The Heart Surgery Forum #2006-1090
9 (6) 2006 [Epub October 2006]
doi: 10.1532/HSF98.20061090

Online address: http://cardenjennings.metapress.com/link.asp?=112496

Pentoxifylline Affects Cytokine Reaction in Cardiopulmonary Bypass

Ihsan Iskesen, MD, Osman Saribulbul, MD, Mustafa Cerrahoglu, MD, Ece Onur, MD, Bugra Destan, MD, Bekir Hayrettin Sirin, MD

Department of Cardiovascular Surgery, Celal Bayar University School of Medicine, Manisa, Turkey

ABSTRACT

Background. Cardiac surgery is associated with an inflammatory response that may cause myocardial dysfunction after cardiopulmonary bypass. We examined the efficacy of pentoxifylline to attenuate the cardiopulmonary bypass–induced inflammatory response during heart operations.

Methods. In a prospective, randomized study, 30 patients undergoing coronary artery bypass graft surgery received either pentoxifylline (group P, n = 15) (continuous infusion of 1.5 mg/kg per hour during operation) or not (group C [control], n = 15). Blood samples for measurements of tumor necrosis factor (TNF)-α, interleukin (IL)-6, IL-8, and IL-10 were taken from the arterial line in both groups at 5 different time points.

Results. TNF-α, IL-6, and IL-8 plasma levels increased in both groups after cardiopulmonary bypass, with a higher increase in the control group ($P < .05$).

Conclusions. Our results indicate that pentoxifylline infusion during cardiac surgery inhibits the proinflammatory cytokine release caused by cardiopulmonary bypass.

INTRODUCTION

Cardiac surgery and cardiopulmonary bypass (CPB) activate a systemic inflammatory response and cause some harmful changes in cardiovascular and pulmonary function. This SIR after CPB may be caused by contact of blood components with the extracorporeal circulation and leukocyte activation. These mechanisms may be activated by operative trauma, ischemia-reperfusion injury, or body temperature changes [Gol 2002; Samankatiwat 2003]. Release of the cytokines and oxygen-free radicals, activation of the complement system, expression of adhesion molecules with the activation of leukocytes, metabolites of arachidonic acid, and endothelin and platelet activating factor all have major roles in systemic inflammatory response [Schmartz 2003; Bittar 2005]. This inflammatory system produces some proinflammatory cytokines such as interleukin (IL)-6, IL-8, and antiinflammatory cytokines such as IL-10. Many factors such as an ischemia-reperfusion event cause the release of cytokines. The release of cytokines also can be stimulated by other cytokines.

The emergence of proinflammatory cytokines during CPB can damage the heart and body. This inflammatory response may cause the development of postoperative complications such as bleeding disorders and pulmonary or renal dysfunction. Fortunately, significant morbidities are rare and many patients can recover successfully from CPB, despite inflammatory reaction. However, there must be inhibitory mechanisms to protect against inflammatory reactions and thereby prevent organ damage after heart operations. The balance of proinflammatory and anti-inflammatory cytokines is important for the development of the inflammatory response and the clinical features of the patient. The release of proinflammatory cytokines may contribute to the development of multiorgan failure [El Azab 2002]. On the other hand, the release of the anti-inflammatory cytokine IL-10 during CPB may play a protective role against inflammation by suppressing the production of proinflammatory cytokines [Giomarelli 2003].

Pentoxifylline, a methylxanthine derivative with rheologic effects, may be a useful agent to attenuate the negative effects of CPB on postoperative organ function. The aim of this prospective, randomized, double-blinded study was to investigate whether the prophylactic infusion of pentoxifylline prevents CPB-induced cytokine reaction and myocardial ischemia–reperfusion injury.

METHODS

Thirty adult patients undergoing elective coronary artery bypass graft surgery were studied in a randomized trial. The study was approved by the local medical ethics committee. All patients gave their informed consent. Exclusion criteria were severe left ventricular dysfunction (defined as a left ventricular ejection fraction of <30% or an end-diastolic pressure of >16 mmHg), emergency or redo operation, recent myocardial infarction (<6 weeks), pulmonary disease, renal or hepatic dysfunction, insulin-dependent diabetes, age over 80, white blood cell count

Received July 7, 2006; received in revised form August 7, 2006; accepted August 21, 2006.

