

# Blood or no blood for coronary artery bypass surgery: simple concept but a sublime scientific argument

## Abstract

Cardiopulmonary bypass (CPB) exposes blood to artificial surfaces that gives rise to major haemostatic defects. This often results in transfusion of autologous or allogeneic blood products. Transfusion thus expose cardiotomy patient to additional risks of transfusion reactions, viral transmissions, and immunosuppression. Alternatively, pharmacological strategies to decrease peri-operative bleeding have been investigated in a large number of clinical trials, most of which have shown a decrease in blood loss; though some studies lacked sufficient power to detect a beneficial effect on clinically more relevant outcomes. This review summarizes the pharmacological and non-pharmacological interventions as means to attenuate the alterations in the hemostatic system during CPB surgery in an attempt to reduce excessive bleeding and transfusion requirements.

**Keywords:** blood transfusion, rFVIIa, coagulation, cardiac surgery, antifibrinolytics, off-pump cardiac surgery, cell salvage

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## Introduction

Bleeding disorders post cardiopulmonary bypass (CPB) is a common complication of cardiac surgery. It results from impaired hemostasis and coagulation system and requires transfusion of autologous or allogeneic blood products such as platelet concentrates, fresh frozen plasma, and cryoprecipitate.<sup>1,2</sup> Consequently, transfusion of allogeneic blood products may expose the patient to additional risks such as transfusion reactions, viral transmissions, and immunosuppression and increased expense.<sup>1-3</sup> The excessive activation of the CPB modulated haemostatic system, relating to interaction of blood with nonendothelial CPB surface, activation of the extrinsic clotting pathway secondary to surgical trauma and retransfusion of pericardial blood has given rise to numerous pharmacologic and non-pharmacologic strategies as means to attenuate this alterations in the haemostatic system.<sup>4,5</sup>

During CPB, thrombin mediates the conversion of fibrinogen to fibrin monomer, initiating fibrinolysis by mediating release of tissue plasminogen activator (t-PA). t-PA release contributes to consumptive process. This in turn activates the inflammatory system specifically complement and fibrin split products by internalization or destruction of the adhesive glycoprotein Ib receptor on the platelet surface that may detrimentally affect IIb/IIIa receptors.<sup>6,7</sup> Experimental reports have suggested that inhibition of the complement membrane attack complex attenuates the reduction in platelets and decreases formation of platelet-leukocyte complexes during simulated CPB. Moreover to that inhibition of the complement cascade using an antibody against C5 resulted in a 40% reduction in myocardial injury, an 80% reduction in cognitive defects, and a 30% reduction in postoperative chest tube drainage.<sup>8,9</sup>

Several specific points regarding the complex interrelation between coagulation and inflammation, in the context of CPB, deserve attention. Pro-inflammatory cytokines play a key role in initiating the coagulation process locally at sites of inflammation, by activation of the endothelium, induction of the expression of tissue factor, eliciting the expression of leukocyte adhesion molecules on the intravascular cell surfaces, and stimulating production of

platelet-activating factors.<sup>10,11</sup> This, combined with down-regulation of thrombomodulin expression and of the fibrinolytic and protein C anticoagulant pathways, alters the balance between procoagulant and anticoagulant activities, resulting in a markedly procoagulant state.<sup>11</sup>

Whereas, heparin and protamine, which are used to modulate coagulation in patients undergoing cardiac surgery have important immunomodulatory effects.<sup>12</sup> The heparin-protamine complex is particularly deleterious. The heparin-protamine interaction activates the inflammatory response by complement activation, histamine release, thromboxane and nitric oxide production, and antibody formation.<sup>13</sup> These results in widespread vascular injury following CPB may result in uncontrolled platelet activation, thrombin generation, and disseminated intravascular coagulation.<sup>13</sup> Enhancement of the antithrombotic properties of heparin by antithrombin III (ATIII) supplementation can preserve the haemostatic system during CPB, especially in patients who have acquired ATIII deficiency from preoperative heparin infusions.<sup>14</sup> or CPB-related hemodilution or consumption.<sup>15</sup> In addition, it has been shown that transgenic ATIII can reduce the requirement for fresh frozen plasma (FFP) in patients with heparin resistance.<sup>16</sup> Use of newly developed antithrombotic agents may be useful when heparin cannot be used (e.g., heparin induced thrombocytopenia with thrombosis) or as adjuncts to decrease consumption of coagulation factors and platelets by overcoming the inability of heparin to completely inhibit clot-bound thrombin.<sup>14</sup> and platelet bound Va/Xa activity.

