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The Systemic Inflammatory Response Syndrome and Off-Pump Cardiac Surgery

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INTRODUCTION

One of the perceived advantages of "off-pump" coronary artery bypass (OPCAB) surgery is the elimination of the many inflammatory insults associated with the use of the extracorporeal circuit and the ischemia/reperfusion injury associated with cardioplegic arrest and non-physiological flow. However, there are reports of a clinical systemic inflammatory response syndrome (SIRS) after OPCAB surgery (Bannon, Personal Communication, 2000). This manifests as a pyrexial state with low systemic vascular resistance, high cardiac outputs and hypotension, requiring the use of pressor agents such as noradrenaline.

The popular theory of the SIRS seen after cardiopulmonary bypass (CPB) involves contact activation with the extracorporeal circuit and ischemia/reperfusion causing complement activation, release of pro-inflammatory cytokines, and the activation of leukocytes and endothelial cells. This cascade culminates with the egress of activated neutrophils and fluid across the endothelium causing end-organ dysfunction [Bone 1996, Boyle 1997]. This syndrome is minor in the majority of patients but may contribute to significant morbidity and mortality in some patients.

OPCAB surgery eliminates the extracorporeal circuit and global myocardial ischemia/reperfusion as inflammatory insults influencing the SIRS after coronary artery bypass grafting (CABG). Ischemia/reperfusion is limited to the coronary artery territory being grafted and the effects of stabilizer displacement of the heart during coronary artery grafting. Surgical tissue trauma remains a constant between the two techniques.

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In this paper we review what is known of the SIRS seen after off-pump surgery and correlate this with studies comparing the deleterious effects of on-pump and off-pump cardiac surgery.

DISCUSSION

General Inflammatory Markers and OPCAB Surgery

Nonspecific markers of acute inflammation have been used to compare the differences between the SIRS seen after on-pump and off-pump surgery. In a non-randomized, prospective study, Fransen examined lipopolysaccharide binding protein (LBP) and C-reactive protein (CRP) as markers of the acute phase response in patients undergoing CABG with or without CPB. There was a significant increase in LBP and CRP in both groups 18 hours post-reperfusion with no statistical difference between the groups [Fransen 1998]. In a non-randomized prospective study, Brasil compared pre- and post-operative erythrocyte sedimentation rates (ESR) as a marker of generalized acute inflammation in patients having CABG on- and off-pump, finding no difference between the groups. The on-pump group in this study had more post-operative pyrexia, hypotension requiring inotropes, and increased endotracheal intubation times, suggesting a higher incidence of SIRS in the on-pump group [Brasil 1998].

Complement Activation and Off-Pump Surgery

The activation of the complement system is an early response to an inflammatory stimulus that triggers and amplifies the acute inflammatory response. It has generally been assumed that the contact activation with the extracorporeal circuit has been responsible for the activation of the alternative complement pathway [Kirklin 1983, Edmunds 1993]. The membrane attack complex (C5b-9/MAC) produced by the alternative pathway activates leukocytes and endothelial cells. Release of the anaphyla-

toxins C3a and C5a has been observed after CPB [Kirklin 1983, Bruins 1997]. The anaphylatoxins may cause vasodilatation with increased vascular permeability, leukocyte activation, chemotaxis, and leukocyte adhesion.

The absence of the extracorporeal circuit in off-pump surgery is thought to eliminate the influences of the complement cascade on the development of the SIRS. In a prospective, non-randomized trial of infants undergoing cardiac surgery with and without cardiopulmonary bypass, Sonntag demonstrated that complement activation occurred in all infants, but was significantly higher in the CPB group [Sonntag 1998]. In a prospective, randomized study, Ascione demonstrated that both complements C3a and C5a were significantly elevated one hour after on-pump surgery relative to off-pump surgery [Ascione 2000]. Struber compared complement activation in patients undergoing off-pump CABG through a mini-left anterior thoracotomy (MIDCAB) with patients having CABG with CPB. The patients were not well matched (single-vessel disease versus multi-vessel disease and different surgical approaches), but significant complement activation was demonstrated in the CPB group versus the MIDCAB group. In a prospective study, comparing off-pump CABG via median sternotomy or anterolateral thoracotomy, Gu demonstrated a significant increase in complement C3a after the initial incision in both groups that persisted in the median sternotomy group at the end of the operation [Gu 1999].

