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Stress and Inflammatory Response after Beating Heart Surgery Versus Conventional Bypass Surgery: The Role of Thoracic Epidural Anesthesia

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ABSTRACT

Cardiac surgery elicits a cascade of stress responses mediated by the release of various cytokines and stress hormones [Roth-Isigkeit 1998]. Apart from the stress induced by the surgical process, cardiopulmonary bypass (CPB) has been documented to play a major role in the perioperative stress response seen following cardiac surgery [Butler 1993, McBride 1995, Hall 1997]. The imbalance in pro- and anti-inflammatory responses may affect outcome in cardiac surgery patients [Casey 1993, McBride 1995, Menasché 1995]. Contact of blood with the CPB circuit, along with hypoperfusion of various organs prior to and during CPB, may aggravate this stress response and contribute to adverse outcomes in the perioperative period [Casey 1993, Menasché 1995, Tonnesen 1996]. Splanchnic hypoperfusion that occurs in cardiac surgery patients [Landow 1991] can result in increased permeability of the gut mucosal barrier, resulting in endotoxemia and release of proinflammatory cytokines. Lungs and kidneys play a role in sequestrating the proinflammatory cytokines and, in the presence of hypoperfusion, may be damaged by these cytokines [Gilliland 1999, Liebold 1999, Gormley 2000]. Avoiding CPB may reduce this stress response. Anesthetic techniques such as thoracic epidural analgesia (TEA) that improve splanchnic perfusion [Moore 1995, Kapral 1999, Ai 2001] may have a role in improving patient outcome. It is further known that ischemic myocardium can be a major source of proinflammatory cytokines [Wan 1999a]. The cardiac sympathetic block resulting from TEA has been shown to reduce ischemia reperfusion injury [Blomberg 1989, Blomberg 1990, Liem 1992a, Liem 1992b, Liem 1992c, Kirno 1994, Stenseth 1994].

Beating heart surgery done without the aid of CPB significantly attenuates cytokine and stress response [Brasil 1998, Fransen 1998, Gu 1998, Wan 1999b, Ganapathy 1999a, Ganapathy 2000a]. There is reduced renal dysfunction following beating heart surgery [Ascione 1999], which may be related to reduced proinflammatory cytokine surge. Thoracic epidural analgesia inhibits intraoperative cortisol as well as catecholamine surge but does not add further to the reduction in cytokine response [Ganapathy 1999b].

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INTRODUCTION

Cardiac surgery performed with the aid of cardiopulmonary bypass (CPB) is associated with a well-defined stress and cytokine response [Butler 1993, McBride 1995, Hall 1997]. Apart from the use of CPB, a number of factors contribute towards this response, including surgical trauma and general anesthesia. While the stress response plays a major role in initiating the catabolic state that follows surgery, such as alteration in substrate utilization [Carli 2000], muscle breakdown, hyperglycemia [Schricker 1999, 2000a, 2000b], and altered immune function [Tonnesen 1987], the cytokine response contributes to end organ dysfunction [Casey 1993, Menasché 1995, Tonnesen 1996, Gilliland 1999, Liebold 1999, Gormley 2000]. Prior to and after the initiation of CPB, there is alteration in perfusion of various organs such as the intestines, kidneys, brain, and the myocardium resulting in cellular ischemia. This results in ischemia of various organs, and ischemia reperfusion injury plays a role in the activation of a stress response cascade. The major changes, for the most part, occur upon initiation of CPB. Therefore, if we avoid CPB, could we modulate the stress and cytokine response to cardiac surgery? Additionally, can anesthetic techniques such as thoracic epidural analgesia (TEA) contribute further towards improved stress reduction and outcome?

