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Rat Cardiopulmonary Bypass Models to Investigate Multi-Organ Injury

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Abstract

Cardiopulmonary bypass (CPB) has been an essential modality in cardiovascular surgery. Although the technique has since undergone dramatic refinement, prolonged CPB-related multi-organ complications due to contact activation, ischemia–reperfusion injury, coagulation, endotoxemia and/or production of oxygen free radicals still compromise the outcome of cardiovascular surgeries. Animal models recapitulating the clinical usage of CPB help elucidate the pathophysiological processes following CPB, and aid in the development of strategies aimed at preventing these complications. Rat CPB models mimicking clinical situations in cardiovascular surgery have been refined and have gradually taken the place of large-animal models because of greater cost-effectiveness, convenient experimental processes, abundant testing methods at the genetic or protein levels, and genetic consistency. In the present review, we discuss various beneficial aspects of rat CPB models for investigating CPB-related multi-organ injury and for mitigating the severity of complications in an organ-specific manner (lung/kidney/brain/liver/myocardium/intestine). The interventions established through basic research using rat CPB models may further improve the safety of cardiovascular surgery in the future.

Keywords: Rat cardiopulmonary bypass; Multi-organ injury; Kidney

Introduction

In 1953, Gibbon successfully performed the first cardiac surgery in the world using cardiopulmonary bypass (CPB) [1]. CPB subsequently became an essential modality in cardiovascular surgery, and the technique has since undergone dramatic refinement. However, multi-organ complications related to prolonged CPB still compromise the outcome of cardiovascular surgeries, and may deteriorate postoperative morbidity and mortality [2]. CPB-related organ damage is caused by contact activation, ischemia–reperfusion injury, coagulation, and endotoxemia during CPB, leading to immune system activation and synthesis of proinflammatory cytokines, compliment activation, and production of oxygen free radicals [2].

Animal models recapitulating the clinical usage of CPB enable us to clarify the pathophysiological processes that occur after CPB, and facilitate pre-clinical studies to develop strategies protecting against these complications. Because of similarities to humans in terms of body size and anatomy, large animals were initially used in CPB models [3]. Since Popovic et al. first reported using a rat CPB model in 1967 [4], rat CPB models have been refined, and have gradually taken the place of large-animal models due to, among other reasons, greater cost-effectiveness, including the cost of the animals and experimental devices, convenient experimental processes, and abundant testing methods at the genetic or protein levels. Furthermore, inbred rats can be genetically identical, reducing possible biological biases.

Various methods for simulating the clinical situations of CPB-related multi-organ injury have been reported. Fabre et al. [5] first established a recovery model that allowed the study of the long-term multiple organ sequelae of CPB. A cardiac arrest model, developed by de Lange et al. [6], can be used to characterize the enzymatic, genetic, and histologic responses to myocardial injury, and aid in forming protective strategies. Moreover, a deep hypothermic circulatory arrest model, established by Jungwirth et al. [7], is suitable to further elucidate the mechanisms associated with adverse cerebral outcome after cardiac surgery and deep hypothermic circulatory arrest (DHCA), and allows us to investigate potential neuro protective strategies. These models are advantageous for evaluating the various effects of CPB, closely mimicking clinical situations in cardiovascular surgery.

Table 1: Overview of studies using rat cardiopulmonary bypass models.

