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Pulmonary reperfusion injury in post-palliative intervention of oligaemic cyanotic CHD: a new catastrophic consequence or just revisiting the same old story?

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Review

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Abstract

Pulmonary reperfusion injury is a well-recognised clinical entity in the setting pulmonary artery angioplasty for pulmonary artery stenosis or chronic thromboembolic disease, but not much is known about this complication in post-palliative intervention of oligaemic cyanotic CHD. The pathophysiology of pulmonary reperfusion injury in this population consists of both ischaemic and reperfusion injury, mainly resulting in oxidative stress from reactive oxygen species generation, followed by endothelial dysfunction, and cytokine storm that may induce multiple organ dysfunction. Other mechanisms of pulmonary reperfusion injury are "no-reflow" phenomenon, overcirculation from high pressure in pulmonary artery, and increased left ventricular end-diastolic pressure. Chronic hypoxia in cyanotic CHD eventually depletes endogenous antioxidant and increased the risk of pulmonary reperfusion injury, thus becoming a concern for palliative interventions in the oligaemic subgroup. The incidence of pulmonary reperfusion injury varies depending on multifactors. Despite its inconsistence occurrence, pulmonary reperfusion injury does occur and may lead to morbidity and mortality in this population. The current management of pulmonary reperfusion injury is supportive therapy to prevent deterioration of lung injury. Therefore, a general consensus on pulmonary reperfusion injury is necessary for the diagnosis and management of this complication as well as further studies to establish the use of novel and potential therapies for pulmonary reperfusion injury.

Background

Patients with cyanotic CHD and decreased pulmonary blood flow may require palliative interventions before the corrective surgeries, especially those with complex lesions or severe desaturation. Blalock–Taussig–Thomas shunt is one of the surgical approach of these palliative interventions.[1,2] However, transcatheter approaches such as patent ductus arteriosus stenting in duct-dependent CHD or the recently developed right ventricular outflow tract stenting in tetralogy of Fallot are preferable for selected cases in some centres compared to surgical approach which is associated with significant mortality and morbidity.[3] Although these palliative procedures aim to increase pulmonary blood flow, the sudden increase of blood flow in the previously underperfused pulmonary vasculature may cause acute pulmonary reperfusion injury.[4,5]

Pulmonary reperfusion injury is a well-recognised clinical entity in the setting of pulmonary artery angioplasty for pulmonary artery stenosis or chronic thromboembolic disease. Pulmonary reperfusion injury manifests as temporary and localised pulmonary oedema in an area of increased lung tissue perfusion which impairs gas exchange.[5,6] One study reported that 10 out of 46 patients (22%) developed pulmonary reperfusion injury after pulmonary artery angioplasty.[5] Another study reported three out of four patients with Williams syndrome developed clinical pulmonary reperfusion injury after pulmonary artery balloon angioplasty, thus indicating higher risk of pulmonary reperfusion injury in these patients.[7] Nevertheless, the incidence of pulmonary reperfusion injury in post-palliative intervention in cyanotic CHD is unknown. The exact mechanism of pulmonary reperfusion injury in these specific population is still poorly understood. Therefore, this review aims to evaluate and collect the evidence as well as to review the mechanism of pulmonary reperfusion injury in post-palliative intervention in cyanotic CHD.

Pulmonary reperfusion injury and its clinical manifestations

Ischemia-reperfusion injury is a complex pathological process as a result of paradoxical exacerbation of cellular dysfunction and death, following restoration of blood flow to previously ischaemic tissues.[8] All tissues and organs are indeed susceptible to ischaemia, but there is difference between the susceptibility to an ischaemic insult.[9] Despite being resistant to ischaemia due to the availability of oxygen from both alveolar gas exchange and the blood supply via a dual circulatory system (pulmonary and bronchial arteries), lungs can still suffer from ischaemia in situations that impair alveolar oxygenation or pulmonary blood flow. Therefore, ischaemia-reperfusion injury may affect lungs, otherwise known as pulmonary reperfusion injury.[10]

Pulmonary reperfusion injury or lung ischaemia-reperfusion injury is a complex pathological process triggered by lack of oxygen supply, followed by a period of reperfusion in the lung.[11] Pulmonary reperfusion injury causes increased pulmonary vascular resistance and increased vascular permeability manifesting as varying levels of non-cardiogenic pulmonary oedema with pulmonary wedge pressures typically less than 18 mmHg. Pulmonary oedema will cause ventilation/perfusion (V/Q) mismatch which affects the oxygenation. Chest X-ray of pulmonary reperfusion injury usually shows ranging severity from mild infiltrates to diffuse opacifications, similar to an acute respiratory distress syndrome.[11]