Pathophysiology of Inflammatory Response

Patients undergoing cardiac surgery may have ischemia of various organs, such as the heart and gut. There is also contact of blood with the CPB circuit, a foreign surface. During CPB, pulmonary blood flow is mainly through the bronchial arteries, resulting in reduced pulmonary blood flow. A number of these events result in endotoxemia [Anderson 1987]. The activity of endotoxin is magnified several-fold by the plasma lipopolysaccharide binding protein [Schumann

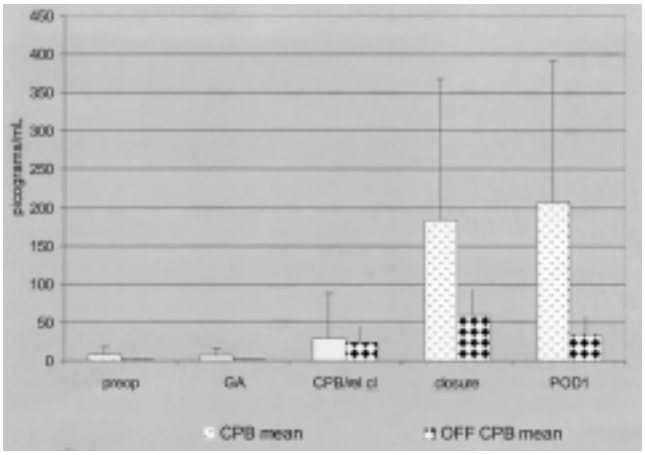

Figure 1. IL-6 response (mean+SD) in patients undergoing cardiac surgery using CPB vs. off-pump. Values are expressed in picograms/mL. Time points in X axis: Preop = baseline, GA = after induction of general anesthesia, CPB/rel clamp = initiation of CPB or release of coronary clamp in off-pump, Closure = closure of chest, POD1 = postoperative day 1.

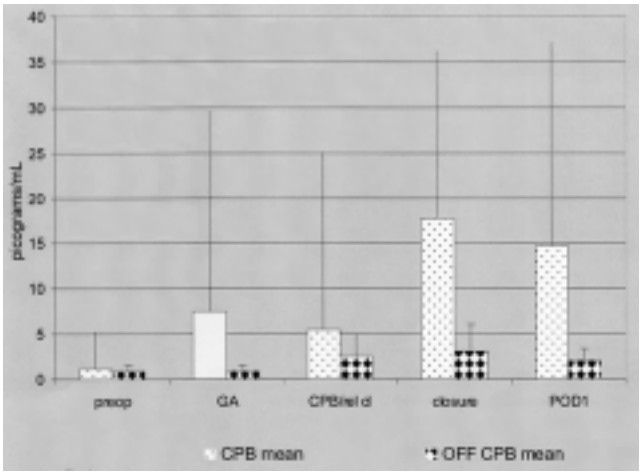

Figure 3. IL-8 response (mean+SD) in patients undergoing cardiac surgery using CPB vs. off-pump. Values are expressed in picograms/mL. Time points in X axis: Preop = baseline, GA = after induction of general anesthesia, CPB/rel clamp = initiation of CPB or release of coronary clamp in off-pump, Closure = closure of chest, POD1 = postoperative day 1.

1990]. This complex binds to CD14 on the macrophage/monocyte and initiates production of proinflammatory cytokine TNFα, which is accompanied by activation of polymorphonuclear cells, platelets, and monocytes. The intracellular adhesion molecules released by the endothelial cells facilitate margination of these activated cells that eventually degranulate, undergo lysis, and release the cytokines both locally and into the circulation. Ischemia reperfusion injury and splanchnic hypoperfusion may augment this response. This response is followed by the release of anti-inflammatory cytokines such as IL10, IL-1ra, and IL12 in the postoperative period, which is a host response [Butler 1993, McBride 1995]. The balance of pro- and anti-inflammatory cytokines may play a role in postoperative outcome [Casey 1993, Menasché 1995, Hall 1997]. Because kidneys and lungs play a role in the elimination of these cytokines, they may become damaged in the process, resulting in pulmonary and renal insufficiency in the postoperative period [Landow 1991, Tonnesen 1996, Liebold 1999, Massoudy 1999]. The major surges of cytokines occur upon initiation of CPB. A number of therapeutic interventions have been explored, such as the use of heparin-bonded CPB circuits, steroids, pentoxyphylline, aprotinin, ketamine, and ulinastatin. It is logical to assume that avoidance of CPB would