Organ	Authors	Year	Rat strain	n	Flow (ml/kg/min)	Duration (min)	Euthanasia (hrs after CPB)	Temperature	Intervention	CPB	Specific method
Lung	Hamamoto et al. [21]	2004	Sprague-Dawley	18	60	60	1	Normothermia	Rolipram	Beating	
	Shao et al. [11]	2007	Sprague-Dawley	24	100	60	24	Normothermia	Simvastatin	Beating	
	Yamazaki et al. [20]	2010	Sprague-Dawley	18	60	60	1	Normothermia	APC	Beating	Clamping PA
	Liu et al. [12]	2010	Sprague-Dawley	60	100	60	24	Normothermia	Curcumin	Beating	
	Wang et al. [15]	2014	Sprague-Dawley	48	100	60	6	Normothermia	Doxycycline	Beating	
	Taki et al. [17]	2017	Lewis	21	50	30	1	Normothermia	MSC	Beating	
Kidney	Wang et al. [29]	2009	Sprague-Dawley	40	100	60	1	Normothermia	Melatonin	Beating	
	Wang et al. [27]	2012	Sprague-Dawley	30	100	60	1	Normothermia	EPO	Beating	
	Liu et al. [28]	2013	Sprague-Dawley	120	100	60	24	Normothermia	rhEPO	Beating	
	Funamoto et al. [30]	2016	Goto-Kakizaki	29	100	30	24	Normothermia	EGCG	Beating	
Brain	Zhang et al. [35]	2015	Sprague-Dawley	24	160	90	1	Hypothermia	Sufentanyl	Beating	
	Wang et al. [38]	2015	Sprague-Dawley	32	160–180	60	168	Hypothermia	microRNA29c	DHCA	DHCA 60 min
	Homi et al. [42]	2010	Wister	16	160–1180	60	24	Normothermia	Aprotinin	Beating	MCAO
Liver	Huang et al. [47]	2008	Sprague-Dawley	48	100	60	24	Normothermia	Exogenous melatonin	Beating	
	An et al. [45]	2007	Sprague-Dawley	30	120	120	3	Normothermia	rhGH	Beating	
Heart	Günzinger et al. [50]	2007	Wistar	8	120	60	1	Normothermia	Cardioplegic arrest	CA	CA (30 min snare)
	Cao et al. [52]	2013	Sprague-Dawley	32	100	60	4	Normothermia	Ghrelin	Beating	
Intestine	Sun et al. [58]	2011	Sprague-Dawley	48	80–1100	60	2	Normothermia	Penehyclidine	Beating	
	Sun et al. [59]	2013	Sprague-Dawley	24	90–1100	60	2	Normothermia	Probiotic cocktail	Beating	

CPB: Cardiopulmonary Bypass; APC: Activated Protein C; MSC: Mesenchymal Stem Cells; EPO: Erythropoietin; rhEPO: Recombinant Human Erythropoietin; EGCG: Epigallocatechin-3-gallate; rhGH: Recombinant Human Growth Hormone; DHCA: Deep Hypothermic Cardiac Arrest; CA: Cardiac Arrest; PA: Pulmonary Artery; MCAO: Middle Cerebral Artery Occlusion

In this review, we discuss recent basic research using rat models to investigate therapeutic strategies aimed at preventing multi-organ injury during CPB. An overview of the studies discussed in this review is shown in Table 1.

Lung Injury

Acute lung injury (ALI) induced by CPB, a common and serious complication, is an important factor influencing morbidity and mortality after cardiac surgery. It is caused by the activation of several cellular immune responses resulting from contact activation and ischemia–reperfusion injury [2]. Acute respiratory distress syndrome (ARDS) is a rare but serious complication associated with significant mortality. The incidence and mortality of ARDS in patients undergoing CPB were reported to be 0.4%–0.6% and 15%–41.5%, respectively [8,9].

Inflammation

Numerous studies on CPB-related lung injury have been conducted in rat models because of the usefulness of these models for investigating protective strategies in the context of systemic inflammatory responses.

The proinflammatory cytokines tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and IL-8 play a pivotal role in the pathogenesis of CPB-induced lung injury, and nuclear factor kappa B (NF-κB), a major regulator of proinflammatory cytokine induction, has been recognized as a key factor in the inflammatory reaction after CPB [10]. Shao et al. [11] reported that pretreatment with simvastatin, a statin, attenuated inflammatory cell infiltration in the lungs, and reduced proinflammatory cytokine expression in serum, lung tissues, and bronchoalveolar lavage fluid. They additionally showed effects on down regulation of toll-like receptor 4 (TLR4) and NF-κB expression,

indicating potential protective mechanisms of simvastatin. Liu et al. [12] also reported that a polyphenol, curcumin, attenuated CPB-related lung injury by suppressing NF-κB activation via inhibition of the TLR4-mediated MyD88-dependent signaling pathway.

Wang et al. focused on matrix metalloproteinase-9 (MMP-9), a subgroup of zinc endopeptidases, which has been found to degrade basement membrane components [13]. MMP-9 is therefore thought to be essential for polymorphonuclear neutrophil granulocyte migration and alveolar capillary leakage activity in CPB-related lung injury [14]. Wang et al. [15] also showed increased MMP-9 activity and gene expression in CPB-related lung injury. In addition, the authors showed that doxycycline, a tetracycline derivative, might have a therapeutic effect on the lung injury process by suppressing MMP-9 during CPB.

