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The Significance of the Intra- and Post-Operative Inflammatory Cytokine Filtration

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Introduction

Cardiopulmonary bypass (CPB) is the technique, where the functions of the heart and the lung are temporarily taken over by a machine during surgery, in order to maintain the circulation of blood and the oxygen supply to the body. Usually, CPB is used in open heart and coronary bypass surgeries, as it is difficult to operate on a beating heart. In addition, CPB can be used during other thoracic surgeries if the patient, while being operated, becomes hemodynamically instable, in association with hypoxia, progressive hypercarbia, and or persistent low pH (<7.2) [1].

In the Toronto general hospital, CPB is initiated in 35% of cases of bilateral lung transplant. CPB may be initiated in the following cases [2]:

- Patients with reduced pulmonary vascular bed
- Patients with pulmonary arterial hypertension
- Patients undergoing lobar transplantation
- Patients undergoing combined thoracic and cardiac surgery
- During lung transplant, if the native diseased lung is unable to maintain oxygenation, while the first lung being implanted
- During the implantation of the second lung (in bilateral lung transplantation), when the newly implanted first lung receives all the cardiac output, but unable to function properly due to the development of edema.

Disadvantages of CPB can be summarized as [1,2]:

- Hemodilution, heparinization, and platelet dysfunction, leading to coagulopathy
- RBCs trauma, leading to hemolysis
- Complement and leukocytes activation, leading to a systemmic inflammatory response

Cardiothoracic surgery involving CPB is also associated with ischemic reperfusion injury (IRI), which activates the TLR4-Pyk2-NFκB pathway and results in increased production of pro-inflammatory cytokines [3,4]. Stimulation of TLR4 with lipopolysaccharides, *in vitro*, showed significant increase in cytokine production (TNFα within 1-2 hours, IL1β within 2-3 hours, and IL6 within 4-6 hours) [3,4].

IRI is associated with increased reactive oxygen species production and inhibition of KATP channels, which results in inflammasomes activation and increased IL1β and IL18. Both cytokines are able to induce IL6. In addition, TNFα increases with the onset of perfusion, which might explain the significant post-operative increase of these cytokines [5]. However, co-treatment of astrocytes and microglial cells *in vitro* with lipopolysaccharides and IL6 resulted in the down regulation of TNFα and IL1β production, and the enhancement of LPS-induced release of IL10 [4].

Anne Burke-Gaffney, and her colleagues, reported the independent post-operative enhancement of Slit2-Robo4 signaling pathway and IL10 [5]. Such independency might be explained by the notion that; the activation of TLR4 through the IRI of cardiopulmonary bypass, as well as other surgical injuries, results in signaling that leads to the up- regulation of various inflammatory cytokines. However, with the rise of the levels of those cytokines, indirect feedback mechanisms will be directed towards the attenuation of their production, and giving the immune regulatory mechanisms the upper hand [3,4]. As the Slit2-Robo4 signaling pathway has been identified as anti-inflammatory [4], its up-regulation together with IL10 would be expected, however, without being dependent on each other.

On the practical side, the uncontrolled post-operative increase in cytokines is not favored as they may be involved in kidney, liver, lung and or other organs injury. Accordingly, filtration of cytokines during cardiac and thoracic surgery requiring CPB might be of great value to decrease their circulating levels, which might correlate with better post-operative outcome. In addition, with a profound IRI injury during organ transplantation, which is augmented by the direct contact between the donor's and the recipient's antigens and immune cells, the stimuli for the cytokine production are intense and last longer, leading to the possibility of reaching a level of cytokine storm, which by itself could result in a massive uncontrolled systemic inflammatory response syndrome (SIRS), leading to multiple organ dysfunction syndrome (MODS) and or multiple organ failure (MOF) [6].

Accordingly, monitoring the levels of the circulating inflammatory cytokines following transplant and exposing the transplant patients to post-operative cytokine hemofiltration (e.g. at 24 hours post-operative) might lead to a significant improvement of the patient's general condition and decreased incidence of post-operative complications (for example, IL6 correlates with the 30-day mortality after lung transplant, and

IL8 correlates with the incidence of primary lung graft dysfunction) [7]. Clinical studies should be conducted to confirm the application of the above mentioned recommendations.

Conflicts of Interest

- No funding was provided for the development of this work.
- The author welcomes funding cooperation for experimental and clinical studies.

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