These studies suggest that although the extracorporeal circuit is the major factor in the activation of the complement cascade in cardiac surgery, surgical trauma and regional myocardial ischemia/reperfusion may be contributing factors. Therefore the role of complement activation must be considered in the SIRS reaction to off-pump surgery.

Cytokines and Off-Pump Surgery

Cytokines are a group of polypeptides produced by many different cell types. Cytokines are mediators of metabolic, immunological and endocrine responses to inflammatory injury. Several studies have examined the systemic release of pro- and anti-inflammatory cytokines during off-pump surgery.

Tumor Necrosis Factorα

Tumor necrosis factorα (TNFα) is a polypeptide pro-inflammatory cytokine produced by macrophages and monocytes. It acts as a potent pyrogen, activates neutrophils, and activates vascular endothelial cells. Brasil demonstrated significant increases in TNFα in patients having CABG with CPB with no detectable TNFα in patients undergoing OPCAB surgery [Brasil 1998]. Struber measured soluble TNF receptors 1 (TNFR1) and 2 (TNFR2) as markers of TNFα release [Kollias 1999], comparing patients having the MIDCAB procedure with patients having conventional CABG with CPB. A threefold increase in soluble TNFR1 was noted immediately and two hours post-operatively in the CPB group. A similar pattern was seen with TNFR2 [Struber 1999].

Interleukin-6

Interleukin-6 has both pro- and anti-inflammatory properties. Pro-inflammatory properties include the induction of the acute phase response, stimulating the release of hepatic proteins such as CRP, and a role in neutrophil-mediated ischemia/reperfusion injury [Sawa 1998]. Anti-inflammatory properties include the suppression of the actions of the potent pro-inflammatory cytokines IL-1β and TNFα and the induction of glucocorticoid release [Tilg 1997].

Several studies have compared the release of IL-6 after on-pump and off-pump surgery. In studies by Wan, Corbi and Fransen, comparing off-pump CABG to on-pump CABG via median sternotomy, IL-6 peaked 4-8 hours post-operatively and did not differ between groups [Fransen 1998, Wan 1999, Corbi 2000]. Struber compared the IL-6 response in patients having CABG on-pump to patients having a MIDCAB procedure off-pump through a left anterior thoracotomy (minimally invasive incision). The CABG patients demonstrated a significant increase in IL-6 (baseline 0 pg/ml) 2-8 hours post-operatively (1000 pg/ml), whereas the MIDCAB patients demonstrated a steady increase during the post-operative course to a peak at 24 hours (350 pg/ml). However the maximal IL-6 level in the CPB group was threefold that of the MIDCAB group [Struber 1999]. In a prospective study comparing the inflammatory response to off-pump CABG via a median sternotomy or anterolateral thoracotomy, Gu demonstrated significantly higher post-operative IL-6 levels in the median sternotomy group [Gu 1999].

The data from these studies suggest that CPB itself plays a secondary role in stimulating the release of IL-6 after cardiac surgery. Surgical tissue trauma is the most important inflammatory stimulus for IL-6 release, and the levels of IL-6 are related to the degree of surgical trauma inflicted.

Interleukin-8

Interleukin-8 is a potent pro-inflammatory cytokine, released from a variety of cell types, including activated endothelial cells, monocytes and T cells [Smith 1991]. IL-8 is a potent activator of neutrophils, which are key mediators of inflammatory injury.