Lisle et al. [16] focused on the adenosine A_{2A} receptor ($AA_{2A}R$), which increases intracellular cyclic adenosine monophosphate (cAMP). They reported that ATL313, an agonist of $AA_{2A}R$, attenuated inflammatory lung injury through inactivation of inflammatory cells, decreased proinflammatory cytokine production, and suppressed neutrophil recruitment and activation.

In addition to strategies involving bioactive chemical components or molecules, approaches using stem cells are emerging. We previously reported that intravenous administration of allogeneic mesenchymal stem cells from fetal membrane (FM-MSCs) attenuated systemic inflammation and lung injury after CPB in a rat model [17]. Administration of FM-MSCs suppressed the production of proinflammatory cytokines, alleviated ALI, inhibited neutrophil infiltration to interstitial spaces of the lung, and protected alveolar structure by stimulating secretion of organ-protective humoral factors.

Neutrophil activation

CPB-induced ALI is also thought to be associated with neutrophil activation [2]. To evaluate neutrophil excitation, two signal intensity of adhesion molecules, CD11b and CD62L, expressed on the cell surface, have been reported to be crucial. CD11b contributes to the tight adherence between neutrophils and endothelial cells, and this binding plays an important role in the further activation of neutrophils [18]. CD62L is highly expressed on inactivated neutrophils and participates in the initial weak adherence between neutrophils and endothelial cells, while activated neutrophils promote rapid shedding of CD62L along with the progression of inflammatory responses [19]. Yamazaki et al. reported that administration of activated protein C inhibits neutrophil activation and attenuates proinflammatory cytokine production through increased CD11b and decreased CD62L expression in the lungs. They also showed increased lung content of macrophage inflammatory protein-2 [20]. Hamamoto et al. [21] reported that rolipram, a selective phosphodiesterase type 4 inhibitor, attenuates the intracellular stimulatory signaling of neutrophils after CPB by blocking the decrease in levels of cAMP associated with neutrophil activation. Furthermore, Xing et al. [22] suggested that new therapeutic approaches based on manipulating immature $CD14^{low}CD16^-$ monocytes, which contribute to blood-circuit contact-induced ALI by generating TNF-α-producing, mature monocytes, might help minimize CPB-related lung injury.

Oxidative stress

During CPB, a large number of oxygen free radicals are generated, exceeding the oxidant scavenging capacity of the endogenous antioxidant enzymes and thus causing cellular injury [2]. Several stress proteins and antioxidant enzymes are activated to limit the damage at the cellular level. Heme oxygenase1 (HO-1) plays an important role in removing harmful free radicals [23]. Liu et al. [24] examined the potential effects of curcumin on the expression of oxidative stress markers like malondialdehyde (MDA) and myeloperoxidase (MPO), and its impact on the activation of the HO-1 protein. Wang et al. [25] reported that an antioxidant, pyrrolidine dithiocarbamate, improves pulmonary function after CPB.

Kidney Injury

Although considerable progress has been made in surgical techniques and perioperative intensive care, kidney injury remains a serious complication of cardiac surgery. Kidney injuries are reported to affect approximately 5%–31% of patients undergoing cardiac surgery with CPB. Acute kidney injury (AKI) requiring hemodialysis occurs in approximately 1% of cases, with a mortality rate as high as 64% [26].

Wang et al. reported that erythropoietin (EPO) protected against CPB-induced renal injury and exerted anti-inflammatory effects on rat renal tissues. They showed that EPO lessened renal histological injury, and decreased levels of inflammatory markers like TNF-α, IL-1β, and IL-6 in renal tissues. Furthermore, they found a potent down-regulation of NF-κB p65, ICAM-1 protein, and mRNA in EPO-treated rat kidneys. The authors concluded that EPO may act as an anti-inflammatory factor via suppression of NF-κB p65 expression, leading to attenuation of CPB-induced kidney injury [27]. In another report using EPO, Liu et al. [28] showed that recombinant human EPO suppressed the canonical transient receptor potential channel 6, which plays crucial roles in hereditary glomerular dysfunction, by down regulating nuclear factor of activated T-cells pathways induced by CPB.

