Vascular reactivity in cardiopulmonary bypass

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Chapter 1

Introduction and the aims of the thesis
Clinical aspects of cardiopulmonary bypass

Cardiopulmonary bypass (CPB) is a widely used technique in cardiothoracic surgery, including procedures such as coronary artery bypass grafting, valvular heart surgery, repair of aortic aneurysms, surgical treatment of congenital heart defects, heart-, lung or heart-lung transplant, and pulmonary thromboendarterectomy. The first successful open-heart surgery with extracorporeal circulation on a patient was performed in 1953, by John Gibbon in Philadelphia (USA) and consisted of an atrial septal defect repair. Surgery with CPB has now become a standard procedure. The principal components of the cardiopulmonary circuit include tubing, a pump, an oxygenator and cannulae. They enable clinicians’ to reach the main goal of CPB, namely temporarily taking over the function of heart and lung (fig. 1).

However, CPB is also associated with serious postoperative clinical complications, including dysfunction of vital organs such as heart, kidney, lung, and liver. Several clinical syndromes are related to CPB, including increased pulmonary vascular resistance with postoperative pulmonary insult, pulmonary dysfunction, myocardial ischemia and atrial fibrillation, postoperative renal function deterioration, renal ischemic injury up to dialysis-dependent renal failure, intestinal ischemia, stroke, neurocognitive dysfunction and neurologic complications. The post-CPB incidence of these syndromes and associated conditions is substantial, and associated with a high morbidity and mortality rate or prolonged hospital stay. Moreover, a transient organ dysfunction may be observed in patients with preoperatively normal function.

Renal complications

Acute kidney injury is thought to represent the most frequently occurring adverse effect of CPB, present in up to 30% of the patients after cardiac surgery. Because of reduced clearance, decreased renal function results in metabolic disturbances with metabolic acidosis and hyperkalemia, which in turn affect function in other organs. Kidney injury post-CPB varies from mild renal dysfunction up to full blown renal failure requiring dialysis. The etiology of the CPB associated renal injury is multifactorial and includes perioperative renal hypoperfusion with possible ischemia-reperfusion injury, presence of nephrotoxins and microembolism. Moreover, activation of neutrophils, monocytes, endothelial cells and the complement system resulting from this systemic inflammatory response, further adds to glomerular and tubular disturbances. In addition, postoperative renal dysfunction negatively affects long-term survival after cardiac surgery.

Pulmonary complications

Another severe complication of CPB is a postoperative lung dysfunction with interstitial pulmonary edema and subsequent abnormal gas exchange. Clinical data demonstrated that approximately 25% of the patients following open heart surgery exhibited signs of pulmonary impairment for at least one week thereafter. Several CPB-related pathophysiological processes were described in the lung, namely, increased vascular permeability, water content, vascular resistance, neutrophils
sequestration, arterial-alveolar gradient, decrease in pulmonary compliance, alveolar-capillary injury, rise in shunt fraction, and likelihood of atelectasis and pneumonia.\textsuperscript{15,16,23} The induction of such critical complications can be explained by the specifics of the lung perfusion during CPB, since lungs are deprived of the majority of their normal blood supply in this period. Thus extracorporeal circulation causes serious pulmonary injury with vascular injury and edema, atelectasis, collapse of non-ventilated lungs, and massive or submassive pulmonary embolism.\textsuperscript{17,24}

\textit{CPB-related hypotension}

Although the phenomenon of CPB-induced hypotension has been addressed during the last decade, the exact underlying mechanisms are still unknown. In this context, platelet-mediated serotonin release is thought to be one of the most prominent explanations as extracorporeal circulation, contact of blood with artificial surfaces and the roller pump induces platelet activation and triggers release of serotonin.\textsuperscript{25} Serotonin may act as a vasodilator through activation of the most sensitive and widespread 5-HT\textsubscript{2B} receptors, mediating enhanced NO-release.\textsuperscript{25} Prolonged anesthesia, which is common in surgery employing CPB, may have an additional impact on hemodynamic state during the operation. Volatile anesthetics have been shown to modulate vascular smooth muscle tone and depress the cardiovascular system. The systemic hypotensive effect of isoflurane reported previously\textsuperscript{26-29} has been ascribed to a direct inhibitory effect on vascular endothelial and/or smooth muscle cells, involving a decrease in myofilament calcium-sensitivity, intracellular calcium concentration and voltage-gated calcium influx.\textsuperscript{30} Lower arterial pressure under isoflurane anesthesia may also be explained by isoflurane-induced activation of ATP-sensitive potassium channels of vascular smooth muscle cells causing cellular membrane hyperpolarization and inhibition of calcium influx.\textsuperscript{29-32} Moreover, Pypendop et al. (2003) showed that addition of 70% nitrous oxide to isoflurane anesthesia improved arterial pressure and central venous pressure, but the mechanism of this effect was not investigated.\textsuperscript{31,33}