There is currently no specific diagnosis criteria for pulmonary reperfusion injury; thus, it is primarily a diagnosis of exclusion. There were various criteria used by a few reports, but they were not yet established for the diagnosis of pulmonary reperfusion injury.[12–14] The International Society of Heart and Lung Transplant (ISHLT) criteria was the best available criteria to identify and grade segmental pulmonary reperfusion injury, though they are designed for whole-lung graft reperfusion. The criteria stated that PaO_2/FiO_2 ratio of 200–300 indicates pulmonary reperfusion injury and a ratio of less than 200 indicates severe pulmonary reperfusion injury.[14] Post-intervention pulmonary oedema or haemorrhage, unilateral or bilateral chest radiograph infiltrates, ICU admission, as well as unplanned intubation and post-operative mechanical ventilation may serve as a predictive clinical features of pulmonary reperfusion injury.[9]

Aetiology of pulmonary reperfusion injury

Lung ischaemia occurs when oxygen supply fails to meet the metabolic demands of the pulmonary parenchyma either due to decreased ventilation or limited blood flow. Therefore, we can divide the causes of pulmonary reperfusion injury into two groups: ventilated ischaemia and anoxic ischaemia. In **ventilated ischaemia**, the ventilation is normal while the blood supply to the lung is interrupted, which can be seen in thrombotic situations (acute chest syndrome in sickle cell patients and pulmonary artery embolic phenomena) and stenotic situations (pulmonary artery stenosis). In this group, pulmonary reperfusion injury follows the correction of the interrupted blood supply by thromboendarterectomy or catheter-directed thrombolysis and balloon angioplasty. On the contrary, there is complete cessation of blood flow and ventilation in **anoxic ischaemia**. Pulmonary reperfusion injury occurs less frequently in this group which includes the cold ischaemia time occuring in cardiopulmonary bypass and lung transplantation. Factors possibly associated with pulmonary reperfusion injury are length of ischaemic time, hypotension, overzealous fluid administration, mechanical ventilation, infection, cause of death of lung transplant donor, and extent of immune response.[11]

Pathogenesis and pathophysiology of pulmonary reperfusion injury

The five main cellular mechanisms in pulmonary reperfusion injury include sterile immunity, complement activation, activation of coagulation, activation of cell death pathways, and finally, endothelial dysfunction. Sterile immunity includes the activation of adaptive and innate immunity, while complement activation amplifies the immune response. Activation of coagulation includes platelet activation and aggregation, microvascular vasoconstriction, and thrombus formation.[11] Endothelial dysfunction causes increased vascular permeability (pulmonary oedema), activation of complement and coagulation systems, imbalance of vasoconstricting and vasodilating factors, as well as "no re-flow phenomenon."[15–17] The end result of these pathologic processes may be seen microscopically as alveoli with marked perivascular oedema, focal interstitial and intraalveolar leucocyte infiltration, and proteinous exudate.[11]

The pathological processes of pulmonary reperfusion injury can be divided into two parts: ischaemia injury and reperfusion injury.[9,18] Imbalance of oxygen supply and demand in ischaemia will cause hypoxia, leading to dysfunction in the electron transport chain in mitochondria. Decreasing adenosine triphosphate production will induce anaerobic metabolism, dysfunction of sodium–potassium pumps (Na^+/K^+-adenosine triphosphate synthase), and detachment of ribosomes.[16,19] Anaerobic metabolism produces a lower level of adenosine triphosphate and antioxidative agents in the cells as well as lactic acidosis which may lead to metabolic acidosis. Failure of sodium–potassium pumps and calcium pumps (Ca^{2+}-adenosine triphosphate synthase) on the cell surface will cause retention of sodium and calcium in cells and potassium out of cells. Activity of sodium–hydrogen exchanger pumps (Na^+/H^+) is decreased as a result of a higher level of sodium in cells, thus causing accumulation of hydrogen in cells. Dysfunctional calcium pumps on endoplasmic reticulum will also limit calcium reuptake. The cells will accumulate sodium, calcium, and hydrogen ions resulting in hyperosmoloarity and cell swelling. Decreased cellular pH also leads to impaired enzyme activity and clumping of nuclear chromatin. Detachment of ribosomes decreases synthesis of protein.[18]

Despite the believe that the lung is resistant to ischaemic injury because of its independent source of oxygen in the alveolar space, multiple studies have described that the lung becomes vulnerable to ischaemia-reperfusion injury because of this feature.[20–22] Alveolar oxygen does help maintain aerobic metabolism and prevent hypoxic reactive oxygen species formation.[23] However, a high concentration of oxygen in the gas mixture in addition to the absence of blood flow with a low oxygen gradient in the lung tissue can cause reactive oxygen species formation, even more in the case of ventilation.[24]

