Tumor necrosis factor and clinical and metabolic courses after cardiac surgery in children

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Objective: This study was undertaken to determine the relationship between plasma tumor necrosis factor concentrations and hemodynamic and metabolic parameters during the postoperative clinical course in children undergoing cardiac surgery.

Methods: Tumor necrosis factor levels of 10 consecutive children undergoing surgery for repair of congenital heart defects were analyzed in blood samples drawn at predetermined time points during surgery and up to 24 hours thereafter. Clinical data were collected at these times for correlation to tumor necrosis factor levels.

Results: All the patients survived. Tumor necrosis factor was detected in all 10 children. Tumor necrosis factor levels declined after induction of general anesthesia (201 ± 65 pg/mL) steadily decreasing during surgery, reaching 80 ± 50 pg/mL at 24 hours after the operation. Tumor necrosis factor levels were found to be inversely correlated with mean blood pressure values and indicators of acidosis (bicarbonate levels and base excess, $P < .03$). They were not correlated with the durations of cardiopulmonary bypass and aortic crossclamping.

Conclusions: Tumor necrosis factor released into the circulation during and after pediatric cardiac surgery under cardiopulmonary bypass may be related to the hemodynamic and acid-base changes observed after cardiac surgery. Elucidation of the relationship between tumor necrosis factor and patient outcome in high-risk patients awaits further studies.

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Cardiopulmonary bypass (CPB) may initiate a systemic inflammatory response, which sometimes leads to significant postoperative hemodynamic deterioration. Tumor necrosis factor (TNF) is a major proinflammatory cytokine known to be produced in excessive amounts after CPB. There are also immunologic sequelae to this abundance, which may lead to organ injury and postoperative morbidity. TNF is one of the earliest and most important of the endogenous mediators released as a result of the inflammatory response. Its essential role in the inflammatory response,¹ the activation of coagulation and complement,²⁻⁴ and the development of septic shock syndrome and multiple organ failure^{5,6} are widely recognized.

Previous reports on the plasma TNF response to CPB have yielded conflicting results. Whereas some authors have demonstrated a significant increase of TNF concentrations⁷⁻⁹ and stated that TNF is a cardinal mediator in the pathogenesis of the systemic inflammation, sepsis, and multiple organ failure often seen after cardiac surgery, others have failed to find any significant changes in TNF levels whatsoever,¹⁰⁻¹² and some have even reported a decrease in these levels.^{13,14} Thus despite

TABLE 1. Cardiac malformations (n = 10)

Type	No.
Tetralogy of Fallot	3
Atrial septal defect	3
Ventricular septal defect	2
Atrioventricular canal	1
Mitral stenosis	1

the extensive studies that had been carried out on TNF, its possible association with morbidity and mortality in the postoperative course after CPB in infants and children is still being disputed.

We evaluated a cohort of children undergoing cardiac surgery under CPB and plotted the time course of plasma TNF concentrations during and after surgery. We also tried to correlate plasma TNF levels with the clinical status of the subjects.

Methods

Patients and Methods

This prospective cohort study included 5 boys and 5 girls (age range 9 months to 13.5 years) with congenital heart defects for which they underwent elective cardiac surgery under hypothermic CPB at the Chaim Sheba Medical Center. We did not include children with known preexisting causes of vascular injury, such as recent cardiac arrest, sepsis, or recent severe hypotension. Preoperative informed consent was obtained from the parents, and the institutional ethics committee approved this study.

Selected Patient Data

Demographic data, medical history, and medical variables were recorded before the operation. Intraoperative parameters and complications included type of cardiac malformation, perfusion management, and the anesthetics that each child received. Postoperative data were collected at time points corresponding to TNF sampling and included hemodynamic measures, ventilator status, and blood gas variables.

Anesthetic Technique

Induction and maintenance of anesthesia were carried out in a standard manner and consisted of weight-related dosages of fentanyl, midazolam, and pancuronium bromide. All patients were ventilated to normocapnia with 50% oxygen in air.

Extracorporeal Circulation

The extracorporeal circuit (Baxter Healthcare Corporation Cardiovascular Group, Irvine, Calif) was uncoated and included a Bentley membrane oxygenator, a roller pump (COBE Laboratories, Gloucester, England) and an arterial filter primed with Ringer's lactate solution, blood, and heparin. Conventional CPB techniques were used. Five minutes before CPB, 300 IU/kg bovine heparin was administered to achieve anticoagulation. The activated clotting time was monitored and maintained between 400 and 500 seconds with a Hemochron system (Hemochron; International Techdyne Corp, Edison, NJ).

