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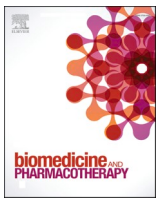

Review

Therapeutic benefits of nitric oxide in lung transplantation

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ABSTRACT

Lung transplantation is an evolutionary procedure from its experimental origin in the twentieth century and is now recognized as an established and routine life-saving intervention for a variety of end-stage pulmonary diseases refractory to medical management. Despite the success and continuous refinement in lung transplantation techniques, the widespread application of this important life-saving intervention is severely hampered by poor allograft quality offered from donors-after-brain-death. This has necessitated the use of lung allografts from donors-after-cardiac-death (DCD) as an additional source to expand the pool of donor lungs. Remarkably, the lung exhibits unique properties that may make it ideally suitable for DCD lung transplantation. However, primary graft dysfunction (PGD), allograft rejection and other post-transplant complications arising from unavoidable ischemia-reperfusion injury (IRI) of transplanted lungs, increase morbidity and mortality of lung transplant recipients annually. In the light of this, nitric oxide (NO), a selective pulmonary vasodilator, has been identified as a suitable agent that attenuates lung IRI and prevents PGD when administered directly to lung donors prior to donor lung procurement, or to recipients during and after transplantation, or administered indirectly by supplementing lung preservation solutions. This review presents a historical account of clinical lung transplantation and discusses the lung as an ideal organ for DCD. Next, the author highlights IRI and its clinical effects in lung transplantation. Finally, the author discusses preservation solutions suitable for lung transplantation, and the protective effects and mechanisms of NO in experimental and clinical lung transplantation.

1. Introduction

Lung transplantation is currently the mainstay of therapy for patients with different types of end-stage respiratory diseases worldwide. It provides these patients with a better quality of life and survival benefits. This form of surgical treatment involves the transfer of donor lungs procured from circulation-intact, brain-dead individuals and from those with circulatory arrest into transplant recipients. Advances in both basic science and clinical research aspects of this field have resulted in success in clinical lung transplantation in terms of patient outcomes due to continuous refinement in donor selection criteria, and improvements in donor lung preservation techniques, perioperative and post-transplant management and better treatment of post-transplant complications including immunosuppressive therapy [1–5].

1.1. Historical account of clinical lung transplantation

From its experimental origin at the beginning of the twentieth century and after decades of a hiatus because of failed clinical attempts, lung transplantation has evolved into a well-established and routine life-saving intervention for patients with a variety of terminal lung diseases refractory to medical management [1–5]. The first human lung transplantation was performed by James Hardy and his team in 1963 in a 58-year-old man who was diagnosed with a squamous cell carcinoma of the left main bronchus with retro-obstructive pneumonitis [6]. However, the procedure was not successful enough to be accepted as a lung replacement therapy for terminal lung diseases, as the lung transplant recipient unfortunately died on post-operative day 18 due to renal dysfunction. Interestingly, autopsy revealed no graft rejection [7]. About 3 weeks later, the second lung transplantation in human was performed by Magovern and Yates in a 44-year-old man but the patient died on post-operative day 8 [8]. Following these failed attempts, a total of 23 lung transplants were performed by 20 lung transplant surgeons globally, which also resulted in no success, as the survial periods were consistently less than 1 month [9]. The breakthrough finally came in 1971 when Derom et al. [10] in Belgium performed the first successful

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lung transplantation in a 23-year-old man, who worked as a sandblaster and was diagnosed with end-stage silicosis due to heavy exposure to silicon dust for 2 years. After transplantation, the patient survived for 10 months although he spent most of his post-operative life in intensive care unit [10]. In 1995, a group led by Robert Love also performed another successful lung transplantation [11], and 6 years later, Steen and his surgical team also performed another successful lung transplantation in a 54-year-old woman with chronic obstructive pulmonary disease [12]. In this remarkable lung transplantation, the transplanted lung exhibited excellent function only 5 min after reperfusion and ventilation, and during the first 5 months of follow-up [12]. This success continued in lung transplants performed in the 21st century, with improved survival rate [156]. It is important to note that all the human lung transplantations performed thus far were single-lung transplants including the first successful heart-lung transplantation performed by Reitz and his team in 1981 in a 45-year-old woman with primary pulmonary hypertension [13]. Patterson and Cooper were the first to perform a successful double-lung transplantation in 1986 in a 42-year--old woman, who was diagnosed with emphysema secondary to alpha-1 antitrypsin deficiency-associated lung disease. In this patient, the lungs were transplanted *en bloc* [14]. Although the surgeons observed tracheal dehiscence as one of the post-transplant complications in their transplant patient, their surgical technique laid the foundation for the development of the modern technique of sequential double-lung transplantation and anastomosis performed at the level of the mainstem bronchus. In summary, lung transplantation has evolved into the mainstay of therapy, with short- and long-term outcomes for many patients with different types of end-stage pulmonary disease.