In the reperfusion phase, restoring the blood flow to the ischaemic lung tissue will not only restore the oxygen supply but also increase the generation of reactive oxygen species, such as superoxide anions, hydrogen peroxide, and the most unstable, hydroxyl radicals leading to secondary injury. Reperfusion in condition of mitochondrial damage and electrolyte imbalance

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promotes oxidative stress from three major systems: xanthine oxidase system, nitric oxide synthase system, and reduced nicotinamide adenine dinucleotide phosphate oxidase system. A compensatory mechanism is activated to nullify the effect of the reactive oxygen species in normal circumstances. However, the large amount of reactive oxygen species generated from both ischaemic phase and reperfusion phase as well as the lower concentration of antioxidative agents in the ischaemic cells can lead to oxidative stress that promotes endothelial dysfunction, deoxyribonucleic acid damage, and local inflammatory responses.[11,18]

These inflammatory cascades and oxidative stress may lead to a cytokine storm, resulting in damage to cellular structures. The cell response is dependent on the severity of tissue injury and can be correlated with the duration of ischaemia-reperfusion injury. A shorter duration or mild ischaemia-reperfusion injury may activate cell survival programmes to control reactive oxygen species generation and cell damage, while moderate ischaemia-reperfusion injury cause cell dysfunction by autophagy but may activate recovery systems for survival. However, prolonged ischaemia-reperfusion injury may lead to cell death via four pathways: autophagy, mitoptosis, necrosis and necroptosis, and apoptosis.[18,25] Ischaemia-reperfusion injury of a single organ, the lung in this case, causes the release of various pro-inflammatory mediators which may induce infllammation in other organ, thus potentially contributing to multiple organ dysfunction or failure.[9,19]

As mentioned before, "no-reflow phenomenon" may occur as a consequence of endothelial dysfunction during the reperfusion phase. Activation of leucocyte, platelet, and complement may lead to endothelial dysfunction and subsequently, formation of thrombi and impaired vascular relaxation, thereby decreased microvascular flow despite reperfusion. This may further delay the recovery of the ischaemic cells in ischaemia-reperfusion injury as shown in some cases of delayed graft function or persistent organ dysfunction despite adequate reperfusion.[11]

Another hypothesis on the pathophysiology of pulmonary reperfusion injury is the exposure of the pulmonary circulation to higher pressure after angioplasty as shown by the sudden increase of pulmonary artery mean distal pressure exceeding 20 mmHg or a sudden increase of the pressure more than 150 per cent from the baseline, or possibly the increase in the end-diastolic volume of a non-compliant left ventricle.[9,26] This pathophysiology concept was in line with a case series by Ho et al which reported pulmonary reperfusion injury following stent implantation in patients with ductal-dependent unilateral disconnected pulmonary artery. Ho et al proposed that in the early phase, unilateral pulmonary oedema results primarily from acute pulmonary reperfusion injury to the stented lung, exacerbated by increase in left ventricular end-diastolic pressure due to the acute increase in preload. Following recovery from the early phase, there was evidence of a high pulmonary blood flow state to both lungs leading to pre- and post-capillary pulmonary hypertension as shown by the evidence of high right ventricular pressures and marked right ventricular dilatation.[27]

Pulmonary reperfusion injury in cyanotic CHD

Cyanotic CHD can be broadly classified into two subgroups: decreased pulmonary blood flow and increased pulmonary blood flow (Fig. 1). The main cause of pulmonary injury in cyanotic CHD is hypoxia which may be acute or chronic. Acute hypoxia leads to acidosis and depletion of glycogen and adenosine triphosphate causing the heart to rely on anaerobic metabolism. Similarly, chronic hypoxia leads to cyanosis as well as glycogen and adenosine triphosphate depletion though in a much longer period of time.[28]

It is known that infants with normoxic myocardium have increased tolerant to ischaemia because of adaptive mechanism.[31,32] An animal model study also showed that CHD rats under hypoxia conditions and volume-overloaded hearts had higher n-3/n-6 polyunsaturated fatty acid ratios which may upregulate antioxidant signalling pathway, thus providing cardioprotection against ischaemia-reperfusion injury.[33] However, chronic hypoxia in cyanotic CHD eventually depletes endogenous antioxidant in myocardium and other organs making them more susceptible to oxygen-mediated injury, thereby increasing the risk of pulmonary reperfusion injury.[33,34]