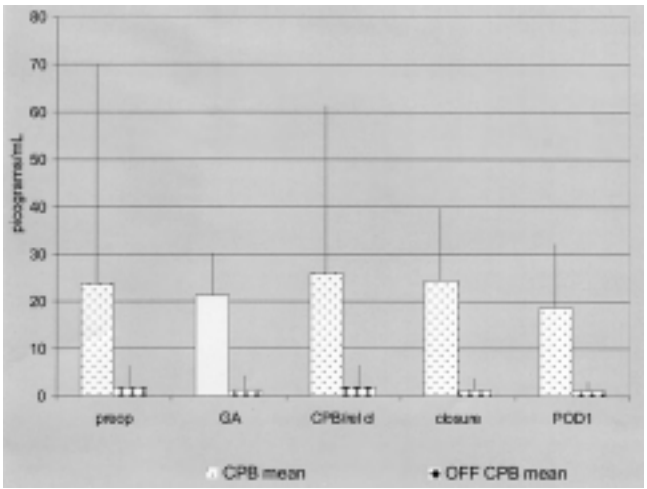

Figure 2. TNFα response (mean+SD) in patients undergoing cardiac surgery using CPB vs. off-pump. Values are expressed in picograms/mL. Time points in X axis: Preop = baseline, GA = after induction of general anesthesia, CPB/rel clamp = initiation of CPB or release of coronary clamp in off-pump, Closure = closure of chest, POD1 = postoperative day 1.

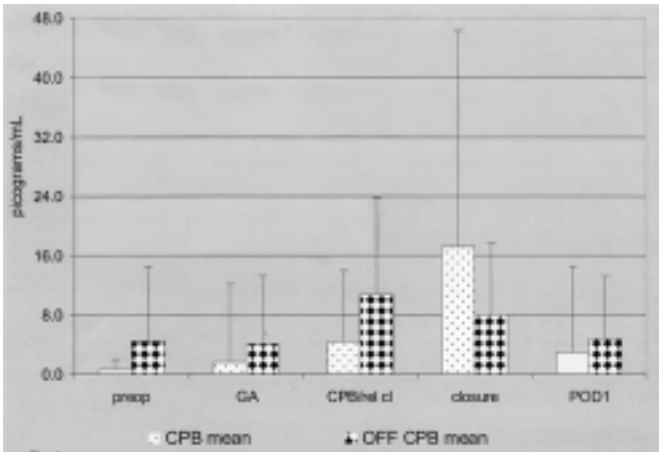

Figure 4. IL-10 response (mean+SD) in patients undergoing cardiac surgery using CPB vs. off-pump. Values are expressed in picograms/mL. Time points in X axis: Preop = baseline, GA = after induction of general anesthesia, CPB/rel clamp = initiation of CPB or release of coronary clamp in off-pump, Closure = closure of chest, POD1 = postoperative day 1.

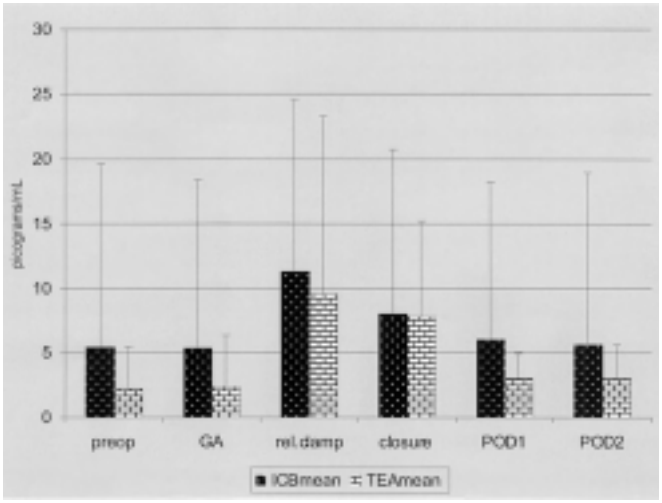

Figure 5. IL-10 response (mean+SD) in patients undergoing off-pump CABG with and without TEA. Values are expressed in picograms/mL. ICB = intercostal block/general anesthesia group, TEA = thoracic epidural analgesia. Time points in X axis: Preop = baseline, GA = after induction of general anesthesia, Rel clamp = release of coronary clamp, Closure = closure of chest, POD1 = postoperative day 1, POD2 = postoperative day 2.