Surface cooling was obtained by maintaining low room temperature and by a cooling mattress in addition to ice packs placed near the child's head. Cooling was achieved by cold (4°C) crystalloid antegrade cardioplegia, which was infused through the aortic root. The core temperature was reduced to $27^{\circ}\text{C} \pm 4.5^{\circ}\text{C}$.

At the end of the procedure, the crossclamp was removed and the patient was rewarmed while remaining under conditions of CPB. No modified ultrafiltration or leukocyte depletion techniques were used for any of the children in this study. The heparin that was administered during surgery was neutralized with protamine sulfate at a ratio of 1:1.

Blood Samples

Thirteen serial arterial blood samples were collected from each child from the arterial line or the extracorporeal circuit. The sample taken after the induction of anesthesia was considered as the baseline value; the other 12 time points were after connection to CPB, 1 hour after CPB, at aortic clamping and declamping, at CPB cessation, at the end of the operation (skin closure), and at 1, 2, 4, 8, 12, and 24 hours after the operation, while the child was in the intensive care unit. Plasma was recovered immediately from these samples by centrifugation at 3000g for 10 minutes at 4°C, divided into aliquots, and frozen at -70°C until use.

TNF Assay

TNF was detected with a Bio-source Cytoscreen kit (BioSource International, Inc, Camarillo, Calif). This is a highly sensitive enzyme-linked immunosorbent assay that measures both free and receptor bound TNF, and is capable of detecting TNF levels of less than 1 pg/mL. All the results from the enzyme-linked immunosorbent assay measurements represent the means from duplicate measurements.

Statistical Analysis

All parameters are expressed as mean $\pm$ SD. TNF levels and clinical data were evaluated with analysis of variance and covariance with repeated measures. The correlation between TNF levels and the clinical variables was investigated by regression and correlation tests.

Results

The types of cardiac malformation and the surgical and perioperative data of the 10 study children are presented in Tables 1 and 2. All the patients survived surgery. TNF was detected in each. The plasma TNF concentrations across time are shown in Figure 1. The TNF levels decreased immediately after CPB connection and continued to decrease during surgery and in the intensive care unit ($P < .0001$). The TNF levels were 201.4 ± 134 pg/mL at induction and decreased to 145.5 ± 62.8 pg/mL after the beginning of CPB ($P < .03$). They continued to decrease until they reached a trough—although they were still at higher than normal levels—at the end of surgery (80.2 ± 57.3 pg/mL) and stayed at these abnormal levels for 24 hours thereafter.

We found an inverse correlation between TNF concen-

trations and mean blood pressure ($P < .003$; Figure 2). The pH values decreased as soon as the child was connected to CPB and reached their lowest level at 1 hour after CPB was initiated (Figure 3). The TNF levels were also inversely correlated with two acidosis indicators, bicarbonate levels and base excess ($P < .03$; Figures 4 and 5).

Discussion

This prospective cohort study involved children undergoing cardiac surgery under CPB for the repair of congenital heart defects. To the best of our knowledge, this is the first study to show that TNF is correlated with indicators of metabolic acidosis, well-known markers of tissue perfusion, and indicators of cellular hypoxia. Furthermore, plasma TNF levels were demonstrated to be inversely correlated with mean blood pressure.

The TNF response to CPB has been widely investigated, because both of result in the same complications: inflammation, infection, edema, leukocytosis, fever, and multiple organ dysfunction syndrome (MODS).^{5,7,15} The contact of blood with the extracorporeal circuit activates various cascades, including the synthesis of inflammatory mediators.^{8,15,16} The data on TNF response to CPB are inconsistent. Whereas some authors have observed an increase in TNF concentrations in these patients,^{7,8,17} others have found either no significant change whatsoever¹⁰⁻¹² or even a decrease in TNF levels.^{13,14}