Wan, in a study of CABG with CPB versus OPCAB surgery, demonstrated a significant increase in the levels of IL-8 2-8 hours post-CPB, with no significant increase in IL-8 in the OPCAB group. In this study the levels of IL-8 correlated positively with the levels of cardiac Troponin I, suggesting a role for IL-8 in myocardial injury post-cardiac surgery [Wan 1999]. Struber demonstrated greater elevation of IL-8 levels post CABG with CPB when compared to patients undergoing MIDCAB surgery [Struber 1999]. These studies suggest that CPB is the main stimulus for IL-8 release post-cardiac surgery.

Interleukin-10

Interleukin-10 is a potent anti-inflammatory cytokine that plays a significant role in the amelioration of ischemia/reperfusion injury [Yang 2000]. IL-10 release is protective in many inflammatory syndromes such as sepsis,

reducing neutrophil adhesion to activated endothelial cells and decreasing endothelial adhesion molecule expression [Krakauer 1995, Lane 1997, Marie 1998].

Wan has demonstrated that serum IL-10 levels are increased early post-reperfusion in patients undergoing CABG with CPB but is not altered in patients undergoing OPCAB surgery [Wan 1999]. The IL-10 response to CPB may indeed be protective, ameliorating the SIRS.

Other Cytokines

The role of other important mediators such as the potent pro-inflammatory cytokines IL-1β [Haeffner-Cavaillon 1989], IL-2, IL-12, and the anti-inflammatory mediator TGFβ1 [Sablotzki 1997], which have been elevated in patients undergoing CABG with CPB, have not been evaluated in off-pump cardiac surgery.

Leukocytes and Off-Pump Surgery

Several authors have demonstrated a significantly greater leukocytosis post-CABG with CPB than that seen after off-pump CABG surgery [Brasil 1998, Ascione 2000]. Similarly, using plasma markers of leukocyte activation, including neutrophil elastase [Gu 1998, Ascione 2000] and bactericidal permeability protein [Fransen 1998], CABG with CPB has been shown to cause more significant neutrophil activation than off-pump surgery.

The above studies would suggest a significant role of CPB in the leukocyte response to the post-CPB SIRS. However, like serum markers of endothelial cell activation (see below), serum markers of leukocyte activation may be an unreliable marker of the cell-surface expression of proteins. Neutrophil activation, with increased cell-surface expression of adhesion molecules such as the integrin complex CD11b/CD18, has been well-documented post-CPB [Galinanes 1996, Ilton 1999]. Neutrophil cell-surface studies have not been undertaken in off-pump cardiac surgery. In the absence of cell-surface studies, the role of leukocyte activation in the SIRS to off-pump surgery remains open to debate.

Endothelial Cell Activation and Off-Pump Surgery

Endothelial cell activation is a central feature to the SIRS [Bone 1996]. This involves the exposure of the endothelium to an external insult resulting in the synthesis and expression of cell-surface proteins, which mediate many events central to the SIRS. This includes the cell-surface expression of adhesion molecules which mediate the adhesion and transmigration of leukocytes into the subendothelial space, expression of vasoactive compounds such as endothelin and nitric oxide, which influence vasomotor tone, and expression of proteins such as tissue factor, which can initiate pathological thrombosis.

An increase of soluble endothelial cell adhesion molecules has been demonstrated in circulating plasma post-CPB in some studies [Boldt 1998, Kalawski 1998] but not in others [Boldt 1995]. Soluble E-selectin is an endothelial cell-specific adhesion molecule (as opposed to VCAM-1 and ICAM-1, which are expressed by other cell types, including macrophages and monocytes [Ryan 1991, Pforte 1993]) and its elevation in serum is highly suggestive of endothelial cell activation [Bevilacqua 1993]. In a prospective, randomized study, Matata has demonstrated a significant increase in soluble E-selectin 8 hours post-CABG with CPB, but no increase post-OPCAB [Matata 2000]. Levels of other soluble adhesion molecules (ICAM-1, VCAM-1, P-selectin) have not been evaluated in off-pump surgery.

Another marker of endothelial cell activation is the release of the vasoactive peptide endothelin into the circulation. Wildhirt demonstrated a significant increase in plasma big-endothelin in patients undergoing CABG with CPB, but not for OPCAB surgery [Wildhirt 2000].