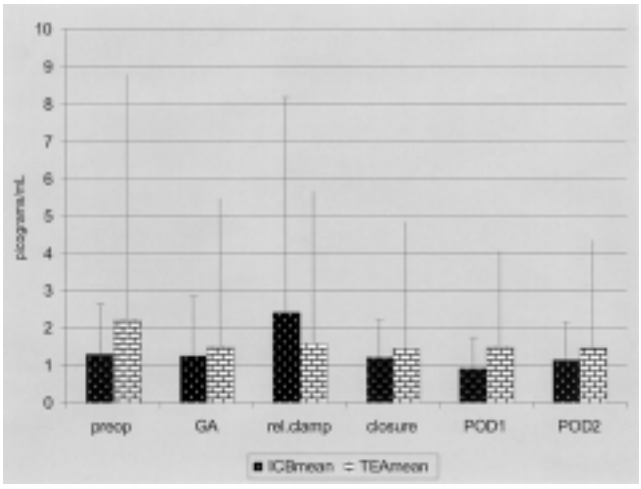

Figure 7. TNFα response (mean+SD) in patients undergoing off-pump CABG with and without TEA. Values are expressed in picograms/mL. ICB = intercostal block/general anesthesia group, TEA = thoracic epidural analgesia. Time points in X axis: Preop = baseline, GA = after induction of general anesthesia, Rel clamp = release of coronary clamp, Closure = closure of chest, POD1 = postoperative day 1, POD2 = postoperative day 2.

result in reduced stress and cytokine response. However, little is known about the cytokine response when CPB is avoided.

Benefits of TEA

Thoracic epidural analgesia (TEA) has been documented to improve splanchnic perfusion [Kapral 1999, Ai 2001] and reduce ischemia reperfusion injury in the myocardium as a result of cardiac sympathectomy [Kirno 1994]. TEA also results in pulmonary vasodilation [Garutti 1999] and thus

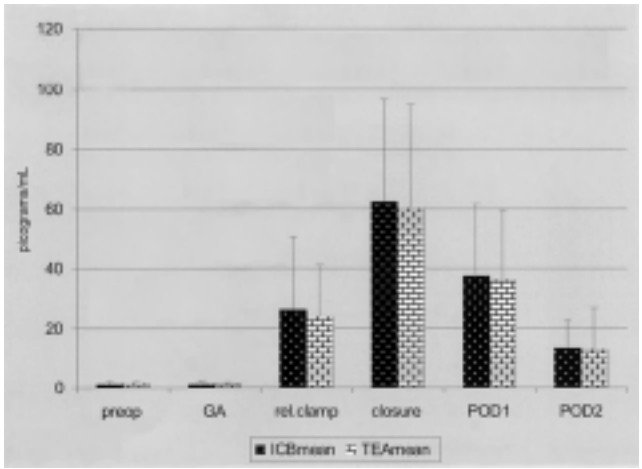

Figure 6. IL-6 response (mean+SD) in patients undergoing off-pump CABG with and without TEA. Values are expressed in picograms/mL. ICB = intercostal block/general anesthesia group, TEA = thoracic epidural analgesia. Time points in X axis: Preop = baseline, GA = after induction of general anesthesia, Rel clamp = release of coronary clamp, Closure = closure of chest, POD1 = postoperative day 1, POD2 = postoperative day 2.

may reduce sequestration of polymorphonuclears (PMNs) as well as facilitate washout of sequestrated PMNs. While it is known that TEA does not modulate the cytokine and acute-phase protein responses in patients undergoing cardiac surgery with CPB, the role of TEA in beating heart surgery is less defined. The major stimulus for cytokine release in the absence of CPB is likely to be the stress response to surgery and ischemia reperfusion injury. Ischemia may be aggravated by the lowflow states and hypercoagulability seen in the post-operative period [Speiss 1996]. Regional anesthesia has been documented to result in reduced graft occlusion [Rosenfeld 1993], which has been attributed to its effect on levels of plasminogen activator inhibitor 1 (PAI 1). Local anesthetics in the plasma also have been documented to play a beneficial role in ischemia reperfusion injury [Picard 1998, Kohrs 1999]. These observations suggest that TEA should reduce stress response and cytokine surge in patients undergoing cardiac surgery.