We found that high levels of TNF in our study children were inversely correlated with the levels of bicarbonate and base excess. These findings are in accordance with previous reports showing that serum lactate may be an accurate predictor of the postoperative course.¹⁸ Despite the fact that serum pH and bicarbonate do not always correlate with intracellular pH, and it is the latter that is of primary importance, only extracellular plasma pH and lactate can be easily measured in patients to provide an accurate assessment of acid-base status. Elevated lactate levels represent inadequate oxygen delivery as a result of hypoperfusion and hypoxemia. Lactic acidosis during surgery was found to be an early and specific indicator of patients at high risk for morbidity and mortality after operations for congenital cardiac disease.¹⁸ High lactate levels were found to predict MODS, the requirement of extracorporeal membrane oxygenator support, circulatory arrest, and death.^{19,20} It can be assumed that the endothelial reaction to the institution of the extracorporeal circulation, causing the release of TNF, is also reflected by the degree of vasoconstriction, hypoperfusion, and the evolving metabolic acidosis, as reflected by low bicarbonate and pH values.

We also found that TNF levels were inversely correlated with mean blood pressure, in agreement with the findings of Jansen and colleagues.²¹ Attempts to correlate cytokine levels with the clinical course of the patients after CPB have also been made before by others. Casey and coworkers⁷

TABLE 2. Study patients' surgical and perioperative data (n = 10, 5 male and 5 female patients)

Variable	Mean $\pm$ SD	Range
Age (y)	4.36 $\pm$ 4.49	0.75-13.5
Weight (kg)	17.27 $\pm$ 14.28	6-52
Surgery duration (h)	4.08 $\pm$ 0.77	3-5.3
CPB duration (h)	1.33 $\pm$ 0.83	0.2-2.4
Aortic clamp duration (h)	0.82 $\pm$ 0.60	0.3-1.8
Stay in intensive care unit (d)	6.0 $\pm$ 2.6	2-9
Mechanical ventilation (d)	2.50 $\pm$ 1.51	1-6
Minimal temperature (°C)	27 $\pm$ 4.50	25-34

described a higher heart rate and a lower central venous pressure in patients with high TNF levels, and our results appear to confirm their findings. Steinberg and colleagues¹⁰ could not find a significant correlation among hemodynamic variables or pulmonary function and TNF after CPB. Oudemans-van Straaten and associates²² reported that increased oxygen consumption after CPB was associated with the inflammatory response and TNF secretion. Similarly, Khabar and coworkers²³ found an association between increased TNF and systemic inflammatory response followed by MODS in the postoperative period after cardiac surgery. Pilz and associates²⁴ suggested that TNF levels and TNF receptors could predict postsurgical clinical outcome and mortality in adults. The levels of TNF and its soluble receptors, p55 and p75, were higher in patients with presurgical criteria for high risk of development of postsurgical sepsis than in the control group. The former group showed more clinical complications and a higher mortality rate, and Pilz and associates²⁴ therefore concluded that these mediators hold prognostic value.

Similar to our results, other studies showed a decrease in TNF concentrations with time after the institution of CPB in adults.^{13,14} Kawamura and associates¹⁴ investigated 11 adult patients who underwent surgery with CPB and reported that serum TNF levels did not increase during the operation relative to preoperative levels; in fact, TNF levels decreased at 60 minutes after aortic occlusion. Markewitz and colleagues¹³ reported a decrease in TNF levels on the first day after surgery relative to preoperative levels and that they remained depressed for 7 days; the administration of indomethacin resulted in a substantial increases in TNF synthesis. Steinberg and colleagues¹⁰ demonstrated significant increases in complement and interleukins but failed to find any evidence of TNF. Butler and coworkers¹¹ detected TNF in only half their adult subjects and observed no variations in its levels. They reasoned that their findings were due to the short half-life of TNF and the consequent likelihood that it might be missed or released locally in specific organs, such as the lung. Several additional similar studies in children and adults have reported either no increase in TNF^{25,26} or no evidence of it at all.²⁷⁻²⁹

Figure 1. Changes in plasma TNF levels with time before, during, and after CPB. End of surgery was defined as skin closure. First 6 samples were collected at fixed time intervals after CPB cessation. *Ao Cl on*, Aortic crossclamp placement; *Ao Cl off*, aortic crossclamp removal.

Whereas data on TNF in the adult population are well known, the pediatric population has been far less studied. Importantly, cytokine production has been shown to differ in various age groups.^{20,30} Casey and coworkers⁷ reported an increase of endotoxin and TNF in 88% of children during heart surgery, but they could not relate TNF levels to intraoperative clinical data or postoperative morbidity. Hattler and associates³¹ demonstrated TNF messenger RNA transcription in all their adult patients during CPB, with the highest values in the ones in whom the duration of CPB was longest.