Wang et al. reported that melatonin (N-acetyl 5-methoxytryptamine), a powerful antioxidant, exerted a renoprotective effect evidenced by biochemical and histopathologic results through antioxidant functions. Melatonin reduced MPO and MDA, while antioxidant enzymes such as catalase and superoxide dismutase were significantly increased. In addition, HO-1 transcript and protein levels in the kidneys were dramatically increased in melatonin-treated rats during CPB [29].

We previously reported on the renoprotective effect observed with preoperative oral administration of epigallocatechin-3-gallate (EGCG), a major component of the polyphenolic fraction of green tea [30]. We used a specific animal model consisting of multigenetic rats with type 2 diabetes mellitus, which would be at increased risk for AKI after CPB [31]. In our study, EGCG attenuated tubular injury, reduced serum creatinine and neutrophil gelatinase-associated lipocalin levels, and decreased mRNA expression of kidney injury molecule-1 and 8-hydroxy-20-deoxyguanosine, indicating attenuated oxidant stress. This simple method could be applied in a clinical setting as prophylactic renal protection against AKI after CPB, especially in high-risk patients with diabetes mellitus [30].

Brain Damage

Cardiac surgery involving CPB has been associated with a frequent incidence of postoperative cognitive dysfunction [32]. The etiology of cognitive impairment after cardiac surgery may include cerebral microembolization, increased cerebral perfusion, systemic and cerebral inflammation, cerebral temperature perturbations, cerebral edema, and possible blood–brain barrier (BBB) dysfunction, all of which may be superimposed on genetic influences that may alter susceptibility to injury or repair from injury once it has occurred [33].

Recently, some neuroprotective strategies have been investigated in rat CPB models. De Lange et al. reported that the combination of hypothermic CPB coupled with limited rewarming and prolonged postoperative hypothermia decreased postoperative cognitive dysfunction after CPB. Rats were assessed by cognitive testing in the Morris water maze 7 days after CPB [33]. Cao et al. reported the effect of penehyclidine hydrochloride, an anti-cholinergic drug, on regulatory mediators during the neuroinflammatory response and cerebral cell apoptosis following CPB. They examined plasma levels of neuron specific enolase and S-100B, a type of neuropeptide that is highly expressed in blood serum in severe cerebral injury, and evaluated mRNA expression levels of MMP-9, IL-10, caspase-3, Bcl-2, and p38 in brain tissue. Additionally, the ultrastructure of hippocampus tissue was examined under an electron microscope. The authors found ultrastructural disorders of neuronal cells in the vehicle group, with a nearly round nucleus, aggregated and edged nuclear heterochromatin, a fuzzy nuclear membrane, and the occurrence of endocytic vacuoles within swollen mitochondria [34].

Zhang et al. [35] showed that sufentanil pretreatment had protective effects on cerebral injury during CPB by reducing water content and total calcium of the brain tissue, and expression of S-100B in serum. Ouk et al. performed assessments of spatial and learning memory using a Y maze cognition experiment. To evaluate short-term memory, they used the passive avoidance test and a test based on fear memory consolidation. The authors demonstrated that reduction of CPB-induced inflammation and endothelial dysfunction by lipid-lowering drugs prevented cognitive impairment and preserved neuronal integrity in hippocampal regions [36].

Bartels et al. presented results from a pilot study using magnetic resonance imaging (MRI) and molecular analysis to assess BBB characteristics in a rat CPB/DHCA model. The results indicated that MRI successfully detected increased brain capillary permeability to a commercially available low-molecular-weight contrast agent, while no significant quantitative changes in select proteins relevant for BBB structure were observed [37]. Wang et al. [38] showed that inhibition of microR-29c attenuates neurologic injuries induced by prolonged DHCA through a peroxisome proliferator-activated receptor gamma co-activator 1-alpha pathway. Moreover, rat cardiac arrest models are useful for studies in emergency preservation and resuscitation [39,40]. These models serve as a valuable platform to link basic biochemical disorders and organ dysfunction in an effort to design better therapeutic applications for the treatment of cardiac arrest [40].

An experimental model of stroke induced by middle cerebral artery occlusion during CPB was established by Homi et al. [41]. The authors reported that a protinin, a nonspecific serine protease inhibitor, decreased the systemic inflammatory response to CPB and reduced functional neurologic injury in the short-term, but did not reduce cerebral infarct size [42].

