. Circulating endotoxin and cytokines after cardiopulmonary bypass: differential correlation with duration of bypass and systemic inflammatory response/multiple organ dysfunction syndromes. *Clin Immunol Immunopathol*. 1997;85:97-103.
- Cremer J, Martin M, Redl H, Bahrami S, Abraham C, Graeter T, et al. Systemic inflammatory response syndrome after cardiac operations. *Ann Thorac Surg*. 1996;61:1714-20.
- Marti F, Munoz J, Peiro M, Bertran E, Ferran C, Octavio C, et al. Higher cytotoxic activity and increased levels of IL-1 β , IL-6, and TNF- α in patients undergoing cardiopulmonary bypass. *Am J Hematol*. 1995;49:237-9.
- Tønnesen E, Christensen VB, Toft P. The role of cytokines in cardiac surgery. *Int J Cardiol*. 1996;53:S1-S10.
- McMurray J, Abdullah I, Dargie HJ, Shapiro D. Increased concentrations of tumor necrosis factor in cachectic patients with severe chronic heart failure. *Br Heart J*. 1991;66:356-8.
- Levine B, Kalman J, Mayer L, Fillit HM, Packer M. Elevated circulating levels of tumor necrosis factor in severe chronic heart failure. *N Engl J Med*. 1990;323:236-41.
- Jansen NJ, van Oeveren W, Gu YJ, van Vliet MH, Eijssman L, Wildevuur CR. Endotoxin release and tumor necrosis factor formation during cardiopulmonary bypass. *Ann Thorac Surg*. 1992;54:744-8.
- Loppnow H, Werdan K, Reuter G, Flad H-D. The interleukin-1 and interleukin-1-converting enzyme families in the cardiovascular system. *Eur Cytokine Netw*. 1998;9:670-5.
- Loppnow H, Westphal E, Buchhorn R, Wessel A, Werdan K. Interleukin-1 and related proteins in cardiovascular disease in adults and children. *Shock*. 2001;16(Suppl 1):3-9.
- Matsumori A, Yamada T, Suzuki H, Matoba Y, Sasayama S. Increased circulating cytokines in patients with myocarditis and cardiomyopathy. *Br Heart J*. 1994;72:561-6.
- Latini R, Bianchi M, Correale E, Dinarello CA, Fantuzzi G, Fresco C, et al. Cytokines in acute myocardial infarction: selective increase in circulating tumor necrosis factor, its soluble receptor, and interleukin-1 receptor antagonist. *J Cardiovasc Pharmacol*. 1994;23:1-6.
- Loppnow H, Werdan K, Werner C. The enhanced plasma levels of soluble tumor necrosis factor receptors and interleukin-10 in patients suffering from chronic heart failure are reversed in patients treated with β -adrenoceptor antagonist. *Auton Autacoid Pharmacol*. 2002;22:83-92.
- MacGowan GA, Mann DL, Kormos RL, Feldman AM, Murali S. Circulating interleukin-6 in severe heart failure. *Am J Cardiol*. 1997;79:1128-31.
- Fransen E, Maessen J, Dentener M, Senden N, Geskes G, Buurman W. Systemic inflammation present in patients undergoing CABG without extracorporeal circulation. *Chest*. 1998;113:1290-5.
- Diegeler A, Doll N, Rauch T, Haberer D, Walther T, Falk V, et al. Humoral immune response during coronary artery bypass grafting: a comparison of limited approach, "off-pump" technique, and conventional cardiopulmonary bypass. *Circulation*. 2000;102(Suppl):III95-100.
- Wan S, Izzat MB, Lee TW, Wan IYP, Tang NLS, Yim APC. Avoiding cardiopulmonary bypass in multivessel CABG reduces cytokine response and myocardial injury. *Ann Thorac Surg*. 1999;68:52-6.
- Czerny M, Zimpfer D, Kilo J, Gottardi R, Dunkler D, Wolner E, Grimm M. Coronary reoperations: recurrence of angina and clinical outcome with and without cardiopulmonary bypass. *Ann Thorac Surg*. 2003;75:847-52.
- Jemielity MM, Perek B, Buczkowski P, Lesniewska K, Wiktorowicz K, Dyszkiewicz W. Inflammatory response following off-pump and on-pump coronary artery bypass grafting. *Heart Surg Forum*. 2003;6(Suppl 1):40-1.
- Khan NE, De Souza A, Mister R, Flather M, Clague J, Davies S, et al. A randomized comparison of off-pump and on-pump multivessel coronary-artery bypass surgery. *N Engl J Med*. 2004;350:21-8.