2. The lung as an ideal organ for donation-after-cardiac-death

Despite the success and continuous refinement in lung transplantation techniques, the widespread application of this life-saving intervention is severely hampered by poor allograft quality offered from donors-after-brain-death (DBD; heart-beating neurologically deceased donors). Although DBD was introduced and accepted since 1968 and has provided most of the organs used in transplantation today, it negatively impacts donor lung quality, as it leads to hemodynamic, metabolic, and neuroendocrine abnormalities, and ruptured alveolar capillary endothelium, culminating in neurogenic pulmonary edema, along with acute inflammatory lung injury and acute respiratory distress syndrome [15,16]. Also, the lungs in DBD may be subjected to airway aspiration, respiratory tract infection, atelectasis, and pulmonary contusion, which may contribute to graft injury prior to procurement [15,16], and may further be amplified by ischemia and reperfusion during graft procurement, preservation and implantation. This has increased the scarcity of suitable lung donors, which has resulted in an annual increase in the number of patients on the transplant waiting list, with longer waiting times and an annual increase in morbidity and mortality while on the waiting list. It has also resulted in strict selection criteria for lung transplant recipients [17–19]. This problem suggests that many more lives could be extended or improved with sufficient supply of donor lungs. In addition to the donor lung shortage crisis, early graft dysfunction (ischemia-reperfusion injury) and late graft dysfunction (bronchiolitis obliterans syndrome) also complicate the long-term success of DBD lung transplantation [20,21].

Avoiding the stresses of DBD and resistance to ischemia suggests donors-after-cardiac-death (DCD; previously known as non-heart-beating donors) as an additional source to expand the pool of donor lungs, and could serve as a valuable option especially in countries such as Japan, where the concept of DBD is not widely accepted. Unlike other solid organs, the lung may be ideally suitable for DCD due to its tolerance for warm ischemia at substantial time intervals because of its low metabolic requirement, in addition to being normally well-perfused and its alveoli filled with oxygen. It has been demonstrated that lung epithelial cells can be cultured from specimens obtained several hours after death, and the inflated lung will remain viable for at least 2 hours after death without perfusion since its oxygen delivery to tissues is independent of perfusion, and respiration of lung parenchymal cells occurs through diffusion from air spaces [22,23]. Using a rat model of DCD, non-ventilated and nitrogen-ventilated lungs retrieved at 2, 4, 8 and 12 hours after cardiac death showed progression of ischemic injury and ultrastructural damage, characterized by nuclear chromatin clumping, mitochondrial degeneration, intracellular edema, and loss of cellular membrane integrity [24,25]. However, postmortem at 2, 4, 8 and 12 hours after cardiac death showed preservation of lung ultrastructural integrity and delay in cell death in oxygen-ventilated lungs after circulatory arrest [24,25], with maintenance in the levels of adenosine triphosphate (ATP) and total adenine nucleotide (TAN) compared to heart and liver, which exhibited progressively reduced ATP and TAN levels after cardiac death [26–29]. A similar observation was made in a canine model of DCD in which dogs were mechanically ventilated with room air for various periods after cardiac death until 6 hours before retrieval of the lungs [30]. Thus, compared to other solid organs, these experimental findings suggest a unique nature of the lung, which allows it to be ideally suitable for procurement at substantial time intervals following cardiac death, and therefore, support the application of postmortem mechanical ventilation with oxygen or room air for DCD lung transplantation. The findings do not only suggest a prospect in controlled DCD (i.e. donors whose deaths are expected in a hospital) but also in several scenarios of uncontrolled DCD (i.e. donors that experience cardiac arrest unexpectedly and usually outside a hospital).

