

Optimization of the Perfusion Circuit and Its Possible Impact on the Inflammatory Response

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Presented at the Perfusion Downunder Meeting, Hayman Island, Queensland, Australia, August 9–11, 2007.

Abstract: Although there has been a steady improvement in cardiopulmonary bypass (CPB) techniques since its early introduction, it is still associated with some morbidity. Further attenuation of bypass-related systemic inflammatory reaction demands multidisciplinary action because the basic physiopathology is complex and cannot be controlled by one approach alone. This is an overview of the literature. Introduction of “mini” CPB circuits makes it easier to compare perfusion outcomes between different centers. Indeed, these circuits have a comparable fluid dynamic characteristic and surface area. All of them have a hemocompatible coating, and the technique avoids return of the pleuropericardial aspirations into the systemic circulation. As a consequence, results are very comparable to those obtained by beating heart surgery. However, vascular access and the resultant change in flow pattern in the aorta still have a negative correlation with neurocognitive outcome. A better understanding of the delicate balance between fluid dynamics, foreign ma-

terial, coagulation, and inflammation is still a major requirement, especially because recent research combining pharmacologic, surgical, and anesthesia techniques with perfusion techniques has shown attenuation of the inflammatory response sequelae. For example, a better neurologic outcome is achieved by combining separation of suction, reducing hemodilution, administration of high-dose aprotinin, and volatile anesthetics and alternative cannulation techniques. Further improvement of CPB requires more uniform CPB circuits with known characteristics. The design should be based on evidence-based medicine philosophy. Combined efforts should be made by anesthesiologists, perfusionists, and surgeons to attenuate contact activation, ischemia-reperfusion injury, blood–material interaction, cell damage, and neurocognitive outcome. **Keywords:** vascular access, shed blood, cell damage, inflammatory reaction. *JECT*. 2007;39:285–288

INTRODUCTION

Although cardiac surgery with cardiopulmonary bypass (CPB) has resulted in an improved quality of life to millions of people over the last five decades, it remains associated with a variably pronounced inflammatory reaction. Until the end of the past century, most clinicians believed the main cause of this reaction was attributed to the use of CPB per se. However, the introduction of beating heart surgery showed that an important part of this inflammatory reaction is more related to surgery itself than to CPB. This report will focus on some aspects of the pathophysiology of CPB and on strategies by which one can modulate the systemic inflammatory response.

HEMODYNAMIC CHANGES

Before starting CPB, one has to establish vascular access. This means that a rigid system, being the CPB circuit, is branched to the elastic compliant vascular system. The

relative small aortic cannula delivers a high-velocity turbulent blood flow in the aorta (1,2). Depending on the insertion site of the cannula, this can result in the inverse rotation of the blood flow into the aorta (3). The high velocity created by the aortic cannula may “sand blast” the aortic wall and can lead to organ embolization (4,5).

After cannulation of the great vessels and institution of extracorporeal blood flow, major changes will occur. The blood from the venous circulation is drained into the circuit and, as an immediate result of this action, the output from the native heart is reduced or abolished. Because the heart is a pulsatile pump, this leads to a reduced or absent pulse pressure in the vascular tree. Finally, the shunting of blood toward the venous reservoir will reduce blood flow through the pulmonary circulation.

The obliteration of pulse pressure in the systemic circulation has a major impact on organ and tissue perfusion, because the shear forces generated by the pulsatile flow are mandatory for endothelial-derived nitric oxide generation. The reduced lung flow will attenuate the clearance of the bradykinin generated by contact activation (6). Indeed, the majority of angiotensin-converting enzyme re-

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ceptors are located in the lung vasculature and thus are bypassed when CPB is instituted. The latter is one of the causes of the hypotension observed after initiating CPB.

BLOOD-MATERIAL INTERACTION

When blood comes in contact with the different artificial surfaces of the CPB circuit, many reactions take place. First of all, there is an important contact activation that generates bradykinin, and the latter will stimulate in a dose-dependent manner the release of endothelial tissue plasminogen activator, the key enzyme in the initiation of fibrinolysis. At the same time, proteins are adsorbed by the mostly hydrophobic materials, and this activates the intrinsic coagulation cascade, blood platelets, and the complement cascade. As a result, thrombin will be generated, and white blood cells will first stick and subsequently migrate through the endothelium into the interstitium.

HEMOLYSIS

Hemolysis is defined as damage to blood elements, but in general, many clinicians will narrow this definition to damage to red blood cells. However, one could wonder if red blood cell destruction should still be our major concern in today's perfusion technology. Indeed, in most cases, the total amount of destroyed red blood cells will not exceed a few milliliters of blood and is thus negligible for oxygen transport. The largest part of that destruction is not caused by the CPB circuit but by aspirating pleuro-pericardial blood losses (7). However, free plasma hemoglobin remains important, because it is a potent antidote of nitric oxide and will induce pulmonary and systemic hypertension (8). In the literature, most authors are still using plasma free hemoglobin as a measure of red blood cell destruction. However, the same amount of cell destruction can give quite different values of free plasma hemoglobin (Hb) depending on the haptoglobin (Hp) phenotype of the patient. It would be better to state that hemolysis becomes more harmful the moment haptoglobin is no longer present for the formation of stable Hp-Hb complexes (9). These complexes will reduce the loss of Hb through the glomeruli, protect against peroxidative kidney injury, and allow the recycling of heme iron. Haptoglobin will also indirectly exert an anti-inflammatory reaction as the Hp-Hb ligand binding to CD163 on human monocyte-macrophage complexes will secrete interleukin (IL)10 (10). Unfortunately, there is an overrepresentation of patients with haptoglobin phenotype 2-2 in cardiac surgery (11). Patients with this allele have the lowest binding capacity for free iron. The iron retention in Hp 2-2 individuals results in a degree of iron-driven oxidative stress, which is reflected by lower extracellular vitamin C concentrations