While the above studies suggest that endothelial cell activation occurs post-CPB but not post-OPCAB, it must be emphasized that the significance of soluble endothelial cell proteins in the circulation remains controversial [Asimakopoulos 1998]. Increases in plasma levels of these proteins may reflect increased cell-surface expression, increased cleavage from the cell surface, or a decreased clearance of the protein from the circulation. Only endothelial tissue studies truly reflect what is happening at the cell surface. These studies have rarely been undertaken during CPB and have not been undertaken in patients undergoing OPCAB surgery.

Coagulation and Off-Pump Surgery

One of the concerns of OPCAB surgery is early graft failure due to thrombosis and sudden death due to fatal pulmonary embolism [Mariani 1999]. The coagulation and fibrinolytic systems are linked to the inflammatory cascade via such factors as contact factor XIIa and may play a role in the thrombophilic state post-OPCAB.

In a prospective, randomized study, Mariani investigated activation of the coagulation and fibrinolytic systems peri-off-pump surgery in patients having OPCAB or MIDCAB procedures. On post-operative day one a significant procoagulant state was demonstrated in both groups by the increase of prothrombin fragments 1+2 (markers of thrombin production) and a decrease in factor VII levels (indicating conversion to factor VIIa, which binds with tissue factor to initiate the coagulation cascade). Increased fibrinolysis was demonstrated in both groups on day one post-operatively by increased levels of fibrin-degradation products. βThromboglobulin levels were unchanged as were platelet counts suggesting that platelet activation was not a factor in this group of patients [Mariani 1999]. The lack of a control CABG with CPB group in this study limits the comparisons that can be drawn between the two techniques in this study. However, similar studies in patients undergoing cardiac surgery with CPB have demonstrated a procoagulant state post-CPB (increased prothrombin fragments 1+2, decreased factor VII levels), with a delayed initiation of fibrinolysis (soluble fibrin degradation products) [Boisclair 1993, Petaja 1996].

End-Organ Dysfunction and Off-Pump Cardiac Surgery

End-organ injury is one of the deleterious consequences of the SIRS. Indicators of inflammatory injury may be gen-

eral or organ specific. A general indicator of tissue injury is the measurement of oxidative stress. In a randomized study of patients with single or double vessel coronary artery disease (CAD), Matata compared the plasma levels of lipid hydroperoxides, protein carbonyls and nitrotyrosine between patients undergoing CABG with CPB and OPCAB [Matata 2000]. A significant increase in all three oxidative products was seen in the CPB group, but not the OPCAB group. In a similar study, Wildhirt determined the myocardial and plasma levels of malondialdehyde (MDA), a metabolite of lipid peroxidation. A significant increase was seen in plasma MDA in the CPB group two hours after initiation of reperfusion and a significant increase in myocardial MDA 48 hours after the initiation of reperfusion [Wildhirt 2000].

Cardiovascular Injury and Off-Pump Cardiac Surgery

Cardioplegic arrest and generalized myocardial ischemia are features of CABG with CPB. OPCAB surgery, on the other hand, results in regional ischemia caused by occlusion of the target coronary artery by the cardiac stabilizer and displacement of the heart.

The release of myocardial specific enzymes into the circulation is generally considered a useful indicator of myocardial injury. Several researchers have examined the effects of off-pump surgery on the release of these enzymes and correlated this to clinical outcomes, including myocardial infarction rates. In a non-randomized, prospective study, Bouchard demonstrated a decreased myocardial infarction rate (2.5% vs. 12%) and a decreased creatine kinase MB (CKMB) release (14 ± 17 vs. 46 ± 53 IU/ml) in patients undergoing off-pump CABG with CPB compared with patients having conventional CABG with CPB. The inotrope requirement did not differ between the two groups [Bouchard 1998]. The authors defined myocardial infarction as a peak CKMB greater than 50 IU/ml, without taking into consideration EKG or echocardiographic changes, which may explain the unusually high post-operative infarction rate.