3. Ischemia-reperfusion injury in lung transplantation

In lung transplantation, ischemia (temporary cessation of blood flow) begins during the surgical procedure of lung procurement from the donor. This causes an imbalance between metabolic supply and demand, leading to cell death and tissue injury. This type of ischemia, referred to as warm ischemia, is followed by cold ischemia when the lung allograft is intravascularly flushed with and stored in cold preservation solution at 4 °C to decrease its metabolic activity and energy requirement prior to transplantation. While hypothermic preservation is beneficial, it induces a series of pathological events in the donor lung, such as ischemia-induced oxidative stress from over-production of reactive oxygen species (ROS; a destructive mediator of cell and tissue injury) [31], Na^+/K^+-ATPase pump inhibition [32], Na^+ and Cl^- influx, along with flow of water into intracellular space, endothelial cell membrane depolarization (due to absence of mechanotransduction from lack of blood flow) [33,34], intracellular calcium overload [31,35,36], release of pro-inflammatory and pro-apoptotic factors [37,38], all of which mediate cell death and tissue injury (Fig. 1). Prolonged ischemia results in *"no-reflow phenomenon"*, which is characterized by continuous obstruction to blood flow (due to significant microvascular damages) and subsequent ischemia despite reperfusion [39].

Following the ischemic phase is reperfusion phase during which warm oxygenated blood is restored to the ischemic lung allograft after implantation. Interestingly, reperfusion is associated with more cell death, as it exacerbates ischemic-related responses. During reperfusion, there is further production of ROS, extravasation of leukocytes such as macrophages and neutrophils (forming neutrophil extracellular traps) [40,41], activation of the complement system, upregulated expression of adhesion molecules (e.g. selectins and integrins), increased release of pro-inflammatory mediators (e.g. cytokines and damage-associated molecular patterns) and pro-apoptotic factors [41–43], as well as activation of toll-like receptors, and formation of endothelial gap from increased endothelial permeability [44]. All these pathological changes worsen lung tissue injury during and after reperfusion, and contribute to pulmonary dysfunction after lung transplantation (Fig. 1). Collectively, this inevitable paradoxical phenomenon of blood cessation and restoration is referred to as ischemia-reperfusion injury (IRI), and negatively impacts lung allograft quality and increases post-transplant