The TNF concentrations that were determined in our study were high compared with the TNF levels reported in other similar works, possibly because we used an immunoassay that measures free TNF as well as the TNF in TNF-receptor complexes and therefore would be expected to show high TNF concentrations. The highest levels of TNF were identified immediately after induction of anesthesia. Because all lines were installed after induction of anesthesia, no blood samples were taken earlier. Therefore the exact relationship between anesthesia and TNF levels could not be defined. However, the highest TNF levels in our study were detected at the time point after induction of anesthesia. This could be explained by the effect of anes-

thetic drugs. Both intravenous anesthetics³² and inhalational agents³³ have been shown to be capable of promoting a significant cytokine response, resulting in the release of TNF. When the element of a CPB connection is added there is dilution of the plasma, and this event lowers the concentrations of cytokines.

Whereas this evidence supports a pathogenic role for TNF in the postoperative course, experimental studies on inhibition of TNF are beginning to emerge. For example, hemofiltration during CPB removes excess fluids and filters out some cytokines.³⁴⁻³⁶ Moreover, TNF may be inhibited by steroids,^{5,18,37} by the use of anti-TNF monoclonal antibodies,^{38,39} or by other cytokines, such as interleukin 10, interleukin 4, and granulocyte colony-stimulating factor.^{6,40,41} Bonding TNF to specific receptors can prevent postpump syndrome,⁴¹ and synthesis of TNF can be inhibited by amrinone, cyclosporine (INN: ciclosporin), or desensitization.⁶ Other means of antagonizing TNF activity after CPB include the administration of aprotinin, a serine protease inhibitor, or specific receptors that can bind TNF, thus preventing its activity after being released to the bloodstream.⁴¹⁻⁴³

TNF was sampled 13 times in each child, most frequently during CPB and in the first postoperative hours, to

Figure 2. Changes in plasma TNF (*squares*) and mean blood pressure (*MBP, circles*) with time. End of surgery was defined as skin closure.

Figure 3. Changes in plasma TNF (*squares*) and pH (*circles*) with time. End of surgery was defined as skin closure. *Ao Cl on*, Aortic crossclamp placement; *Ao Cl off*, aortic crossclamp removal.

exclude the possibility of missing a transient but significant TNF surge. The frequent sampling increased the validity of the results and enabled us to examine the TNF response in

relation to each surgical step. TNF was detected in all the children. TNF levels were highest after induction and decreased gradually during and after the operation. Thus the

Figure 4. Changes in plasma TNF (*squares*) and bicarbonate level (*HCO₃*, *circles*) with time. End of surgery was defined as skin closure. *Ao Cl on*, Aortic crossclamp placement; *Ao Cl off*, aortic crossclamp removal.

Figure 5. Changes in plasma TNF (*squares*) and base excess (*BE*, *circles*) with time. End of surgery was defined as skin closure. *Ao Cl on*, Aortic crossclamp placement; *Ao Cl off*, aortic crossclamp removal.

results of this study add more lines of evidence to a growing body of literature describing the robust proinflammatory response to CPB.

Our data lend additional support to the hypothesis that TNF is associated with acid-base disturbances after cardiac surgery. It is unclear whether TNF and acid-base abnormal-

ities are causally related phenomena or simply independent markers of injury after cardiac surgery. Interpretation of our results is limited by the small number of study children, a feature shared by most studies such as ours. Furthermore, ours was a relatively low-risk population, and none of the patients had any adverse effects during or after CPB. Another limitation of the study is that TNF was measured after induction of anesthesia. Therefore these data can serve as a baseline to indicate cytokine production in routine cardiac surgical procedures. Additional investigations on larger numbers of patients at higher risk and the use of the same immunoassay kit for all blood samples are essential to finding potential stimuli for TNF release and to confirming the relationship that we have described between TNF levels and the postoperative clinical course in children undergoing cardiac surgery.

In conclusion, children undergoing cardiac surgery exhibited high TNF levels after anesthetic induction. These values decreased gradually during and after surgery. TNF levels were inversely correlated with mean blood pressure, bicarbonate levels, and base excess. These novel data may have far-reaching therapeutic implications and thus warrant further large-scale investigation. Further studies will be necessary to clarify the association between TNF and the postoperative course in patients undergoing cardiac surgery.

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