The risk of pulmonary reperfusion injury in cyanotic CHD raises a concern for patients in the decreased pulmonary blood flow subgroup.[1,2] Despite the temporary relieve of cyanosis by reperfusion of the pulmonary vasculature, palliative interventions may paradoxically cause acute pulmonary reperfusion injury.[4,5] Yacouby et al reported incidence of pulmonary reperfusion injury in 22% of patients (10 out of 46 subjects) who underwent pulmonary artery balloon angioplasty.[5] Several case reports also showed that patients who underwent pulmonary artery balloon angioplasty were more vulnerable to acute pulmonary reperfusion injury when they had pre-existing long-standing pulmonary stenosis or persistently high pulmonary artery pressure after dilation. Therefore, cyanotic CHD with decreased pulmonary blood flow may have similar risk of pulmonary reperfusion injury.[35–38] The traditional palliative intervention for cyanotic CHD is Blalock–Taussig–Thomas shunt surgery. Aside from the surgical approach, there is room for transcatheter approach which is minimally invasive. Patent ductus arteriosus stenting or right ventricular outflow tract stenting/balloon are feasible to increase pulmonary blood flow in severe right ventricular outflow tract obstruction and duct-dependent cyanotic CHD.[29]

Palliative intervention in oligaemic cyanotic CHD

Surgical aortopulmonary shunt (Blalock–Taussig–Thomas shunt)

Blalock–Taussig–Thomas shunt is a surgical procedure of bridging the subclavian or innominate artery to pulmonary artery, first reported in 1945.[39] Despite being considered as the sole treatment for patients with tetralogy of Fallot in the past, Blalock-Taussig-Thomas shunt is currently indicated for infants with complex single-ventricle physiology or patients with late presentation. Primary tetralogy of Fallot repair is the definitive management of tetralogy of Fallot, though many centres still palliate infants before the definitive procedures.[40] Modified Blalock–Taussig–Thomas shunt, originated from the Great Ormond Street Group, is developed from Blalock–Taussig–Thomas shunt by interposing a prosthetic tube between the subclavian artery and pulmonary artery. This technique is more advanced with less dissection compared to the previous technique while guaranteeing a proximal and distal anastomosis of large diameter. The maximal flow is regulated by the patient's uninterrupted subclavian artery diameter, thus allowing for a possible increase in shunt flow with growth. However, Blalock–Taussig–Thomas shunt has been associated with high morbidity and mortality (10–20%) even with

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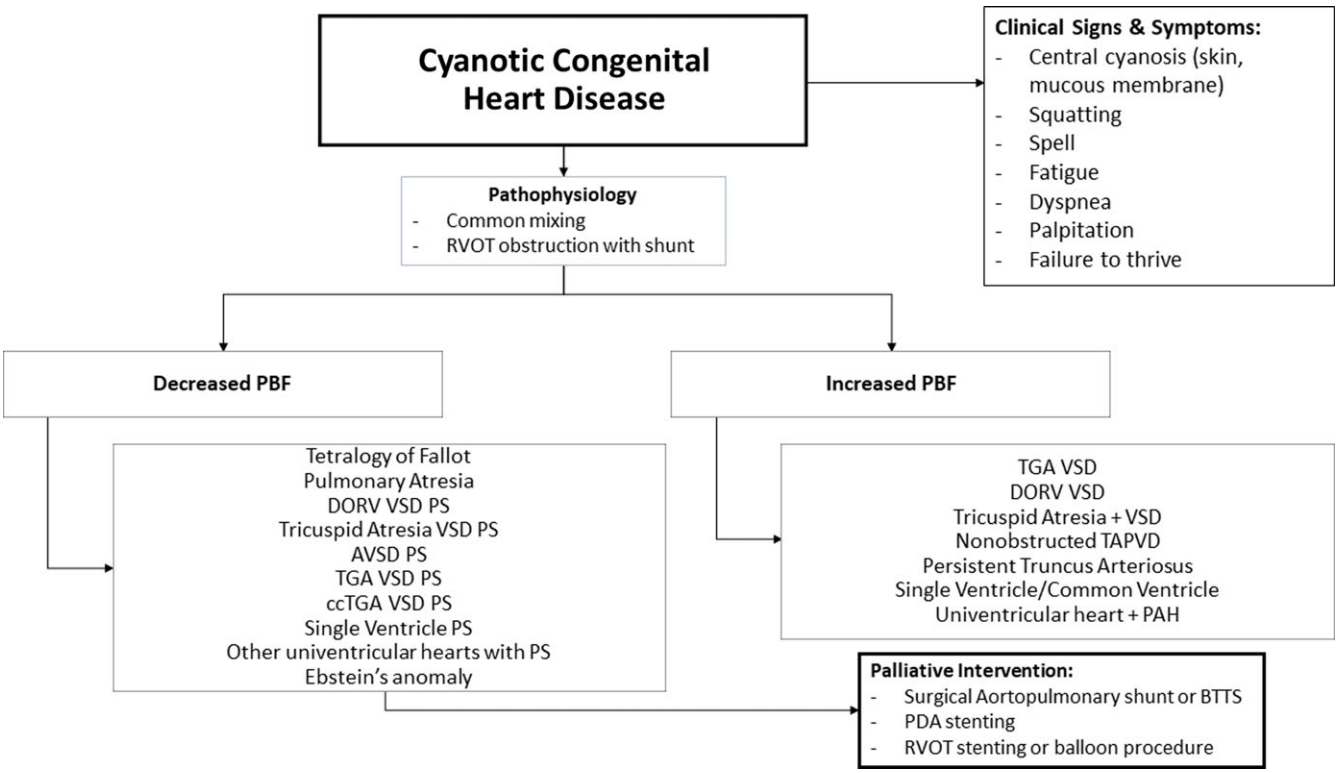