In cardiac surgery with CPB, multiple haemostatic defects can develop from thrombocytopenia, platelet dysfunction, generalised coagulation factor deficiency and fibrinolysis, all of which can contribute to coagulopathic bleeding. Recombinant activated factor VII (rFVIIa) with its mechanism of action has been shown to restore thrombin generation in these conditions and promote the formation of a platelet plug and a fibrin clot. rFVIIa binds to most tissue factor molecules, initiating the extrinsic pathway of the coagulation cascade, which in turn leads to activation of maximum quantities of factor X with subsequent massive generation of thrombin. At the same time, factor IX of the intrinsic pathway of the coagulation cascade is also activated and consequently, procoagulation activity increases. Administration

of rFVIIa shortens the tissue-factor independent activated partial thromboplastin time (aPTT), as well as the prothrombin time (PT),<sup>17</sup> which is tissue-factor dependent. Independent of tissue factor, rFVIIa can activate factor X on the surface of the activated platelets,<sup>18</sup> and monocytes,<sup>19</sup> potentially augmenting both intrinsic and extrinsic Xase enzyme function. Because rFVIIa can initiate coagulation independent of factors VIII and IX, it is useful as treatment in patients with haemophilia A or B complicated by high-responding inhibitors.

The foremost mechanical methods of peri-operative conservation of red blood cells are intra-operative cell salvage and acute peri-operative normovolaemic haemodilution. Intraoperative cell salvage is the most widely used method in elective cardiac surgery.<sup>20</sup> Huet C et al.<sup>21</sup> performed meta-analyses of randomized trials to determine whether cell salvage reduces patient exposure to allogeneic blood, and evaluated the effectiveness and safety of cell salvage in cardiac elective surgery. The primary outcome was the proportion of patients who received at least one peri-operative allogeneic red cell transfusion. Twenty-seven studies were included in the meta-analyses. It was deduced that cell salvage devices that do not wash salvaged blood were marginally effective in cardiac surgery patients when used postoperatively (relative risk.<sup>RR</sup> = 0.85, 95% confidence interval.<sup>CI</sup> = 0.79-0.92).

Results from McGill et al.<sup>22</sup> study indicated that acute peri-operative normovolaemic haemodilution does not confer additional benefits in terms of reduced use of allogeneic transfusion (odds ratio 1.05 (0.56 to 1.98)). Normally, after induction of anaesthesia blood is removed from the patient and is replaced with an equivalent volume of colloid. The blood is anticoagulated during removal to prevent thrombus formation. This blood has a haematocrit equal to that of the patient, usually 0.350.45. After the termination of bypass the patient's haematocrit will usually be considerably lower than that of the stored blood. This blood is then re-transfused, thereby increasing the patient's haematocrit. A meta-analysis of the treatment across surgical specialties concluded that it reduces the need for allogeneic red blood cells (odds ratio 0.31 (0.15 to 0.62)), but that the evidence in cardiac surgery was less compelling (0.51 (0.26 to 0.99)). This meta-analysis included 11 randomised controlled trials in cardiac surgery.<sup>23-26</sup> Overall the evidence for the benefit of acute peri-operative normovolaemic haemodilution in reducing use of allogeneic red blood cells during cardiac surgery was equivocal.

Beating-heart cardiac surgery is fast becoming a safe alternative to conventional CABG. By avoiding CPB, OPCAB is a potentially more physiologic method to maintain the functional integrity of major organ systems with the possibility of reducing mortality and morbidity. In a prospective randomized trial comparing the transfusion requirements Puskas et al.<sup>27</sup> showed that CPB was an independent predictor of transfusion (odds ratio 2.42,  $P = .0073$ ) by multivariate analysis. This study found that multiple indices of coagulopathy were significantly less deranged in OPCAB than in CABG with CPB and that patients undergoing OPCAB received fewer units of blood, were more likely to avoid transfusion altogether, and had a higher hematocrit at the time of hospital discharge.

Donor blood is a limited resource and its transfusion is associated with significant adverse effects. Therefore, alternatives have been searched, the ultimate being artificial oxygen (O<sub>2</sub>) carriers. There are two main groups of artificial O<sub>2</sub> carriers: haemoglobin based and perfluorocarbon emulsions. Other modifications serve to decrease O<sub>2</sub> affinity in order to improve O<sub>2</sub> off-loading to tissues, and certain products are polymerized to increase the haemoglobin concentration at physiologic colloid oncotic pressure.<sup>28</sup> Perfluorocarbons are carbon-

fluorine compounds characterized by a high gas dissolving capacity for O<sub>2</sub> and CO<sub>2</sub> and chemical and biologic inertness.<sup>29</sup> In contrast to haemoglobin, which delivers less oxygen to the tissues at lower temperatures, solubility of oxygen in perfluorocarbon emulsions increases with decreasing temperature.<sup>30</sup> These agents should provide enhanced tissue oxygen delivery compared with hemoglobin during hypothermic CPB. Because perfluorocarbon emulsions enhance solubility for other gases in addition to oxygen, gaseous emboli developing during CPB also may be reduced,<sup>31</sup> now undergoing clinical trials as an oxygen therapeutic agent.<sup>32</sup>