Can We Modify Stress and Cytokine Response with TEA?

Brix-Christensen et al. looked at cytokine and inflammatory response to cardiac surgery done with CPB using either high-dose opioids or a combination of TEA and low-dose opioids [Brix-Christensen 1998]. They could not demonstrate any difference between the groups with regard to cytokine response. Moore et al. documented reduced cortisol and catecholamine levels for 24 hours in patients receiving TEA for cardiac surgery compared to general anesthesia [Moore 1995]. Roth-Isigkeit et al. have reported a 3-to-16-fold increase in cortisol and catecholamine following cardiac surgery, which occurs predominantly in the postoperative period [Roth-Isigkeit 1998]. The intraoperative stress response was inhibited even by balanced anesthesia using

sufentanil, isoflurane, and midazolam. Thus the role of TEA in stress response and cytokine response in cardiac surgery with CPB is less impressive.

Compared to cardiac surgery with CPB, surgery done without CPB reduces cytokine surge [Brasil 1998, Ganapathy 1999a, Wan 1999a, Wan 1999b, Ganapathy 2000a]. Ganapathy et al. compared the cytokine response of patients who had minimally invasive direct coronary artery bypass (MIDCAB) to a cohort of patients having CABG with CPB [Ganapathy 1999a, Ganapathy 2000a]. The proinflammatory cytokine response was tenfold higher in the CPB patients upon initiation of bypass than in the MIDCAB patients (Figures 1-3, ◎). Ultra-sensitive assay kits had to be used to measure the response in the MIDCAB patients, as the levels were very low. The anti-inflammatory cytokine responses occurred earlier in the MIDCAB group than in the CPB patients (Figure 4, ◎). Most of the studies in this area document levels of cytokine in the plasma, which may represent only the spillover from the cellular and organ level where the primary release and resultant dysfunction occur. The second caveat to the measurement of plasma cytokine levels is the inability to use the results as a predictive tool for complications. There is no data in the literature describing levels of plasma cytokines that are consistently associated with adverse outcomes.

Within the subgroup of patients having surgery without CPB, TEA had very little effect in altering the minimal cytokine surge seen in that group (Figures 5, 6, 7, ◎). However, TEA did inhibit intraoperative cortisol surge compared to general anesthesia. The plasma catecholamine levels were also significantly lower in the TEA group both intraoperatively and postoperatively.

Endogenous glucose production measured with stable isotope infusion confirms the reduction in stress induced by TEA [Ganapathy 2000b]. Unfortunately, this is seen only during the intraoperative period. Whether continuation of a more intense sensory block in the postoperative period would extend this stress reduction into the postoperative period is unknown.

CONCLUSION

Stress and inflammatory responses occur due to the use of CPB as well as individual patient factors. Avoidance of CPB significantly reduces cytokine surge. Thoracic epidural anesthesia reduces the perioperative stress response but does not reduce the minimal cytokine response seen with beating heart surgery. Larger prospective studies are needed to evaluate the implications of these results on surgical outcome.