\textbf{Pathogenesis of the CPB-associated complications}

Despite recent progress, the pathological mechanisms involved in CPB-associated complications, being complex and multifactorial, still are largely unknown. CPB circuit and CPB surgical procedure consist of different elements, each of them can be accounted as a contributory factor for the CPB-related complications.\textsuperscript{34} The main cause of the systemic inflammatory response is thought to be contact of blood with the artificial plastic surfaces of the circuit.\textsuperscript{34-37} The priming solutions of the CPB circuit induce a drop of hematocrit and colloid oncotic pressure that leads to decreased oxygen delivery and formation of tissue edema.\textsuperscript{34,38} The usage of the roller pump is responsible for blood cell damage, hemolysis and complement activation.\textsuperscript{34,39} Thus, CPB is associated with a wide range of the etiological factors that evoke different compensatory and/or pathological processes. Systemic inflammatory response syndrome, ischemia-reperfusion injury, hemodynamic abnormalities, and vascular dysfunction are thought to play a major role.
CPB-related pathophysiological processes
Surgical trauma, contact of blood with artificial surfaces of the extracorporeal circuit and ischemia-reperfusion injury due to insufficient perfusion cause stimulation of local and systemic cellular and humoral defense mechanisms. Particularly blood interaction with the extracorporeal circuit and air is thought to activate factor XII and the alternative complement pathway that in turn activate cells of the host defense system and stimulate coagulation, fibrinolysis and the kallikrein pathway. Activated white blood cells release cytokines, free oxygen radicals, and other mediators cause activation of the nuclear factor kB and cell adhesion molecules, and as a result initiate SIRS.

![Figure 1. The principal scheme of the cardiopulmonary circuit. The CPB circuit includes a venous reservoir, a pump, an oxygenator, and a heat exchanger. The venous blood is removed from the body to the venous reservoir. The roller pump propels it through the system. The membrane oxygenator enriches the blood with oxygen and removes carbon dioxide. Then oxygenated blood is returned to the body. The figure was produced using Servier Medical Art.](image)

Particularly, CPB is associated with release of inflammatory cytokines tumor necrosis factor-α (TNF-α), interleukin-6 and 8, increased plasma neutrophils elastase level, but also increased anti-inflammatory cytokine interleukin-10 levels. The systemic inflammatory events may manifest itself as a decline of systemic vascular resistance, systemic hypotension, increased heart rate and cardiac output followed by myocardial failure and increased vascular permeability. Changes in systemic vascular resistance and arterial blood pressure may cause substantial hemodynamic alterations that lead to redistribution of the blood to the vital organs (heart and brain), decreased supply of other organs, and to microcirculatory disturbances herein. Such processes in the intestine may initiate release of endotoxins in the blood circulation, which activate both classical and alternative complement pathways. Activated leukocytes, through release of free radicals, inflammatory cytokines and proteolytic
enzymes, evoke endothelial abnormalities and tissue destruction.\textsuperscript{20,38,43} Upregulation of tumor necrosis factor-α, IL-6, IL-8, and vascular endothelial growth factor (VEGF) results in increased vascular permeability and attenuation of endothelial cell integrity.\textsuperscript{44} Capillary leak (due to increased vascular permeability) with decreased plasma colloid osmotic pressure (due to hemodilution) lead to accumulation of the fluid in the interstitial spaces and tissue edema, that diminish tissue perfusion, nutrients and oxygen delivery, and state the stage for organ dysfunction.\textsuperscript{38} Moreover, inflammatory events may cause rigidity of the erythrocytes, decrease their deformability, and affect their ability to flow in microcirculatory beds, which also participate in disturbances of tissue perfusion and oxygen delivery.\textsuperscript{34,38}

Therefore, CPB is associated with hemodynamic abnormalities (centralisation of the circulation, decreased systemic vascular resistance and systemic hypotension), that result in ischemia-reperfusion injury, oxidative stress, and evoke local pathophysiological processes.\textsuperscript{32,44} Augmented local release of nitrous oxide, thromboxane A2 and products generated by inducible cyclooxygenase are thought also to affect vascular reactivity. Oxidative stress after ischemia-reperfusion injury may itself cause endothelial cells dysfunction. Moreover, formation of the peroxynitrite radicals, because of interaction of superoxide anion with NO, has an additional role in the free-radical induced injury.\textsuperscript{32,44}