In a prospective, randomized study of 80 patients (40 on-pump and 40 off-pump), Ascione demonstrated a decrease in Troponin I release in patients having CABG off-pump (0.07 vs. 0.23 mcg/l) four hours post-operatively. Atrial tachyarrhythmias were decreased in the off-pump group (6/40 vs. 15/40). There were no myocardial infarcts in either group.

In contrast to the above studies, a retrospective study by Kshettry of 609 on-pump CABG versus 135 OPCAB procedures describes no difference in the peak CKMB, myocardial infarction rate, or new atrial fibrillation between the groups [Kshettry 2000].

Pulmonary Function and Off-Pump Cardiac Surgery

A retrospective study by Asimakopoulos of 2,464 patients undergoing cardiac surgery with CPB revealed that 12 patients (0.5%) developed adult respiratory distress syndrome (ARDS), with a 91.6% mortality rate [Asimakopoulos 1999]. This study highlights one of the potentially devastating sequelae of the SIRS induced by CPB. The avoidance of CPB may improve post-operative pulmonary function, decreasing morbidity and mortality.

Taggart has reported that cardiac surgery using CPB produces greater respiratory dysfunction than general surgical operations [Taggart 1993]. In a similar non-randomized study by the same author, the respiratory function of patients undergoing OPCAB was compared to those having CABG with CPB. The groups were not well matched: the OPCAB group was younger, received fewer distal grafts, had better pre-operative arterial blood gases, and had lower PMN elastase levels (a marker of neutrophil activation) than the CPB group. Nevertheless there were no significant differences in the arterial gas exchange, ventilation time, and hospital stay between the two groups [Taggart 2000].

The avoidance of a median sternotomy to perform CABG without CPB may improve post-operative pulmonary function. In a non-randomized study, Lichtenberg compared patients undergoing CABG with CPB to those having minimally invasive direct coronary artery bypass (MIDCAB) using a left antero-lateral thoracotomy. The patients were not well matched, with the CPB group having 2.7 ± 0.7 grafts compared to the MIDCAB group having 1.0 ± 0.0 grafts. When compared to the CPB group the MIDCAB group had significantly less duration of mechanical ventilation (300 ± 168 min. vs. 840 ± 342 min.) and better preserved pulmonary function (determined by spirometry). MIDCAB patients also described less post-operative pain, which may have contributed to their improved pulmonary function [Lichtenberg 2000].

Neurocognitive Deterioration and Off-Pump Cardiac Surgery

Neurological injury after cardiac surgery occurs in two forms, gross injury such as strokes and subtle neurocognitive changes. Strokes are generally believed to result from emboli after aortic manipulation such as cannulation and clamping (including the "side-biting" clamp). Subtle neurocognitive impairment is believed to result from microemboli and the non-physiological flow of CPB [Westaby 1996]. It is suggested that CABG without CPB should minimize post-operative cognitive impairment [Benedict 1994].

A recent non-randomized, non-blinded study [Taggart 1999] examined neurocognitive function post-CABG with and without CPB. Neurocognitive testing was performed pre-operatively, at discharge and three months post-discharge in 50 patients undergoing CABG with CPB and 25 patients undergoing OPCAB surgery. Neurocognitive function was impaired at discharge in both groups, but had improved significantly in both groups at 3 months. The findings of this study are in keeping with other recent studies [Vingerhoets 1996, Toner 1998] suggesting that both approaches induce transient cognitive impairment, which resolves by three months.

Non-physiological perfusion and the inflammatory response after cardiac surgery are thought to cause neuronal injury and increased permeability of the blood-brain barrier. Biochemical measures of neuronal injury have been used to quantify the degree of injury after cardiac surgery. Serum S100β is a neuronal specific [Georgiadis

2000] protein that has been used as a marker of neuronal injury and increased blood-brain barrier permeability after cardiac surgery.