REFERENCES

1. Ai K, Kotake Y, Satoh T, et al. Epidural anesthesia retards intestinal acidosis and reduces portal vein endotoxin concentrations during progressive hypoxia in rabbits. Anesthesiol 94:263-9, 2001.
2. Anderson LW, Baek L, Degn H, et al. Presence of circulating endotoxins during cardiac surgery. J Thorac Cardiovasc Surg 93:115-9, 1987.
3. Ascione R, Lloyd CT, Underwood MG, et al. On-pump vesus off-pump coronary revascularization: evaluation of renal function. Ann Thorac Surg 68:493-8, 1999.
4. Blomberg S, Emanuelsson H, Kvist H, et al. Effects of thoracic epidural anesthesia on coronary arteries and arterioles in patients with coronary artery disease. Anesthesiol 78:840-7, 1990.
5. Blomberg S, Emanuelsson H, Rickstein S-E. Thoracic epidural anesthesia and central hemodynamics in patients with unstable angina pectoris. Anesth Analg 69:558-62, 1989.
6. Brasil LA, Gomes WJ, Salomao R, et al. Inflammatory response after myocardial revascularization with or without cardiopulmonary bypass. Ann Thorac Surg 66:56-9, 1998.
7. Brix-Christensen V, Tonnesen E, Sorensen IJ, et al. Effects of anesthesia based on high versus low dose opioids on the cytokine and acute phase protein responses in patients undergoing cardiac surgery. Acta Anesthesiol Scand 42:63-70, 1998.
8. Butler J, Rocker GM, Westaby S. Inflammatory response to cardiopulmonary bypass. Ann Thorac Surg 55:552-9, 1993.
9. Carli F, Schricker T. Modulation of the catabolic response to surgery. Nutrition 16:777-80, 2000.
10. Casey LC. Role of cytokines in the pathogenesis of cardiopulmonary induced multisystem organ failure. Ann Thorac Surg 56:S92-96, 1993.
11. Fransen E, Maessen J, Dentener M, et al. Systemic inflammation present in patients undergoing CABG without extracorporeal circulation. Chest 113:1290-5, 1998.
12. Ganapathy S, Murkin JM, Boyd W, et al. Minimally invasive coronary artery bypass surgery (MIDCABG) reduces release of proinflammatory cytokines compared to conventional bypass surgery. Abstract, ISMICS 1999.
13. Ganapathy S, Dobkowski WB, Murkin JM, et al. Thoracic epidural analgesia (TEA) increases graft flow and reduces cortisol release in minimally invasive coronary bypass surgery (MIDCABG). Anesthesiol 91:3A:A130, 1999.
14. Ganapathy S, Murkin JM, Dobkowski WB, et al. Cytokine response during minimally invasive coronary artery bypass (MIDCAB) surgery: role of anesthetic technique. Canad Cardiovasc Soc Ann Meeting, Abstract 554, Dec. 2000.
15. Ganapathy S, Schricker T, Boyd WD, et al. Thoracic epidural analgesia (TEA) inhibits intraoperative glucose production in minimally invasive coronary artery bypass surgery (MIDCAB). CCS Ann Meeting Abstract 195, 2000.
16. Garutti I, Quintana B, Olmedilla L, et al. Arterial oxygenation during one-lung ventilation: combined versus general anesthesia. Anesth Analg 88:494-9, 1999.
17. Gilliland HE, Armstrong MA, McMurray TJ. The inflammatory response to pediatric cardiac surgery: correlation of granulocyte adhesion molecule expression with postoperative oxygenation. Anesth Analg 89:1188-91, 1999.
18. Gormley SMC, McBride WT, Armstrong MA, et al. Plasma and urinary cytokine homeostasis and renal dysfunction during cardiac surgery. Anesthesiol 93:1210-16, 2000.
19. Gu YJ, Mariani MA, van Oeveren W, et al. Reduction of the inflammatory response in patients undergoing minimally invasive coronary artery bypass grafting. Ann Thorac Surg 65:4520-4, 1998.
20. Hall RI, Smith MS, Rocker G. The systemic inflammatory response to cardiopulmonary bypass: pathophysiological, therapeutic, and pharmacological considerations. Anesth Analg 85:766-82, 1997.
21. Kapral S, Gollmann G, Bachmann D, et al. The effects of thoracic epidural anesthesia on intraoperative visceral perfusion and metabolism. Anesth Analg 88:402-6, 1999.