Hepatic Injury

In clinical settings of cardiac surgery, approximately 10% of patients receiving CPB experience hepatic injury, which directly influences their mortality. Shen et al. reported that CPB may induce and aggravate hepatic injury by facilitating oxidative stress and the systemic inflammatory response, based on a rat CPB model, and with samples collected over a 24-hr period. In the CPB group, serum liver transaminases and TNF-α, activity of inducible nitric oxide synthase, MDA, and MPO in liver tissue were significantly increased. In addition, swollen hepatocytes, vacuolization, and congestion in sinusoids were observed. By contrast, the activities of liver antioxidative enzymes and the concentration of glutathione (GSH) remarkably decreased[43].

An et al. reported that recombinant human growth hormone (rhGH) may prevent acute liver injury associated with CPB by decreasing acute-phase reaction proteins, TNF-α and IL-1β, and hepatocyte apoptosis, which is associated with increases in constitutive hepatic proteins, total liver protein content, and hepatocyte proliferation [44,45].

Huang et al. suggested that N-acetylcysteine (NAC) and exogenous melatonin had protective effects on CPB-induced liver injury by reducing oxidative stress and the systemic inflammatory response. The Ca²⁺-ATPase activity of liver tissues was also determined. NAC and melatonin reduced liver transaminases, TNF-α, liver inducible nitric oxide synthase, MDA, and MPO, while the activity of liver antioxidative enzymes and the concentration of GSH remarkably decreased[46,47].

Myocardial Injury

Previous research focusing on cardio-protective strategies during cardiac surgery has been performed in isolated heart models [48,49]. However, these models are not suitable to investigating the long-term effects of therapeutic interventions on myocardial reperfusion injury and systemic inflammation.

Günzinger et al. developed a cardioplegic arrest model with the use of cold crystalloid cardioplegia after aortic cross clamping through thoracotomy. The authors assessed left ventricular (LV) function parameters by intraventricular conductance catheter. Results indicated impaired LV function after cardiac arrest, and increased myocardial TNF-α and IL-6 mRNA [50]. In another study, the authors investigated MMP and TIMP expression with crystalloid cardioplegia or blood cardioplegia [51]. They showed impaired LV function and increased MMP-2/TIMP-4 ratio on the mRNA and protein level in the crystalloid cardioplegia group. De Lange et al. developed another method to administrate ante grade cardioplegia with endoaortic cross-clamping, without thoracotomy, using a balloon catheter via the carotid artery in a rat CPB model [6]. These cardioplegic arrest models allow us to characterize myocardial injury and investigate new cardio-protective strategies.

By contrast, Cao et al. [52] reported on the cardio-protective effect of ghrelin in a rat CPB model without cardiac arrest. In this study, ghrelin reduced inflammatory responses through the Akt-activated pathway. Pulido et al. [53] demonstrated myocardial-protective effects using pretreatment with inhaled carbon monoxide (CO).The authors suggested that pretreatment with CO may have a modulatory effect on the inflammatory response to CPB without compromising hemodynamics or oxygen delivery.

Intestinal Injury

Mesenteric ischemia develops in 5%–27% of patients who experience abdominal complications after CPB, with a mortality of 30%–93% [54]. In rat models, CPB was shown to induce mesenteric endothelial dysfunction and cause a direct increase in the contractile response to α1-adrenergic agonist. In addition, CPB was associated with microcirculatory injury, decreased tight junction protein expression of intestinal mucosa, and generalized inflammatory responses [55-57].

Sun et al. demonstrated that penehyclidine hydrochloride, a newly developed anticholinergic drug, exerts protective effects by attenuating biochemical and histopathological changes in a dose-dependent manner, and by decreasing intestinal permeability and bacterial translocation[58]. In another study, the authors investigated the effects of pretreatment with probiotic preparations. Pre-administration of probiotics effectively reduced intestinal permeability and the bacterial translocation rate due to improvement of local intestinal immune function, and increased expression of intestinal epithelial tight junction proteins[59].

Conclusion

In the present review, we discussed various beneficial aspects of using rat CPB models to investigate CPB-related multi-organ injury and to mitigate the severity of the complications, which may contribute to improved surgical outcome. The interventions found through basic research using rat CPB models may increase the safety of cardiovascular surgery in the future.

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