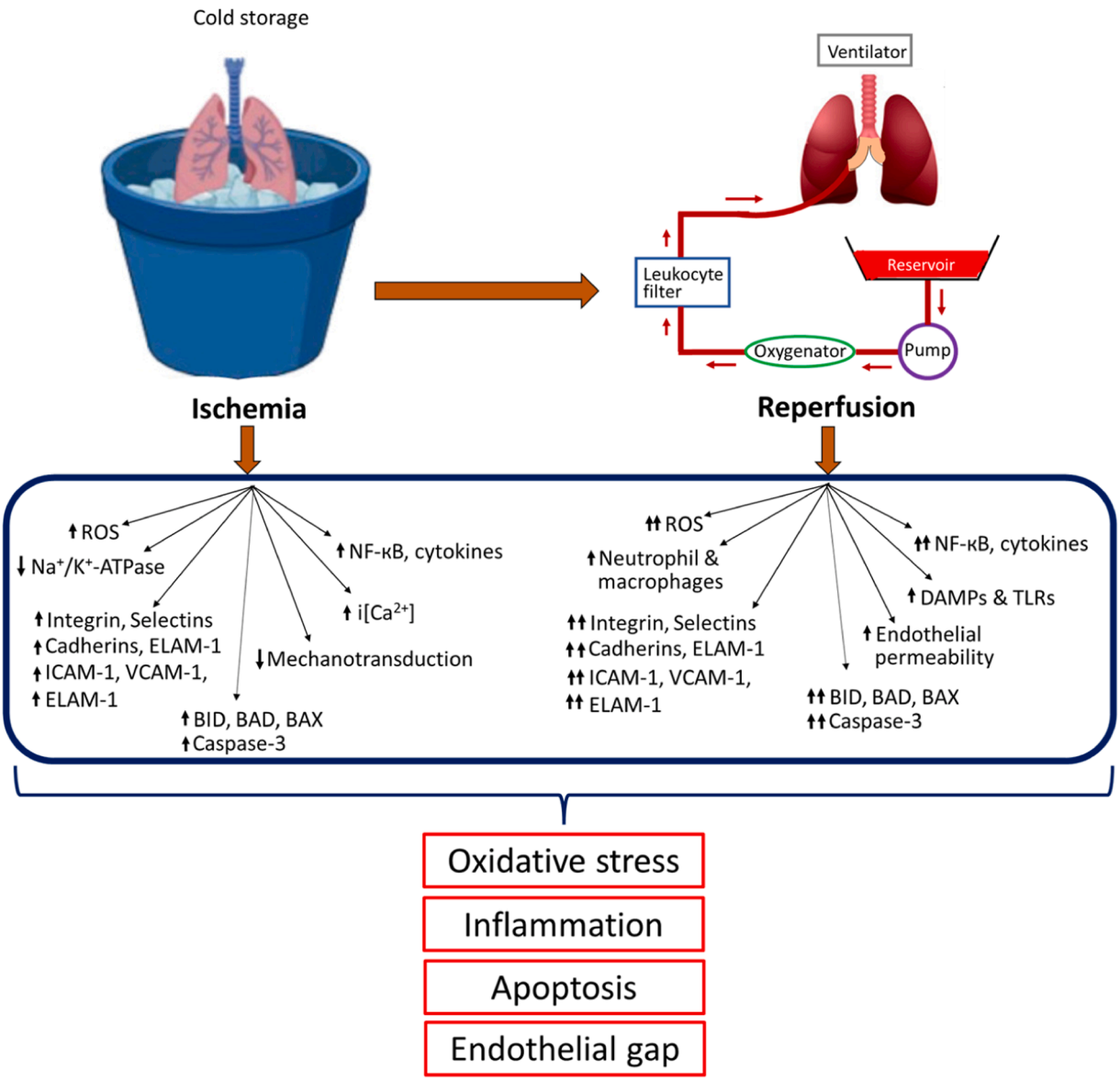

Fig. 1. Schematic view of pulmonary ischemia-reperfusion injury. NF-κB; nuclear factor-kappaB, ROS; reactive oxygen species, ELAM-1; endothelial leucocyte adhesion molecule-1, ICAM-1; intercellular adhesion molecule-1, VCAM-1; vascular cell adhesion molecule-1, DAMPs; damage-associated molecular patterns, TLRs; toll-like receptors, i[Ca^{2+}]; intracellular calcium ion concentration, Na^{+}/K^{+}-ATPase; sodium/potassium-adenosine triphosphatase, BID; BH3 interacting domain death agonist; BAD; Bcl-2-associated death promoter; BAX; Bcl-2-associated X protein.

complications.

3.1. Clinical effect of ischemia-reperfusion injury in lung transplantation

According to available data at the registry of the International Society of Heart and Lung Transplantation, the current 5-year survival rate of lung transplant recipients is approximately 55%, which suggests that lung transplantation is a satisfactory and viable treatment for end-stage respiratory diseases [45]. However, despite the incremental advances in lung transplantation, including refinement of surgical techniques and improvement in peri-operative care, lung transplantation is still associated with various problems such as primary graft dysfunction (PGD), allograft rejection, infection, surgical complications, malignancy and chronic lung allograft dysfunction [46]. Among these problems, PGD is the most significant cause of short- and long-term morbidity and mortality in lung transplant recipients. It is also the cause of prolonged mechanical ventilation and longer hospital stays beyond 72 hours in the post-transplant period [47,48]. PGD occurs in about 10% of lung transplant recipients. Compared to patients without PGD, the mortality rate of lung transplant recipients with PGD is 7-folds higher, which represents 42% of mortality in the month after transplantation [49]. It is worth mentioning that IRI in clinical lung transplantation causes robust inflammation, alveolar damage (decreased alveolar compliance), pulmonary edema (due to increased endothelial permeability) and increased pulmonary vascular resistance within 72 hours after transplantation, which culminate in PGD [49–53]. PGD represents a major risk factor for the development of chronic lung dysfunction such as bronchiolitis obliterans, which has been identified as the major cause of mortality among transplant recipients after 1 year of lung transplantation [54,55]. In addition, IRI also contributes to acute lung allograft rejection, leading to long-term graft dysfunction [54,56,57]. Considering this major clinical consequence of IRI in lung transplantation, there is the need for lung transplant surgeons and their staff to redefine the selection criteria for assessment of donor lungs (i.e. focus on donor lungs that can tolerate several hours of ischemia without losing their function after reperfusion). In addition, assessment of effective

lung preservation technique and improved management of transplanted lungs after reperfusion will help reduce the severity of lung IRI, prevent PGD and improve both short- and long-term outcomes following transplantation.