Figure 1. Classification of cyanotic CHD. *ASD = atrial septal defect; AVSD = atrioventricular septal defect; BTTS = Blalock–Taussig–Thomas shunt; ccTGA = congenitally corrected transposition of the great arteries; DORV = double-outlet right ventricle; HLHS = hypoplastic left heart syndrome; PAH = pulmonary artery hypertension; PBF = pulmonary blood flow; PDA = patent ductus arteriosus; PS = pulmonary stenosis; PV = pulmonary vein; RVOT = right ventricular outflow tract; TAPVD = total anomalous of pulmonary vein drainage; TGA = transposition of the great arteries; VSD = ventricular septal defect.[29,30]

the advancement in technology and technique, thus making transcatheter approach more of an attractive alternative.[40,41]

The incidence of pulmonary reperfusion injury in Blalock–Taussig–Thomas shunt varied between studies. Two patients with univentricular heart complex and pulmonary stenosis had pulmonary reperfusion injury after undergoing modified Blalock–Taussig–Thomas shunt using polytetrafluoroethylene tube and classsic Blalock–Taussig–Thomas shunt.[42] Tassig et al observed that from the 601 patients who survived Blalock–Taussig–Thomas shunt, 20 patients (3.3%) developed pulmonary hypertension.[43] Hofschire et al added that incidence of pulmonary vascular disease increased with time following the Blalock–Taussig–Thomas shunt. There was no patient, from total of 36 patients, developed severe pulmonary vascular changes in less than 8 years following the Blalock–Taussig–Thomas shunt, while 10 of 20 patients (50%) developed some degree of pulmonary vascular disease after having Blalock–Taussig–Thomas shunt 8 years or longer.[44]

The mechanism for pulmonary reperfusion injury in Blalock–Taussig–Thomas shunt was thought simply due to overshunting which is depicted by signs of shock and congested lungs with wide pulse pressure from six readings within 6 hours and saturation above 85 on room air.[45] Overshunting might be caused by a bigger shunt size leading to a diastolic run-off which ends up with decreased coronary and systemic perfusion. However, this notion was denied in the study by Ismail et al, which indicated that a larger shunt size did not correlate with overshunting.[45,46] Degree of shunting or pulmonary flow to systemic flow ratio (Qp:Qs) in Blalock–Taussig–Thomas shunt is also dependent on the ratio of pulmonary to systemic vascular resistance. In case of overshunting, we have to optimise the balance of Qp:Qs by increasing the pulmonary vascular resistance and reducing the systemic vascular resistance. Pulmonary vascular resistance may be increased by reducing fraction of inspired oxygen to 0.21 despite suctioning or nebulising, avoiding hyperventilation with targeted permissive hypercapnea, administering high positive end-expiratory pressure of 6–9, and maintaining blood pH of 7.35–7.40. Systemic vascular resistance may be reduced by administering inodilators.[45,47]

The long duration of Blalock–Taussig–Thomas shunt procedure is one of the risks of pulmonary reperfusion injury because ischaemia-reperfusion injury of the lungs occurs not only after the procedure but also during the surgical procedure by utilisation of cardiopulmonary bypass. Previous animal studies performed in dogs have shown that cardiopulmonary bypass procedures increase malondialdehyde content in the lung interstitium with simultaneous downregulation of superoxide dismutase activity. Malondialdehyde is the end product of lipid peroxidation which is an indicator of the extent of lipid peroxidation, while superoxide dismutase is an oxygen free radical scavenger which reflects the antioxidant activity. Furthermore, the expression of transforming growth factor-beta 1 also increases during cardiopulmonary bypass. Transforming growth factor-beta 1 is usually related with the increase of pulmonary endothelial and alveolar epithelial permeability. Additionally, transforming growth factor-beta 1 also leads to decreased sodium channel on the apical surface of alveolar epithelial cells, thus impairing the removal of water and salt for alveolar lumen. Increased oxygen free radicals could activate pro-inflammatory nuclear factors, such as Nuclear factor kappa B and activator protein 1, which lead to upregulation of transforming growth factor-beta 1. Transforming growth factor-beta 1 can

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reversely promote the expression of oxygen free radicals, thus forming the endless circle of oxygen free radical-transforming growth factor-beta 1-lung injury. All these evidences show that cardiopulmonary bypass use tilts the balance in the lung to pro-inflammatory state which may increase the risk of pulmonary reperfusion injury.[48]