In prospective randomized studies, several researchers have documented an increase in serum S100β protein in patients undergoing CABG with CPB with no significant increase in the OPCAB group [Anderson 1999, Lloyd 2000, Wandschneider 2000]. Anderson noted that the patients undergoing off-pump CABG via a median sternotomy displayed significantly higher S100β levels at the end of the procedure than those having CABG via an anterolateral thoracotomy. An explanation for this may be that aortic manipulation and injury (causing cerebral micro-emboli) occurs during application of the "side-biting" clamp used to perform the proximal saphenous vein graft (SVG) anastomoses. The study by Lloyd compared serum S100 protein levels with the outcomes of neurocognitive testing pre-operatively and 12 weeks post-operatively by a blinded examiner. Despite an increase in S100 protein in the CPB group, there were no differences in the number of deteriorations in neurocognitive tests between the groups [Lloyd 2000]. These studies add weight to the observation made by Westaby and associates that increases in serum S100 protein reflect diffuse microembolic injury and increased blood-brain barrier permeability rather than irreversible cerebral damage via neuronal injury [Westaby 1996].

In a prospective, non-randomized, blinded trial using magnetic resonance imaging, Anderson has demonstrated that cerebral edema is less after OPCAB surgery than after CABG with CPB. The 4.7% increase in extracellular brain water in the CPB group had resolved by one week, and there was no clinical neurocognitive correlation analysis undertaken [Anderson 1999]. Causes of cerebral edema may be inflammatory (mediated by cytokines) or vasoactive (mediated by endothelial cell activation). The clinical neurocognitive significance of these findings is uncertain, but may support the argument that vasoactive and inflammatory edema is more common after CPB.

Renal Function and Off-Pump Cardiac Surgery

Renal impairment after CPB contributes to post-operative morbidity and mortality. In a prospective, randomized trial, Ascione compared the effects on glomerular and tubular function in patients having CABG with CPB to those having OPCAB surgery. An initial improvement in creatinine clearance was observed in the on-pump group which then deteriorated to below pre-operative levels, significantly worse than the off-pump group. CPB also adversely affected urinary-albumin/creatinine ratios, increasing perioperatively in the on-pump group, decreasing to levels similar to that in the off-pump group over 24-48 hours. Similarly, urinary n-acetyl-β-glucosamine levels were increased in the CPB group versus the OPCAB group. This study suggests that off-pump CABG provides better functional preservation than on-pump CABG [Ascione 1999]. However, increased serum plasma creatinine may result from increased muscle catabolism or decreased clearance from the circulation, and with the inability to distinguish between the two, we must interpret these results with caution.

CONCLUSION

From the studies reviewed in this paper we may conclude that the SIRS resulting from off-pump cardiac surgery differs from that seen after conventional on-pump cardiac surgery. Complement activation and the release of pro-inflammatory IL-8 is dependent on the extracorporeal circuit. Likewise, the release of products of endothelial and leukocyte activation into the plasma is more prominent in on-pump surgery, but the paucity of cell-surface studies means that any interpretation of this data should be made with caution.

The absence of a rise in anti-inflammatory IL-10 after off-pump surgery may be deleterious, with IL-10 potentially being protective against ischemia/reperfusion injury after CPB. The procoagulant state seen after off-pump surgery may too be deleterious and this requires further study, especially in view of the apparent clinical significance of off-pump graft thrombosis.

Recent neurocognitive studies comparing on-pump to off-pump patients have questioned the extent of the deleterious effects of CPB and the role of S100 protein as a marker for permanent neuronal injury. Similarly, recent studies investigating pulmonary function post-operatively show questionable benefit for off-pump versus on-pump surgery.

In conclusion, we advocate caution when choosing to use off-pump cardiac surgery on the basis of a theoretical reduction in the SIRS and ensuing end-organ injury. Off-pump cardiac surgery provides an excellent alternative to on-pump surgery in suitable cases, but the physiological benefits of avoiding CPB do not outweigh the benefits of a technically satisfactory operation.

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