Address correspondence and reprint requests to: Dr. Ihsan Iskesen, Celal Bayar Universitesi Tip Fakultesi Kalp Damar Cerrahisi ABD, Manisa, Turkey (e-mail: iskesen@yahoo.com).

Table 1. Preoperative Characteristics of the Groups*

	Control Group	Pentoxifylline Group†
No. of patients	15	15
Age, y	62 ± 7.4	60 ± 8.2
Weight, kg	80.3 ± 10.9	81.2 ± 11.2
No. of grafts	3.0 ± 0.1	2.8 ± 0.2
Duration of CPB, min	87.1 ± 5	70.2 ± 6
Cross-clamp time, min	50.5 ± 2	41.5 ± 3
Use of blood products, units	2.8 ± 0.2	3.1 ± 0.9
Blood drainage, mL	507.5 ± 33	650.0 ± 31

*CPB indicates cardiopulmonary bypass.

†$P > .05$ versus control group

over 10,000/mm^3, infection during the week preceding surgery, preoperative use of antibiotics, corticosteroids, nonsteroidal anti-inflammatory drugs and aspirin, or smoking in the last month.

Preoperatively, the patients were divided into 2 groups randomly: the study group (group P, n = 15) who received a continuous infusion of pentoxifylline at 1.5 mg/kg per hour after the placement of a venous catheter from before anesthesia to the end of CPB; and the control group (group C, n = 15) who did not receive any medication or infused saline solution.

Three patients in the study group and 2 in the control group had previous myocardial infarction more than 6 weeks before surgery. There was no hospital mortality. There was no statistically significant difference between clinical characteristics of the study group and the control group ($P > .05$) (Table 1).

Each patient was monitored with a radial arterial line and a pulmonary artery catheter. The patients were anesthetized with sufentanil. The surgical procedure consisted of median sternotomy with the placement of internal mammary artery and saphenous vein grafts. The CPB was performed using a membrane oxygenator and a roller pump. Heparin (3 mg/kg) was given before cannulation of the aorta. Activated clotting time was more than 400 seconds in all subjects. Patient temperature was reduced to 30 to 32°C. Mean flow rate was performed nearly 2.4 L/min per m^2. Antegrade blood cardioplegia was administered in all patients at 1000 mL initially and repeated after 20 minutes. All operations were performed by the same surgical team. The surgical team and biochemical analysts were blinded with respect to the study medication.

Biochemical Studies

Blood samples for the measurements of tumor necrosis factor (TNF)-α, IL-6, IL-8, and IL-10 were taken from the arterial line to compare both groups at 5 different time points: before induction of anesthesia (T0); 10 minutes after cross clamping (during the cross-clamp period) (T1); 10 minutes after the end of CPB (T2); 4 hours after skin closure (T3); and 24 hours after the operation (T4) (Table 2).

Blood samples were also taken for myocardial muscle creatine kinase isoenzyme (CK-MB) measurements during the preoperative period and 24 hours after operation. The blood samples were immediately centrifuged after collection at 1000g, and the plasma was stored at –70°C until assays were performed. Plasma levels of TNF-α, IL-6, IL-8, and IL-10 were measured using standard, commercially available enzyme-linked immunosorbent assay (ELISA) kits (BioSource Europe SA, Nivelles, Belgium). The limit of sensitivity for IL-10 assay was <1 pg/mL. CK-MB analysis was performed by an immunoassay kit (Elecsys Systems 2010, Hitachi, Tokyo, Japan).

Hemodynamic Measurements

Standard radial arterial, central venous, and Swan-Ganz catheters were inserted preoperatively. Hemodynamic parameters were measured before the operation (H0), just after CPB (H1), and 1 (H2) and 16 (H3) hours after CPB using the thermodilution technique (Datascope-Ohmeda cardiac monitors; Datascope, Montvale, NJ, USA) (Table 3).

Statistical Analysis

Results are expressed as mean ± standard error of the mean. The significance in the difference for these results in the 2 groups was determined using the unpaired Student t test. A difference was considered statistically significant if $P < .05$.