To summarise, systemic inflammatory events and ischemia-reperfusion injury trigger the development of systemic and/or local vascular dysfunction. Hemodynamic disorders and microcirculatory abnormalities, which initiate secondary tissue edema and tissue hypoperfusion, become the basis of the multiple organ dysfunction syndrome, and the serious co-morbidity and – mortality associated herewith.\textsuperscript{3,34,38,45,46}

Changes in vascular motor function

Vascular endothelium and vasculature represent an important aspect/feature of CPB-related complications since major organ pathological conditions result from impaired vascular function.\textsuperscript{47} Alteration of cerebral blood flow with impairment of the mechanisms of cerebral vascular auto-regulation is thought to be the main cause of the CPB-mediated brain injury and early neuropsychological dysfunction.\textsuperscript{48-51} Impairment of the lung vascular function is believed to cause the pulmonary dysfunction of the CPB.\textsuperscript{24,52} CPB with deep hypothermic circulatory arrest is related to major renal and pulmonary artery dysfunction.\textsuperscript{53,54} Endothelial dysfunction was shown to be one of the major contributors to post-CPB intestinal complications.\textsuperscript{55} CPB is also associated with increased numbers of circulating endothelial cells, and studies suggested this to be a marker of the systemic endothelial dysfunction and injury after cardiac surgery with CPB.\textsuperscript{56,57}

CPB is associated with both impairment of the endothelial function and the alteration of the myogenic tone. Short-term CPB (30 minutes) was found to be associated with loss in acetylcholine-induced vasodilatation in preparations of the middle cerebral artery.\textsuperscript{48} Short-term CPB with 90 minutes recovery period resulted in aggravated pulmonary vascular resistance with hyperreactivity to serotonin.\textsuperscript{58} In mesenteric arteries, 90 minutes of CPB followed by 6 hours recovery period induced
endothelial dysfunction and increased vascular reactivity to α1-adrenoceptor agonists.\textsuperscript{59} Heart failure was shown to aggravate mesenteric artery endothelial and smooth muscle dysfunction after CPB due to increased oxidative stress.\textsuperscript{60} CPB was also shown to decrease acetylcholine-mediated relaxation in pulmonary resistances artery and seemed to have no effect on contractile reactivity of these arteries to norepinephrine, vasopressin, and the thromboxane A2.\textsuperscript{52} In another study pulmonary endothelial dysfunction with decreased relaxant response to acetylcholine was shown after fourth day of the post-operative period after CPB.\textsuperscript{61}

The origin of the CPB-related endothelial dysfunction involves inflammatory mechanisms with neutrophils-mediated endothelial injury, while other processes also may contribute herein. Endothelial activation after CPB with increased circulatory levels of the soluble endothelial adhesion molecules (E-selectin and ICAM-1) was even confirmed after 48h of the postoperative period.\textsuperscript{62} The degradation of the endothelial and cardiomyocytes adherens junctions were shown to mediate CPB-related increased vascular permeability and cardiomyocyte dysfunction.\textsuperscript{63} Moreover, apoptosis of endothelial cells might represent another possible mechanism of the CPB-mediated vascular dysfunction and aggravated capillary permeability.\textsuperscript{56,57}

CPB has also been shown to affect peripheral vasomotor tone. Decreased myogenic tone has been reported in CPB-related injury of skeletal microvascular beds.\textsuperscript{64-67} Inhibition of the mitogen-activated protein kinases was suggested to cause decreased coronary myogenic tone after CPB with cardioplegia.\textsuperscript{66} The activation of the large conductance calcium-activated potassium channels (BK\textsubscript{Ca}) was shown to be the main cause of the reduced myogenic tone of the skeletal muscles arterioles after CPB in humans.\textsuperscript{64} Altered alpha-adrenergic receptors and protein kinase C-mediated contractions were observed in skeletal muscle microvessels.\textsuperscript{67} Together, these alteration in vascular tone and reduced peripheral vascular resistance are thought to be responsible for a systemic hypotensive response, which can be observed up to one week post-operatively.\textsuperscript{44} The suggested mechanisms involved in decreased intrinsic tone include increased circulating levels of vasoactive substances, increased expression of iNOS, adrenergic receptor desensitization and uncoupling from the second messenger system.\textsuperscript{43}

In the majority of these studies, vascular responsiveness was evaluated in one vessel type and at one time point post-CPB only, mostly after a relatively short-term recovery period.\textsuperscript{43,48,58,64-67,69} It should be noted, however, that organ dysfunction post-CPB has been shown to influence not only in-hospital mortality and morbidity but also mid-term and long-term survival.\textsuperscript{8-11,19,64,65} However, data on alterations in vasoresponsiveness during the postoperative period that might account for the late effects of CPB are lacking.