4. Preservation solution in lung transplantation

As PGD due to IRI remains a major cause of morbidity and mortality after lung transplantation, one of the practical approaches to mitigate IRI, improve pulmonary graft performance and reduce the increasing incidence of PGD is to optimize existing lung preservation techniques or develop highly effective and reliable alternative lung preservation solutions to minimize lung injury during the period of ischemia. Due to its technical simplicity, most transplant centers have adopted cold single pulmonary artery flush with modified Euro-Collins solution as the standard preservation technique in lung transplantation, with a varying cold ischemic (preservation) time from 4 to 12 hours [58]. Euro-Collins solution, which was originally developed for renal graft preservation in the 1960s and later introduced 3 decades ago for lung allograft preservation, is in the same category of intracellular-type preservation solution (containing high K^+ and low Na^+) with University of Wisconsin solution (UW; historically for liver graft preservation), whose high potassium levels produce pulmonary vasoconstriction [59]. In the quest for a more reliable preservation solution for lung allografts, extracellular-type preservation solution (containing low K^+ and high Na^+) was developed. This includes low-potassium dextran (LPD) and Celsior solution (for cardiac graft preservation) [60]. Unlike intracellular-type preservation solution, the low potassium content in extracellular-type preservation solution supports the integrity of endothelial cells and reduces oxidative stress and pulmonary vasoconstriction [61–63].

Although both intracellular- and extracellular-type solutions are used to preserve lung allografts, LPD is the only one specifically developed for lung allograft preservation, and its modification with glucose (LPD-glucose; also known as Perfadex) has been widely used at many transplant centers due to its superiority over the other solutions for prolonged lung allograft preservation [64]. In a canine model of single-lung transplantation to determine the individual contributions of dextran and low potassium concentration during prolonged (12-hour) preservation of lung allografts, Keshavjee et al. [65] observed that addition of dextran 40 produced excellent immediate pulmonary function (gas exchange, pulmonary hemodynamics and mechanics), which continued on post-transplant day 3 upon follow-up, while its absence in the low-potassium preservation solution resulted in marked deterioration in pulmonary function. In the same study, high-potassium dextran solution produced very poor pulmonary function, characterized by rupture of alveolar septa and severe alveolar edema and hemorrhage, which resulted in death of some of the animals in this group at 6 hours after transplantation [65]. These observations indicate that both dextran 40 and low potassium concentration contribute significantly to preserving lung allograft viability and function after prolonged preservation. This report was later confirmed in a swine model of lung transplantation in which lung allografts were preserved for 8 hours. In addition to preserving pulmonary microcirculation, LPD solution also prevented no-reflow phenomenon and pulmonary edema during reperfusion [66].

At the cellular level, LPD solution significantly suppressed human neutrophil chemotaxis [67], exhibited less cytotoxic effect on type II pneumocytes of rats and humans [68,69], preserved the activity of Na^+/K^+-ATPase in type II pneumocytes of rats [70], and maintained intact endothelial-epithelial barrier during prolonged hypothermic preservation compared to intracellular-type preservation solutions [66]. As type II pneumocytes are synthesizing cells of alveolar surfactant, which lowers surface tension at the air-water interface in the alveoli, thereby preventing alveolar collapse after exhalation, these *in vitro* findings suggest that lung allograft preservation in LPD solution produces higher levels of metabolic activity in recovering epithelial cells, better surfactant function at the end of cold ischemia and after reperfusion, mitigates IRI, and reduces post-transplant complications.