RESULTS

The clinical and demographic characteristics of 30 patients undergoing CPB are summarized in Table 1. There was no significant difference between the 2 groups of patients

Table 2. Biochemical Results at Specified Time Points*

	Control Group					Pentoxifylline Group				
	T0	T1	T2	T3	T4	T0	T1	T2	T3	T4
TNF-α	14.53 ± 1.6	16.79 ± 2.6	52.79 ± 10	45.73 ± 8.3	30.68 ± 4.5	14.90 ± 1.6	14.30 ± 1.3	20.61 ± 6.0†	21.15 ± 5.5†	15.76 ± 2.5†
IL-6	5.15 ± 1.3	9.18 ± 3.0	356.80 ± 5.1	256.80 ± 5.1	216.35 ± 10.1	5.95 ± 1.9	5.33 ± 2.3	281.70 ± 11.4†	190.45 ± 17.3†	168.96 ± 17.2†
IL-8	33.30 ± 10.6	30.38 ± 10.1	164.0 ± 16.6	115.79 ± 14.0	71.92 ± 13.3	24.62 ± 5.0	33.76 ± 13.1	101.74 ± 13.3†	59.05 ± 6.2†	42.35 ± 6.7
IL-10	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
CK-MB	17.3 ± 1.2	—	—	—	55.3 ± 1.7	16.5 ± 1.7	—	—	—	49.7 ± 1.1

*T0 indicates before anesthesia; T1, 10 minutes after cross clamping (during the cross-clamp period); T2, 10 minutes after the end of cardiopulmonary bypass; T3, 4 hours after skin closure; T4, 24 hours after the operation; TNF, tumor necrosis factor; IL, interleukin; NS, insignificant values; CK-MB, myocardial muscle creatine kinase isoenzyme.

†$P < .05$ versus control group.

Table 3. Hemodynamic Results at Specified Time Points *

	Control Group				Pentoxifylline Group			
	H0	H1	H2	H3	H0	H1	H2	H3
CI	1.5 ± 0.1	2.3 ± 0.2	2.5 ± 0.1	2.6 ± 0.2	1.6 ± 0.1	2.2 ± 0.1	2.4 ± 0.1	2.6 ± 0.1

*H0 indicates before the operation; H1, just after cardiopulmonary bypass; H2, 1 hour after cardiopulmonary bypass; H3, 16 hours after cardiopulmonary bypass; CI, cardiac index.

regarding age, weight, duration of CPB and aortic cross clamping, number of grafts, blood drainage volume, or blood products used. There were no significant differences in inflammatory markers and hemodynamic data at baseline.

There were no deaths or perioperative myocardial infarction in our study, and there were no significant differences in clinical outcomes between the group that received pentoxifylline and the group that did not. The difference in average CK-MB values on the first postoperative day did not reach statistical significance between the groups (17.3 ± 1.2 U/L during the preoperative period and 55.3 ± 1.7 U/L on the first postoperative day in the control group; 16.5 ± 1.7 U/L during the preoperative period and 49.7 ± 1.1 U/L on the first postoperative day in the study group) ($P > .05$).

Pre-pump and post-pump blood samples were obtained from both groups and assayed for TNF-α, IL-6, IL-8, and IL-10. In the post-pump period, the difference in the TNF-α, IL-6, and IL-8 levels of the 2 groups was found to be statistically significant ($P < .05$). The time course of blood cytokine levels is shown in Table 2.

TNF-α plasma levels increased to peak level after CPB in group C. Twenty-four hours after the operation, TNF-α was down to the baseline level in group P (15.76 ± 2.5 pg/mL), but it was significantly greater in group C (30.68 ± 4.5 pg/mL) ($P < .05$) (Figure 1).

IL-6 levels reached a peak level just after operation. The peak of IL-6 in group C was significantly higher than in group P ($P < .05$). Four hours after the operation, IL-6 was elevated in both groups with a significantly higher level in the control (256.80 ± 5.1 pg/mL) than in the pentoxifylline group (190.70 ± 17.3 pg/mL, $P < .05$). Twenty-four hours after the termination of CPB, IL-6 levels were still significantly higher in the control group (216.35 ± 10.1 versus 168.96 ± 17.2 pg/mL, $P < .05$) (Figure 2).

IL-8 plasma levels were normal at baseline but increased after surgery until the first postoperative day. This increase was significantly higher in the control group (from 33.30 ± 10.6 at baseline to 164.4 ± 16.6 pg/mL at the end of surgery) than in group P (from 24.62 ± 5.0 at baseline to 101.74 ± 13.3 pg/mL at the end of surgery) (Figure 3).

IL-10 plasma levels of all patients were lower than measurable limits in our study. We cannot draw conclusions about IL-10 from this study.