The simplest solution to prevent cardiopulmonary bypass-induced pulmonary injury is not using cardiopulmonary bypass in the cardiac surgery (inversion to off-pump operation) as shown in off-pump coronary artery bypass graft surgery. However, it is still impossible to perform most cardiac surgeries without cardiopulmonary bypass.[49] There were some strategies explored to minimise these deleterious effects of cardiopulmonary bypass from improved cardiopulmonary bypass devices and methods to pharmacological pre-conditioning and post-conditioning. However, the effectiveness of these strategies are still unclear.[50–52]

Cardiopulmonary bypass machines impose patients with very high oxygen tension of 400–500 mmHg.[53,54] Administration of 100% oxygen may cause oxygen toxicity or absorptive atelectasis as shown in a previous study which reported exacerbation of post-operative lung injury with the administration of 100% oxygen during cardiopulmonary bypass.[55] Therefore, keeping normoxia condition (PO_2 of 80–100 mmHg) of the cardiopulmonary bypass is required to reduce the extent of myocardial and pulmonary dysfunction in regard to reoxygenation injury.[54–56]

Aside from hyperoxia, leucocytes might cause reoxygenation injury by generating oxygen-derived radicals. The method of leucocyte depletion strategy by using leucocyte depletion filters may reduce the effect of reoxygenation injury along with keeping the oxygen tension at a normal level.[34] Additionally, in vivo study by Qiu et al reported that reperfused lung tissues increased the expression of enzymatic product inosine monophosphate deaminase which regulates neutrophil trafficking in the microvessel. This finding may provide an alternative prospect for minimising ischaemic-reperfusion-associated lung injury besides the depletion strategy. On the contrary, an ex vivo study by Luc et al showed that there was increased pro-inflammatory cytokines and leucocytes in the perfusate despite the use of leucocyte filter as it became saturated over 12 hours of ex vivo lung perfusion.[50] Therefore, there is still no objective evidence for the routine use of leucocyte filter in cardiopulmonary bypass.

Circuits coating has been used for the prevention of inflammatory reaction in cardiopulmonary bypass use, especially heparin-coated circuit which is the first and most extensively studied. The concept behind heparin coating is mimicking the endothelial surface that contains heparin sulphate, thus reducing complement activation, reducing inflammatory response, and improving clinical outcomes. Most studies showed improved pulmonary function with heparin-coated circuit, but there was no influence on the ICU stay and intubation time of the patients.[49]

A small observational study conducted by Su et al suggested that deep hypothermic circulatory arrest increased the risk of post-operative pulmonary dysfunction compared to that of the deep hypothermic low flow during cardiopulmonary bypass. Although deep hypothermic circulatory arrest confers predisposition to worse hypoxic conditions, longer exposure of blood in the cardiopulmonary bypass circuit during deep hypothermic low flow may lead to more complement-related injury in the pulmonary endothelium, thus exacerbating the risk of lung injury.[57]

The use of prime solution in cardiopulmonary bypass circuits may cause increased body fluid volume (hemodilution), thus posing a problem for children who have poor ability to regulate and excrete body fluids content. The excessive increase of body fluids volume may result in haemostatic impairment, coagulation disorders, inflammatory response, and myocardial and pulmonary oedema leading to increased post-operative mortality and morbidity.[58] Ultrafiltration is used to minimise hemodilution by removing volume of priming and reducing overall post-operative oedema, specifically that of lungs for better post-operative oxygenation in cardiac surgery. Additionaly, it has been shown that ultrafiltration also removes destructive and inflammatory substances, inflammatory cyokines, and toxin from the circulation as well as increases the colloid oncotic pressure which subsequently prevents the development of pulmonary interstitial oedema.[49]

Both conventional ultrafiltration with or without modified ultrafiltration are used routinely in cardiopulmonary bypass. Conventional ultrafiltration is carried during the running of cardiopulmonary bypass to maintain moderate hemodilution and minimal venous reservoir blood. Modified ultrafiltration, which has greater efficiency in removing excess fluid compared to conventional ultrafiltration, is performed immediately after the termination of cardiopulmonary bypass. Despite its advantage, modified ultrafiltration has some potential disadvantageous such as technical complications, surface-induced inflammatory responses, as well as longer duration and additional cost.[58,59] A meta-analysis of paediatric cardiac surgery showed that conventional ultrafiltration with increased ultrafiltration volume and post-cardiopulmonary bypass haematocrit is compared with conventional ultrafiltration alone. However, modified ultrafiltration did not significantly influence the post-operative aortic occlusion, cardiopulmonary bypass, and hospital stay duration.[58] Another meta-analysis of randomised controlled trial of paediatric cardiac surgery also showed that there was significant improvement of clinical conditions in the immediate postbypass period with modified ultrafiltration over conventional ultrafiltration, but the post-operative outcome parameters were not significantly influenced.[59] Therefore, the advantage of conventional ultrafiltration with modified ultrafiltration over conventional ultrafiltration only in children is still unclear.