Modified extracellular-type preservation solution has been proven to be better than intracellular-type in maintaining lung allograft function [71,72]. This conclusion became increasingly evident after results from several experimental studies in canine, porcine and primate models of single- and double-lung transplantation demonstrated that addition of 1% glucose to LPD solution provided a suitable substrate for aerobic metabolism in inflated lungs and maintained ATP and phosphocreatine levels, and thereby allowing a prolonged cold ischemic (preservation) time for 12–24 h, with preserved lung allograft integrity [73–77]. In addition to serving as an energy source during cold ischemia, saccharides such as glucose (monosaccharide), trehalose (disaccharide) and raffinose (trisaccharide) in preservation solutions also act as an impermeant to prevent cellular edema. In a rat model of left-lung transplantation, for example, supplementation of LPD preservation solution with 30 mmol/L raffinose (superior to other saccharides for this purpose) during 24 hours of lung allograft preservation at 4ºC resulted in significantly higher oxygenation, lower peak airway pressures at 2 hours after allograft reperfusion and a lower wet-to-dry weight ratio (an indicator of pulmonary edema), culminating in marked improvement in lung allograft function compared to control allografts without raffinose supplementation [78]. Using the same model, the same group of researchers conducted a follow-up study a year later in which they observed minimal interstitial edematous expansion, fewer damaged type II pneumocytes, and minimal capillary injury in raffinose-LPD lungs compared to control lung allografts that exhibited significant weight gain, more dead cells, more damaged type II pneumocytes, cellular necrosis, collapsed alveolar capillaries, and interstitial and alveolar edema, with influx of interstitial macrophages [79]. These laboratory results show that modification of LPD solution with saccharides during hypothermic lung allograft preservation exhibits a stronger cytoprotective effect, and could be applied clinically in extending lung allograft preservation. Nonetheless, continuous refinement is still needed with other components such as antioxidants to further improve allograft quality after preservation and limit IRI.

5. Nitric oxide in lung transplantation

Despite the significant strides that have been made within the realm of lung transplantation including optimal preservation of lung allografts, IRI is still a major problem in lung transplantation. This has necessitated continuous search for further improvement of the transplantation protocol. In the light of this, there are studies investigating the effect of selective pulmonary vasodilators such as nitric oxide (NO), administered directly in its gaseous form to lung donors prior to donor lung procurement, or to recipients, or administered indirectly by supplementing lung preservation solutions with NO donor compounds. This approach may provide significantly superior graft protection, considering that endogenous pulmonary NO production is decreased during ischemia and reperfusion. Thus, NO pathway might be a therapeutic target, whose activation might be beneficial in attenuating IRI after lung transplantation. It is important to note that NO is a member of a family of small endogenously produced gaseous signaling molecules that include carbon monoxide and hydrogen sulfide, which are also showing promise in experimental models of organ transplantation [157-160]. NO is produced in the endothelium of blood vessels by a family of enzymes called nitric oxide synthase (NOS), in a reaction in which L-arginine is used as a substrate to produce L-citrulline [80]. The NO produced by NOS, acts on several target proteins and enzymes to exert its physiological function such as vasodilation, through activation of soluble guanylate cyclase, an enzyme that converts guanosine triphosphate (GTP) to cyclic guanosine monophosphate (cGMP) to mediate many of the biological effects of NO [81]. NOS exists in three isoenzymes, namely neuronal NOS (nNOS or NOSI), inducible NOS (iNOS or NOSII) and endothelial NOS (eNOS or NOSIII), all of which are expressed in various cell types despite their names. eNOS and nNOS are constitutively expressed and mediate many

of the beneficial actions of NO while iNOS is a pathological isoform that contributes to pathophysiology of inflammatory conditions [80,81]. Interestingly, results from preclinical and clinical studies have shown marked reduction in endogenous NO level following ischemia and reperfusion of lung grafts, which contributed to lung IRI after transplantation [82–85]. This finding suggests that augmenting endogenous NO level by increasing the activity of NOS in the lung graft could be a novel approach to minimizing lung IRI and preventing its complications after lung transplantation. To this end, exogenous NO gas has been directly administered by inhalation or indirectly via NO donor compounds such as nitroglycerine, nitroprusside, nicorandil, FK409, SIN-1, isosorbide mononitrate and isoamyl nitrate [161]. In addition, the lung donor could also be transfected with an adenovirus containing eNOS before lung graft procurement.