There was no significant difference in either preoperative or postoperative pulmonary artery pressure, pulmonary artery wedge pressure, or cardiac index.

DISCUSSION

CPB causes leukocyte and complement activation, the release of some cytokines and inflammatory mediators, and an increase in the release of oxygen-free radicals [Al-Ruzzeh 2004; Larmann 2004]. Proinflammatory cytokines (TNF-α, IL-1, IL-6, and IL-8) can affect myocardial functions and damage some organs [Edmunds 1999; Laffey 2002; Gessler 2003]. These factors interact with each other and affect one another so that they increase each other's potential for causing injury.

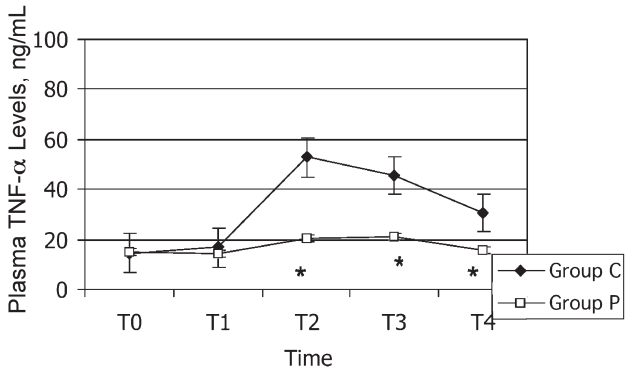

Figure 1. Comparison of plasma tumor necrosis factor-α levels between the pentoxifylline and control groups. *$P < .05$ versus control group.

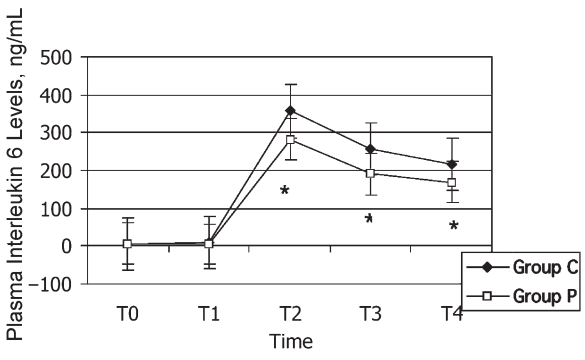

Figure 2. Comparison of plasma interleukin 6 levels between the pentoxifylline and control groups. *$P < .05$ versus control group.

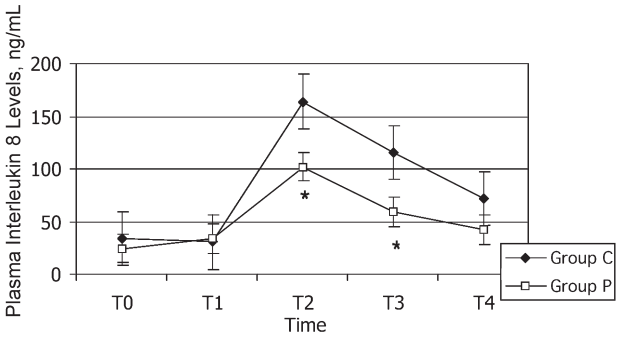

Figure 3. Comparison of plasma interleukin 8 levels between the pentoxifylline and control groups. *$P < .05$ versus control group.

Inflammation and ischemic changes occur at the beginning of CPB and arrive at peak level within 20 minutes; blood levels of IL-1, IL-6, IL-8 and TNF-α increase during CPB, and the recovery time starts as soon as the cross clamp is released [Edmunds 1997]. Reperfusion of the heart and lungs may be the main factor for emergence of systemic inflammatory response. Neutrophils, macrophages, and endothelial cells release cytokines in response to injury [Frangogiannis 2002]. The myocardium is a major source of TNF-α, IL-6, and IL-8, whereas IL-10 emerges from the liver [Wan 1997]. In some studies, the levels of these proinflammatory cytokines have been correlated with the duration of cardiac ischemia during CPB [Wan 1997], but we cannot find any reliable information about the levels of these markers and CPB time.