Steroids have been used as post-operative lung protection after cardiopulmonary bypass for nearly 30 years, but there is still conflicting evidence regarding its effectiveness to reduce post-operative mortality and to improve post-operative complications after cardiopulmonary bypass.[60–63] An experimental study showed improvement of post-operative lung function (alveolar-arterial oxygen gradient, pulmonary vascular resistance, and extracellular lung water) by using methylprednisolone as pre-treatment.[64] However, this was denied by clinical studies by Chaney et al with contradicting results.[65,66] A recent meta-analysis showed that low-dose corticosteroid prophylaxis significantly decreased inflammatory factor concentrations and improved the overall outcome of cardiac surgery with cardiopulmonary bypass in adult patients. However, there was increased risk of myocardial infarction and hyperglycaemia requiring insulin infusion. In children, corticosteroid was associated with shortened cardiopulmonary bypass time, increased risk of insulin infusion, and no substantial changes in mortality and other outcomes.[67] Another review concluded that perioperative corticosteroid did not improve mortality rate or other secondary outcomes such as stroke, renal failure, myocardial infarction, and infection, but there were some benefits: reduced risk of pneumonia and respiratory failure, and shortened length of ICU and hospital stay.[68] Despite this contradicting evidence, many

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centres still use this fast-track recovery protocol as a fundamental strategy.[69–71]

Patent ductus arteriosus stenting

Patent ductus arteriosus stent implantation is a procedure to maintain pulmonary blood flow through the ductus arteriosus, especially in ductal-dependent cyanotic CHD.[72] This procedure has become more popular as it is minimally invasive, avoiding a median sternotomy or lateral thoracostomy, as well as exposure to cardiopulmonary bypass.[72,73] Glatz et al reported no difference in mortality or unplanned intervention between patent ductus arteriosus stenting and Blalock–Taussig–Thomas shunt. Nevertheless, patent stenting had fewer procedural complications, shorter length of stay and ICU stay, lower diuretic use, and more symmetrical with larger size of pulmonary arteries which are beneficial for primary repair.[73] Bentham and colleagues also found that patent ductus arteriosus stenting had a significant mortality benefit, less extracorporeal support, fewer ventilation days, shoreter ICU stay, and overall length of stay.[74] These results were generally similar to a study by Nasser et al, though there is no difference in growth and symmetry of pulmonary artery between both groups.[75] Despite the aforementioned superiority, patent ductus arteriosus stenting usually required more reintervention with higher rate of failure (17%) which is followed by switching to surgical Blalock–Taussig–Thomas shunt.[74,75] The incidence of pulmonary reperfusion injury in patent ductus arteriosus stenting is rare, but it still may occur as a complication compromising haemodynamic. This is evidenced by a study by Bahaidarah et al founding one case of pulmonary reperfusion injury from 43 patent ductus arteriosus stenting procedures in patients with cyanotic CHD.[76,77]

Right ventricular outflow tract stenting or balloon procedure

Severely desaturated infants with acidosis metabolic who are prostaglandin-dependent in cases of stenotic antegrade pulmonary blood flow as a consequence of the narrowing of the right ventricular outflow tract (infundibular or valvar stenosis) or disturbances in the pulmonary arterial tree such as hypoplastic or the presence of multiple aortopulmonary collateral arteries may require early intervention. Comorbidities such as prematurity, low weight, infection, neurological injury, and other conditions requiring non-cardiac surgery may increase the risk or even delay the primary cardiac repair in neonates. Similarly, Blalock–Taussig–Thomas shunt procedures performed in infants with prematurity, low weight, and hypoplastic pulmonary arteries have increased risk of complications such as pulmonary artery stenosis and pulmonary overcirculation. Hence, this becomes a dillema as these patients are at increased risk of morbidity and mortality for either primary repair bridging treatment of Blalock–Taussig–Thomas shunt.[2,78] Right ventricular outflow tract stenting even becomes the primary palliation procedure for tetralogy of Fallot in some centres.[1]