Clopidogrel is increasingly being used in patients awaiting CABG. Ascione et al.<sup>33</sup> suggested that the use of clopidogrel among in-hospital patients within 5 days before CABG may increase early mortality and morbidity, and that the risk of mortality is greatest when the drug is given within 48 hours of surgery. They reported marked increase in blood loss and transfusion requirements {odds ratio (confidence interval) for aspirin without clopidogrel 0.94 (0.51 to 1.82), clopidogrel without aspirin 1.16 (0.18 to 7.42), aspirin and clopidogrel 5.03 (3.03 to 8.33)}. In a separate study comprising 224 patients, of whom 59 had pre-operative clopidogrel within 7 days before surgery, Hongo et al.,<sup>34</sup> reported that clopidogrel in combination with aspirin was associated with significantly higher bleeding, transfusion requirements, and a 10-fold increase re-operation for bleeding. Similar results were reported by Ray et al.<sup>35</sup> Stopping aspirin and clopidogrel 7 days prior to surgery would reduce peri-operative blood loss; however this should be weighed against risk of acute coronary syndrome.

Russell et al.<sup>36</sup> in their meta-analysis observed that albumin prime better preserves platelet counts than crystalloid. Albumin also favourably influences colloid oncotic pressure, on-bypass positive fluid balance, post-operative weight gain, and colloid usage. The clinical significance of these observations merits further investigation. Zelinka et al.<sup>37</sup> suggested the use of retrograde autologous prime with shortened bypass circuits to decrease blood transfusion in high-risk coronary artery surgery patients.

Karkouti et al.<sup>38</sup> in an observational study to look at the association of low hematocrit during cardiopulmonary bypass and increased risk of peri-operative stroke in cardiac surgery concluded that there is an independent, direct association between degree of hemodilution during CPB and risk of peri-operative stroke. Prospective randomized clinical trials comparing different degrees of hemodilution during CPB are required to determine whether this is a cause-effect relationship or a simple association. The Hemobag® Blood salvage device has been successfully incorporated into multi-modality approach to blood conservation. Infusion of the Hemobag® concentrate appears to recover safely substantial proteins, clotting factor and cell concentration for all types of cardiac procedures, maintaining the security of a primed circuit. Recently this technique has also been performed on patients with Jehovah's Witness faith. This technique was only described for use in non-Jehovah's witness patients undergoing CPB. Now the technique can be incorporated into this patient population successfully without interrupting the continuity of the blood with the patient. By this technique autologous blood with all its coagulation components is preserved for re-infusion back to the patient as compared to alternative traditional red cell salvage devices (which retrieves washed RBCs, yet discards viable plasma proteins and other cellular content essential for optimal hemostasis) that many institutions perform at the end of the case. Post-operative replacement of residual pump blood, shed mediastinal blood and autologous transfusion to replace the red cell mass and regular check of clotting parameters, use of protamine to neutralize the heparin associated coagulopathy and helps to and cell salvage.

## Conclusion

CPB is a prerequisite for open-heart surgery, and is a procedure routinely used. CPB exposes blood to artificial surfaces, to mechanical trauma from the pump, to alterations in temperature, and to dilution with fluids, whole blood, plasma products, and drugs, and leads to the activation of platelets, coagulation, and fibrinolysis. Coagulopathy during cardiac surgery with CPB results in impairment in hemostasis and subsequently higher morbidity and mortality. National blood shortages continue to surface periodically, new infectious sequelae of transfusion continue to threaten both the quality and the quantity of blood supply, and incompatibility and other immunologic reactions remain problems associated with allogeneic blood transfusion. In addition, cost and resource efficiency considerations now play a prominent role in mandating a reduction in blood transfusions. Recent advances in surgical techniques and postoperative management have aimed at reducing postoperative morbidity and mortality. Patients who are at a high risk of bleeding in the peri-operative period as well as those who avoid transfusions such as Jehovah's Witnesses are likely to benefit from off-pump myocardial revascularization and may be offered the option of OPCAB surgery if expertise is available. Special attention should be given to a category of patients who have chronic renal impairment and immuno-compromised subjects.

While strategies for preventing blood loss and reducing blood product transfusion warrants a comprehensive approach by the peri-operative team, individual physicians can reduce risks to their patients by maintaining conservative "triggers" for transfusions, prescribing pharmacologic agents to reduce bleeding (antifibrinolytic drugs, serine protease inhibitors, fibrin sealants), and using epoetin alpha to reduce transfusion of red cells in selected patients.

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## Conflicts of interest

There were no financial interest or conflict of interest.

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