Our IL-6 results are similar to the results of some studies. IL-6 is responsible for morbidity associated with inflammatory response to CPB [Miller 1997]. It increases after initiation of CPB, peaks at 4 hours, and, as in our study, is still elevated 24 hours after the end of CPB. IL-6 may cause a depression in myocardial contractility, so its level may be a sensitive indicator of myocardial damage [El Azab 2002]. In our study, the maximum level of IL-6 was significantly reduced in group P. Therefore, TNF-α strongly affects the release of IL-6, and the reduction of the IL-6 level may be the result of an inhibition of TNF-α release. IL-6 peak levels were lower in group P. This finding suggests that there is an effect of pentoxifylline on TNF-α. The inhibition of IL-6 release after CPB may be explained by the blocking of IL-6 by pentoxifylline or by the suppression of the release of TNF-α. According to the results of some studies, the inhibition of IL-6 release may also be explained by the increase of the release of IL-10 [Giomarelli 2003]. But in our study we cannot draw conclusions on this subject.

IL-8 plays a major role in bridging the humoral mediators with the cellular mediators of inflammation, and in our study the same marker level pattern was obtained as in earlier studies [Miller 1997].

IL-10 is a cytokine synthesis inhibitory factor and inhibits the production of IL-1, IL-6, IL-8, and TNF-α, and therefore suppresses inflammatory response. IL-10 may have a protective role after myocardial ischemia–reperfusion through the suppression of the acute inflammatory process. In our study, the levels of this marker were found to be lower than measurable limits in all patients, so we could not draw any conclusion about the release of this cytokine during the CPB.

The balance of the proinflammatory and anti-inflammatory cytokines may affect the degree of whole-body inflammatory reaction and its possible damages [Aleshin 2004]. Many different strategies such as the administration of corticosteroids have been studied to reduce the inflammatory reaction. The effects of pentoxifylline on the production of IL-6, IL-8, and TNF-α have been studied previously [Ji 2004]. Pentoxifylline also decreases endothelial injury and leukocyte infiltration to vascular endothelium during CPB [Tsang 1996].

We studied the effect of infusing pentoxifylline during CPB for CABG surgery on the balance between proinflammatory and anti-inflammatory cytokines. The results suggest that pentoxifylline decreases the production of proinflammatory cytokines during CPB and therefore may alleviate the tissue damage. Postoperative CK-MB levels were not found to be statistically different between the groups. However, this study may be considered a preliminary one and further studies with more patients and more sensible markers may be necessary to clarify this point.

We used 1.5 mg/kg per hour of pentoxifylline for each patient undergoing an operation. Some authors used an infusion of nearly the same doses of pentoxifylline during surgery [Boldt 2001; Ege 2004]. Timing of pentoxifylline administration may be an important subject according to other studies. Prophylactic and continuous administration of pentoxifylline is also important and beneficial to prevent inflammatory injuries. Early use of pentoxifylline before cardiac surgery also has been reported to achieve the attenuation of endothelial injury and permeability that occurred in CPB [Tsang 1996]. In some studies, this agent was administered by adding it to the cardioplegic solution during cardioplegic administration [Ustunsoy 2006]. We administrated the pentoxifylline throughout the operation period with the aim of suppressing the response to CPB and preventing I/R injuries during the operation.

It is widely known that pentoxifylline is a rheologic agent and increases red cell deformation [Ambrus 1995], and there are suspicions that it may cause bleeding. To eliminate these doubts, certain measurements were taken. Total drainage amounts and the number of blood products used (units) were not different beween groups. As in our study, others have reported that pentoxifylline does not increase the risk of bleeding and that it also does not change the coagulation or the bleeding times [Szefner 1995].

CONCLUSION

This trial indicates that infusion of pentoxifylline during cardiac surgery with CPB has significant effects on the release of several inflammatory markers in human subjects without affecting hemodynamic parameters. Systemic proinflammatory cytokine response in patients undergoing CPB can be reduced to a certain level with pentoxifylline infusion.

ACKNOWLEDGMENT

This study was supported by a grant from the Celal Bayar University Scientific Investigation Fund.

REFERENCES

Al-Ruzzeh S, Hoare G, Marczin N, et al. 2004. Off-pump coronary artery bypass surgery is associated with reduced neutrophil activation as measured by the expression of CD11b. Heart Surg Forum 6:89-93.

Aleshin A, Sawa Y, Ono M, Funatsu T. 2004. Myocardial protective effect of FR167653; a novel cytokine inhibitor in ischemic-reperfused rat heart. Eur J Cardiothorac Surg 26:974-80.