(12), a powerful free radical scavenger and first-line antioxidant.

SUCTION BLOOD

During CPB, blood is often lost into the pleuro-pericardial cavities. Until recently, this blood was considered "safe" because it is anti-coagulated. However, recent research clearly showed that blood that has been in contact with damaged tissue is highly contaminated. Suction blood contains high levels of activated platelets represented by high plasma levels of PF4 and β -thromboglobulin (13). The high levels of PF4 inactivate the heparin in the blood, resulting in low anti-coagulation and high thrombin levels (14). The high levels of thromboxane can lead to pulmonary hypertension. Suction blood also has a high fibrinolytic activity (15) and has a negative impact on the coagulation potential of a given patient.

In addition to the above, the blood has high free plasma hemoglobin levels (7) and contains a high load of fat emboli (16). The latter has been increasingly implicated as one of the main causes of cognitive dysfunction after CPB. The fact that these fat emboli cannot be effectively removed out of the circuit with the existing filters makes it a serious problem.

HEMODILUTION

Hemodilution during CPB has been considered for years as beneficial because it counteracted the increased blood viscosity that occurred during hypothermia. However, recent work shows that there is an important relationship between hemodilution and morbidity (17-21). In adults, hematocrit levels < 24% are correlated with a higher incidence of acute renal failure. In pediatric surgery, better neurologic outcome is observed after deep hypothermic circulatory arrest when relatively high ($\pm 30\%$) hematocrit levels are maintained during bypass (22). According to some authors, worse outcome, when using low hematocrit levels during CPB, is more related to an insufficient oxygen delivery than to the hematocrit level per se (21). As a direct consequence, a low hematocrit level will not necessarily increase morbidity as long as sufficient oxygen delivery is maintained (e.g., by increasing blood flow).

When discussing hemodilution, one has to consider the different priming fluids. First, there is the choice between crystalloid fluids and plasma expanders (23). Buffered electrolyte solutions maintain better electrolyte homeostasis and acid-base equilibrium. The higher viscosity of plasma expanders will maintain a better microcirculation. Based on this, buffered gelatin solutions seem to be an excellent choice (24). Starches do have an impact on plate-

let function, but there is some evidence that they can attenuate the inflammatory reaction. Addition of albumin to the priming solution will passivate all foreign surface area and helps to enlarge the buffer capacity of plasma when hypothermia is applied (25). Finally, exclusion of glucose and the addition of mannitol into the priming solution have been shown to be advantageous (26).

THE CIRCUIT

One of the major disadvantages of CPB is the great heterogeneity in circuits between cardiac centers. As a direct consequence, it is very difficult to compare one center against another. The introduction of the so-called mini circuits does allow these comparisons because all systems are constructed the same way. Impact on morbidity of almost every component has been described in the existing literature. However, only in recent years has it become possible to evaluate the combined impact of different components used in the same manner and in large series.

CONCLUSIONS

Several strategies are available to reduce CPB-related morbidity, but it is quite clear that optimal modulation can only be achieved by combining different strategies.

A first strategy is pharmacologic intervention. Aprotinin has a beneficial impact on platelet function, contact activation, and thrombin generation (27–29). It attenuates the inflammatory reaction and can ameliorate neurocognitive outcome (29). However, recently there has been some debate regarding its safety (30). Pharmacologic inhibition of C5a and terminal complement complex looks promising, as shown by some pilot studies (31). Infusion of direct or indirect nitric oxide donors is a relatively simple method to compensate the loss of endogenous nitric oxide production during CPB. The use of methylprednisolone for control of the systemic inflammatory response remains more debatable in recent literature. Finally, the use of sevoflurane has shown to attenuate myocardial damage and to protect kidney function (32).

A second strategy focuses on the CPB itself. Blood-material interaction can be attenuated by the use of surface modification. Two major approaches are available. Heparin coatings are more beneficial for attenuating complement activation, whereas non-thrombogenic coatings are mainly preserving platelet function (33). However, return of pleuro-pericardial aspirations into the systemic circulation will blunt the beneficial interaction of a coating (34).

Returning blood aspirated from pleuro-pericardial cavities into the systemic circulation should be avoided as much as possible (13–16,34).

Pulsatile flow should be instituted whenever possible

without charging the heart, because this will ameliorate tissue perfusion and help to control hypotension (6,35).

Finally, evidence-based medicine should help to define which are the most efficacious combinations.

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