A few studies reported that right ventricular outflow tract stenting may alleviate both infundibular and pulmonary valve obstruction, increasing oxygen saturation and delaying the requirement for early surgery. This procedure also allowed pulmonary arterial and somatic growth with clinical results comparable to early surgical repair in more favourable patients.[2,78] A systematic review and meta-analysis reported that patients with marked obstruction of pulmonary blood flow, low birth weight, or small pulmonary artery size who underwent right ventricular outflow tract stenting had improved conditions as well as pulmonary blood flow.[79] Similar to other palliative interventions, right ventricular outflow tract has risk of developing pulmonary reperfusion injury after reperfusion of the previously under-perfused pulmonary circulation. One study of tetralogy of Fallot patients undergoing right ventricular outflow tract stenting reported 9 out of 12 children (75%) develops post-procedural pulmonary reperfusion injury which mostly resolved in 72 hours.[80] A review hypothesised that the immediate death observed during early post-operative monitoring of right ventricular outflow tract stenting may be caused by acute respiratory distress syndrome induced by pulmonary reperfusion injury or sepsis.[79] Gradual increment of pulmonary blood flow by redilatation of stent may be required in cases of severe form of tetralogy of Fallot physiology with late presentation to reduce the risk of perioperative death from pulmonary reperfusion injury.[81]

Management of acute pulmonary reperfusion injury in post-palliative procedure

Management of pulmonary reperfusion injury post-palliative procedure should focus on diuretics, oxygen, and mechanical ventilatory support until 72 hours. Monitoring should be done in the ICU as titration of diuretics should be done carefully.[26] Although conservative fluid management using diuretics in the children has shown to lower mortality rate as well as shorten ICU stay and mechanical ventilation days, the optimal guideline for fluid management in pulmonary reperfusion injury remains controversial. It is due to the heterogeneous nature of population phenotypes with the disease of interest in real-life settings.[82]

In any chosen mode for ventilatory support, parameter controls must maintain the concept of open-lung ventilation or permissive hypercapnia strategy. This setting would provide a protective effect on the lung, instead of aggravating the lung damage. The recommended adjustment of alveolar protective tidal volume ranges between 4 and 8 mL/kg of ideal weight to prevent unwanted volutrauma. Supplemental oxygen must be adjusted to maintain saturation between 92 and 97%, while ensuring the positive end-expiratory pressure stays below 10 mmHg.[83]

Severe heart failure due to pulmonary overflow is uncommon but may occur if the flow rate is too high thus requiring reduction. This condition may require the use of systemic vasodilator if the systolic blood pressure is above 75 mmHg and diastolic pressure above 30 mmHg. Milrinone may be started from 0.3 to 1 mcg/kg/min in neonates. After milrinone is titrated up to 1 mcg/kg/min, sodium nitroprusside may be started from 0.5 mcg/kg/min and titrated up to 5 mcg/kg/min.[45] Although the concept of bigger shunt size correlating with overshunting is still debatable, minimising overshunting by reducing the shunt size is an option. This may be achieved by replacing the shunt, decreasing the diameter of ductal stent by adding several stents (Russian Doll technique), or increasing the length of tube. Multiple coronary stents would be required to decrease the stent diameter, while increasing the length of the tube can be achieved by using a covered stent. By reducing the diameter and lengthening the duct, this will increase the resistance and decrease the flow rate.[84–88]

There are many potential treatments for thetherapy and prevention of pulmonary reperfusion injury based on its complex pathophysiology. Various methods of preconditioning such as ischaemic, hyperthermic, and chemical preconditioning may stimulate the production of heat-shock proteins in the cells which

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give protective benefits prior to ischaemic reperfusion insult. Therapeutic gases such as nitric oxide, hydrogen, hydrogen sulfide, and carbon monoxide, administration of prostaglandin E1, intravenous injection of soluble complement receptor type 1, administration of platelet-activating factor antagonists, and exogenous surfactant therapy also show potential in prophylaxis and therapy of pulmonary reperfusion injury. All these treatments are still in research, mostly only until in vivo experiments; hence, their clinical evidence remains unelucidated.[84–88]

Conclusion

Pulmonary reperfusion injury is a complex disease trigerred by ischaemia and reperfusion involving multiple molecular and cellular mechanism. The risk of pulmonary reperfusion injury has been recognised a long time ago and is still an important issue today. The incidence of pulmonary reperfusion injury varies depending on multifactors such as the type of cyanotic CHD, baseline condition of the patients including the cardiac and pulmonary function, type of palliative intervention, and other risk factors. The lack of specific diagnosis criteria for pulmonary reperfusion injury also leads to the unawareness of this disease entity. However, pulmonary reperfusion injury does occur and may lead to morbidity and mortality in post-palliative procedures in oligaemic cyanotic CHD. Understanding the risk and mechanisms of this complication will prepare the heart team for this complication, improve periprocedural management and post-operative care, and eventually improve the outcome for the patients. It is necessary to construct a general consensus for pulmonary reperfusion injury as currently the cornerstone of management for pulmonary reperfusion injury is supportive therapy to prevent further deterioration of lung injury. Further studies are also required to establish the benefit of novel and potential treatment for prophylaxis and therapy of pulmonary reperfusion injury.

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