Ambrus JL, Stadler S, Kulaylat M. 1995. Hemorrheologic effects of metabolites of pentoxifylline (Trental). J Med 26:65-75.

Bittar MN, Carey JA, Barnard J, et al. 2005. Interleukin 6 G-174C polymorphism influences outcome following coronary revascularization surgery. Heart Surg Forum 8:E140-5.

Boldt J, Brosch C, Lehmann A, Haisch G, Lang J, Isgro F. 2001. Prophylactic use of pentoxifylline on inflammation in elderly cardiac surgery patients. Ann Thorac Surg 71:1524-9.

El Azab SR, Rosseel PMJ, de Lange JJ, Groenveld ABJ. 2002. Dexamethazone decreases the pro- to anti-inflammatory cytokine ratio during cardiac surgery. Br J Anaesth 88:496-501.

Edmunds LH Jr. 1997. Extracorporeal perfusion. In: Edmunds LH Jr, ed. *Cardiac Surgery in the Adult*. New York: McGraw-Hill; 255-94.

Edmunds NJ, Lal H, Woodward B. 1999. Effects of tumour necrosis factor-alpha on left ventricular function in the rat isolated perfused heart: possible mechanisms for a decline in cardiac function. Br J Pharmacol 126:189-96.

Ege T, Arar C, Canbaz S, et al. 2004. The importance of aprotinin and pentoxifylline in preventing leukocyte sequestration and lung injury caused by protamine at the end of cardiopulmonary bypass surgery. Thorac Cardiovasc Surg 52:10-5.

Frangogiannis NG, Smith CW, Entman ML. 2002. The inflammatory response in myocardial infarction. Cardiovasc Res 53:31-47.

Gessler P, Pfenninger J, Pfammatter JP, Carrel T. 2003. Plasma levels of interleukin-8 and expression of interleukin-8 receptors on circulating neutrophils and monocytes after cardiopulmonary bypass in children. J Thorac Cardiovasc Surg 126:718-25.

Giomarelli P, Scolletta S, Borrelli E, Biagioli B. 2003. Myocardial and lung injury after cardiopulmonary bypass: role of interleukin (IL)-10. Ann Thorac Surg 76:117-23.

Gol MK, Nisanoglu V, Iscan Z, et al. 2002. Inhibition of systemic inflammatory response with sodium nitroprusside in open heart surgery. J Cardiovasc Surg 43:803-9.

Ji Q, Zhang L, Jia H, Xu J. 2004. Pentoxifylline inhibits endotoxin-induced NF-kappa B activation and associated production of proinflammatory cytokines. Ann Clin Lab Sci 34:427-36.

Laffey JG, Boylan JF, Cheng DC. 2002. The systemic inflammatory response to cardiac surgery: implications for the anesthesiologist. Anesthesiology 97:215-52.

Larmann J, Theilmeier G. 2004. Inflammatory response to cardiac surgery: cardiopulmonary bypass versus non-cardiopulmonary bypass surgery. Best Pract Res Clin Anaesthesiol 18:425-38.

Miller BE, Levy JH. 1997. The inflammatory response to cardiopulmonary bypass. J Cardiothorac Vasc Anesth 11:355–66.

Samankatiwat P, Samartzis I, Lertsithichai P, Stefanou D. 2003. Leucocyte depletion in cardiopulmonary bypass: a comparison of four strategies. Perfusion 18:95-105.

Schmartz D, Tabardel Y, Preiser JC, Barvais L. 2003. Does aprotinin influence the inflammatory response to cardiopulmonary bypass in patients? J Thorac Cardiovasc Surg 125:184-90.

Szefner J. Control and treatment of hemostasis in cardiovascular surgery. 1995. The experience of La Pitie hospital with patients on total artificial heart. Int J Artif Organs 18:633-48.

Tsang GM, Allen S, Pagano D. 1996. Pentoxifylline preloading reduces endothelial injury and permeability in cardiopulmonary bypass. Asaio J 42:429-34.

Ustunsoy H, Sivrikoz MC, Tarakcioglu M, Bakir K. 2006. The effects of pentoxifylline on the myocardial inflammation and ischemia-reperfusion injury during cardiopulmonary bypass. J Card Surg 21:57-61.

Wan S, LeClerc JL, Vincent JL. 1997. Inflammatory response to cardiopulmonary bypass. Chest 112:676-93.