5.1. Nitric oxide gas in lung transplantation

Mounting experimental and clinical evidence shows that administration of gaseous nitric oxide (by inhalation) to lung donors prior to donor lung procurement and/or to recipients during and after reperfusion reduces IRI and improves lung graft function after transplantation.

5.1.1. Nitric oxide gas in rat models of lung transplantation

In a rat model of DCD single-lung allotransplantation, at 1 h after cardiac arrest, ventilation of lung allografts with 40 ppm of NO gas in 60% oxygen for another 1 h followed by a 1-hour storage in an inflated state in Perfadex (LPD-glucose) solution at 4 °C and *ex vivo* perfusion at 37 °C with alveolar gas (5% CO_2, 20% O_2, 75% N_2) supplemented with 40 ppm of gaseous NO. This resulted in marked reduction in wet-to-dry weight ratio, pulmonary vascular resistance, improved oxygenation and significantly increased cGMP level in the lung allograft, with improved eNOS level and reduced levels of iNOS and TNF-α compared to control allografts without NO administration [86] (Fig. 2). This finding suggests that administration of gaseous NO to donors before cardiac arrest and after donor lung procurement protects against lung IRI and improves lung allograft function after transplantation partly by activating NO/cGMP signaling pathway. Interestingly, while NO administration had no effect on inflammation-associated transcription factor nuclear factor-kappaB (NF-κB) and mitogen-activated protein kinase (MAPK) in the lung allografts [86], other studies reported that NO inhibited the activation of these two principal mediators of inflammation in rat vascular smooth muscle cells and mesangial cells via activation of the NO/cGMP signaling pathway [87,88]. This may suggest that the effect of NO administration on NF-κB and MAPK is dependent on the cell type. This promising experimental finding from the rat model of DCD single-lung allotransplantation supports results from previous studies of a similar rat model in which donor lungs were retrieved immediately after cardiac arrest or 2 or 3 hours postmortem [89,90]. In these studies, the lung allografts were flushed with cold Celsior solution and stored in the same solution in an inflated state for 2 hours at 4 °C after ventilated with 100% oxygen supplemented with 30 ppm and 40 ppm of gaseous NO either during the period of warm ischemia, during reperfusion or both. While control lung allografts without NO supplementation suffered severe IRI, which was characterized by high wet-to-dry weight ratio, pulmonary vascular resistance and filtration coefficient, significantly lower values of these measurable variables, with improved lung function and reduced neutrophil sequestration as well as increased lung cGMP were observed in NO-treated allografts [89,90]. These observations imply that in addition to activating the NO/cGMP signaling pathway, administration of NO either during warm ischemia, reperfusion or during both periods also suppresses inflammation and oxidative stress-mediated damage in lung allografts as seen by decreased levels of iNOS and TNF-α and reduced activity of myeloperoxidase (MPO; an important inflammatory enzyme that triggers inflammation and oxidative stress) [90] (Fig. 2). Contrary to the positive results from all these studies, one study found that 20 ppm of inhaled gaseous NO together with room air in a closed chamber immediately after lung transplantation in rats, had no positive impact on IRI and lung allograft rejection [91]. This isolated contradictory observation might be due to technical differences, as other researchers used the same concentration of gaseous NO and reported beneficial effects.