22. Kirno K, Friberg P, Grzegorczyk A, et al. Thoracic epidural anesthesia during coronary artery bypass surgery: effects on cardiac sympathetic activity, myocardial blood flow and metabolism, and central hemodynamics. Anesth Analg 79:1075-81, 1994.
23. Kohrs R, Hoenemann CW, Feirer N, et al. Bupivacaine inhibits whole blood coagulation in vitro. Reg Anesth Pain Med 24:326-30, 1999.
24. Landow L, Phillips DA, Heard SO, et al. Gastric tonometry and venous oximetry in cardiac surgery patients. Crit Care Med 19:1226-33, 1991.
25. Liebold A, Keyl C, Birnbaum DE. The heart produces but the lungs consume proinflammatory cytokines following cardiopulmonary bypass. Eur J Cardiothorac Surg 15:340-5, 1999.
26. Liem TH, Booij LHDJ, Hasenbos, MAWM, et al. Coronary artery bypass grafting using two different anesthetic techniques: Part 1: hemodynamic results. J Cardiothorac Vasc Anesth 6:148-55, 1992.
27. Liem TH, Hasenbos MAWM, Booij LHDJ, et al. Coronary artery bypass grafting using two different anesthetic techniques: Part 2: postoperative outcome. J Cardiothorac Vasc Anesth 6:156-61, 1992.
28. Liem,TH, Booij LHDJ, Gielen MJM, et al. Coronary artery bypass grafting using two different anesthetic techniques: Part 3: adrenergic responses. J Cardiothorac Vasc Anesth 6:162-7, 1992.
29. Massoudy P, Zahler S, Becker BF, et al. Significant platelet and leucocyte retention during pulmonary passage after declamping of the aorta in CABG patients. Eur J Med Res 4:178-82, 1999.
30. McBride WT, Armstrong MA, Crockard AD, et al. Cytokine balance and immunosuppressive changes in cardiac surgery: contrasting response between patients and isolated CPB circuits. Brit J Anaesth 75:724-33, 1995.
31. Menasché P. The inflammatory response to cardiopulmonary bypass and its impact on postoperative myocardial function. Curr Opin Cardiol 10:597-604, 1995.
32. Moore CM, Cross MH, Desborough JP, et al. Hormonal effects of thoracic extradural analgesia in cardiac surgery. Brit J Anaesth 75:387-93, 1995.
33. Picard S, Rouet R, Flais F, et al. Proarrhythmic and antiarrhythmic effects of bupivacaine in an in vitro model of myocardial ischemia and reperfusion. Anesthesiol 88:1318-29, 1998.
34. Rosenfeld BA, Beattie C, Christopherson R, et al. The perioperative ischemia randomized anesthesia trial study group. The effects of different anesthetic regimens on fibrinolysis and the development of postoperative arterial thrombosis. Anesthesiol 79:435-43, 1993.
35. Roth-Isigkeit A, Brechmann J, Dibbelt L, et al. Persistent endocrine stress response in patients undergoing cardiac surgery. J Endocrinol Invest 21:12-9, 1998.
36. Schricker T, Klubien K, Carli F. The independent effect of propofol anesthesia on whole body protein metabolism in humans. Anesthesiol 90(6):1636-42, 1999.
37. Schricker T, Klubien K, Wykes L, et al. Effect of epidural blockade on protein, glucose, and lipid metabolism in the fasted state and during dextrose infusion in volunteers. Anesthesiol 92(1):62-9, 2000.
38. Schricker T, Wykes L, Carli F. Epidural blockade improves substrate utilization after surgery. Am J Physiol Endocrinol Metab 279(3):E646-53, 2000.
39. Schumann RR, Leong SR, Flaggs GW, et al. Structure and function of lipopolysaccharide binding protein. Science 249:1429-31, 1990.
40. Speiss BD. Ischemia: a coagulation problem? J Cardiovasc Pharmacol 27:S38-41, 1996.
41. Stenseth R, Bjella L, Berg EM, et al. Thoracic epidural analgesia in aortocoronary bypass surgery II: effects on the endocrine metabolic response. Acta Anaesthesiol Scand 38:834-9, 1994.
42. Tonnesen E, Brinklov MM, Christensen NJ, et al. Natural killer cell activity and lymphocyte function during and after coronary artery bypass grafting in relation to the endocrine stress response. Anesthesiol 67:526-33, 1987.
43. Tonnesen E, Brix-Christensen V, Toft P. The role of cytokines in cardiac surgery. Int'l J Cardiol 53S:1-10, 1996.
44. Wan S, Yim AP. Cytokines in myocardial injury: inpact on cardiac surgical approach. Eur J Cardiothorac Surg 16 Supp1:S107-11, 1999.
45. Wan S, Izzat MB, Lee TW, et al. Avoiding cardiopulmonary bypass in multivessel CABG reduces cytokine response and myocardial injury. Ann Thorac Surg 68:52-6. Discussion 56-7, 1999.