**Treatment and/or prevention of CPB-associated complications**

Several anti-inflammatory pharmacological agents, including nonsteroid anti-inflammatory agents, corticosteroids, aprotinin, antioxidants, complement inhibitors and phosphodiesterase inhibitors have been proposed to inhibit the CPB-related inflammatory processes and vascular dysfunction.\textsuperscript{41,42,45} Though, none of them entirely
prevented the adverse pathological and clinical outcomes that are associated with extracorporeal circulation. While a single dose of dexamethasone after the induction of anesthesia has been shown to reduce IL-6 related to CPB, it had no effect on clinical outcome. However, dexamethasone decreased the concentration of the circulating cytokines in plasma and had anti-inflammatory properties. Several clinical studies also showed that dexamethasone had no effect on perioperative abdominal organ damage. Conversely, recent data suggest that this compound offers a pulmonary protective effect. Another way to reduce the inflammatory response after CPB was to remove activated leukocytes from the circulating blood by leukocyte-depleting filters, but several clinical studies showed controversial data regarding its efficacy.

Alternative therapeutic agents for the prevention of CPB-related complications are still under investigations. One of the possible interventions to limit CPB associated complication is the use of sphingosine-1 phosphate receptors antagonists. Fingolimod (FTY720) is a non-selective sphingosine 1-phosphate (S1P) receptor modulator that acts as an immunosuppressive agent. It was demonstrated to be effective in treatment of the autoimmune disorders (multiple sclerosis, autoimmune neuritis, autoimmune glomerulonephritis) and organ transplant. The main mechanism of its immunomodulatory action concerns activation of the S1P-receptors and is associated with inhibition of the egress of lymphocytes from the secondary lymphoid organs to the peripheral blood. Moreover, FTY720 has been shown to prevent or ameliorate ischemia-reperfusion injury, enhance endothelial barrier and decrease vascular permeability, and improve vascular function through modulation of the S1P receptors. Thus, taking into account the above described pharmacological properties, FTY720 might be a promising therapeutic agent to prevent CPB-related vascular dysfunction.

**Aims of this thesis**

Despite recent progress, there are major questions to be answered concerning the effects of CPB. First, with respect to changes in vascular function following CPB, it should be noted that previously mainly short-term changes (approximately 24 hours period) have been evaluated, while a substantial amount of critical post-operative events take place between the second and fifth day of the recovery period. Also, the association between vascular functionality and inflammatory events has not been addressed sufficiently. Finally, the possibilities of pre-operative and/or intraoperative intervention in vascular reactivity, as an approach to prevent the CPB-related complications, were not formerly evaluated. Thus, the principle aim of this thesis is to investigate the pathophysiology and novel therapeutic options with respect to CPB-related complications in a rat model of CPB.

The first part of this thesis investigates the changes in vascular function evoked by CPB. To this end, vasomotor responses were obtained in different types of vessels during a clinically relevant postoperative recovery period (up to 5 days) in rat. In addition, the relationship between endothelial activation and vascular responsiveness was studied in rat aorta throughout the whole recovery period.
In the second part of this thesis, the pathophysiology of CPB related inflammation was further characterized by measurement of the expression of inflammatory markers in lung and kidney during the entire recovery period by PCR, Western blot and micro-array analysis in our rat model of CPB.

In the last part of the thesis, the effects of drugs are explored. Since anesthetics influence vascular tone, they may add to the CPB-related hypotension. Thus, the impact of different types of anesthesia was studied in a model of extreme hypotension in mice (hemorrhagic shock). Finally, the effect of the novel immunosuppressive drugs on CPB induced changes in vasomotor response was measured to define its therapeutic potential to prevent the CPB-related complications. To this end, rats were pretreated with selective and non-selective agonists of the S1P-receptors and contractile and relaxant vascular reactivity was assessed.

Reference List

1. Lewis FJ, Taufic M: Closure of atrial septal defects with the aid of hypothermia; experimental accomplishments and the report of one successful case. Surgery 1953; 33: 52-9
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89. Dudek SM, Camp SM, Chiang ET, Singleton PA, Usatyuk PV, Zhao Y, Natarajan V, Garcia JG: Pulmonary endothelial cell barrier enhancement by FTY720 does not require the S1P1 receptor. Cell Signal. 2007; 19: 1754-64