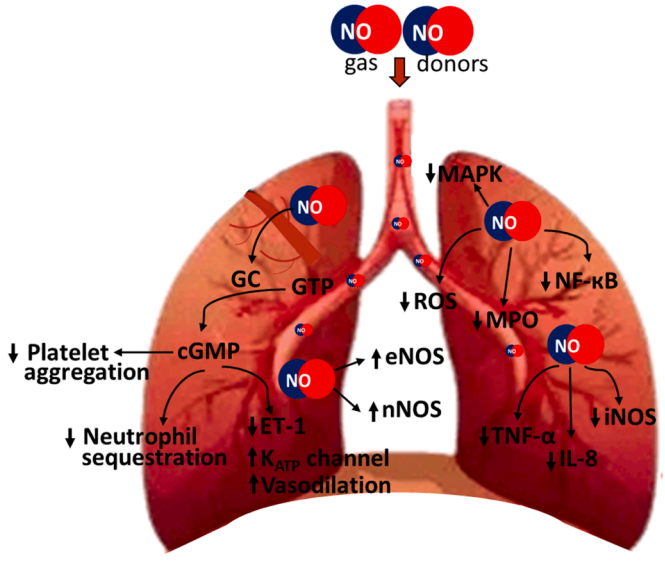

Fig. 2. Mechanism of lung allograft protection by NO. Endogenous NO production or exogenous administration of NO donors mediates lung allograft protection by activating antioxidant and vasodilatory pathways while inhibiting vasoconstrictive and pro-inflammatory pathways. cGMP; cyclic guanosine monophosphate, GTP; guanosine triphosphate, GC; guanylate cyclase, K_{ATP}; potassium-sensitive adenosine triphosphate channel, ET-1; endothelin-1, MAPK; mitogen-activated protein kinase, NF-κB; nuclear factor-kappaB, NO; nitric oxide, sGC; ROS; reactive oxygen species, MPO; myeloperoxidase, eNOS; endothelium nitric oxide synthase, nNOS; neuronal nitric oxide synthase, iNOS; inducible nitric oxide synthase, and TNF-α; tumor necrosis factor-alpha.

5.1.2. Nitric oxide gas in porcine models of lung transplantation

Using a porcine model of DCD single-lung allotransplantation as a large animal model that is directly transferrable to clinical setting, 20 ppm of gaseous NO was added at 2 h after hypoxic cardiac arrest and immediately before perfusion assessment followed by storage in Perfadex solution at 4 °C in an inflated state prior to transplantation. The authors observed significant improvement in pulmonary venous oxygenation, airway pressure and pulmonary vascular resistance along with a marked reduction in neutrophil sequestration in NO-treated lung allografts after transplantation relative to control allografts without NO treatment [92]. Other studies involving DCD single-lung transplantation in minipigs also showed that inhalation of gaseous NO at 20 ppm before and after 2 h of *in situ* warm ischemia followed by a 2-hour preservation period in modified Euro-Collins solution at 4 °C, and inhalation by recipients after allograft reperfusion for 2 h strongly reduced mean pulmonary artery pressure, vascular resistance, lung tissue MPO activity, bronchoalveolar lavage fluid protein content and neutrophils, and increased arterial oxygen tension and pulmonary dynamic compliance, while preserving lung architecture [93,94]. In a porcine model of DCD single-lung autotransplantation in which left lung grafts were preserved in LPD solution in an inflated state for 24 h at 6–8 °C and transplanted into the same donors followed by right pneumonectomy, a 24-hour observation period following transplantation showed that inhalation of gaseous NO in sequential concentration of 5 ppm, 20 ppm and 80 ppm after autotransplantation attenuated endothelial dysfunction by decreasing pulmonary vascular resistance and producing pulmonary vasodilation in proportion to the endothelial dysfunction [95]. To highlight the involvement of neutrophils in lung IRI after lung

transplantation, Gómez and colleagues observed in another porcine model of DCD single-lung allotransplantation that administration of 20 ppm of gaseous NO after cardiac arrest and 30 min before donor lung retrieval followed by reperfusion, resulted in significant improvement in allograft function, which was evidenced by higher dynamic and static compliance and gas exchange, with markedly reduced production of interleukin 8 (a potent neutrophil-specific chemotactic pro-inflammatory cytokine) when compared to control group without NO administration [96]. This result emphasizes the role of neutrophils in allograft IRI after lung transplantation, and also draws attention to the anti-inflammatory property of NO within the pulmonary vessel wall, which contributes to its therapeutic benefit by inhibiting neutrophil activation, aggregation and migration [97] (Fig. 2). This was further demonstrated by Bacha et al. [98] in a porcine model of DCD single-lung allotransplantation in which 30 ppm of gaseous NO was administered to deceased donor and recipient pigs after ventilation with oxygen. In this investigation, lung allografts were flushed with cold Wallworks solution (a type of LPD solution) and the inflated allografts were preserved in the same solution at 4 °C for 2 h after 3 h of postmortem *in situ* warm ischemia, followed by a 9-hour observation period during reperfusion. The authors observed marked inhibition of neutrophil adhesion to pulmonary artery endothelial cells in NO-treated group before and after reperfusion, which positively correlated with reduced neutrophil sequestration in lung allografts, along with improved preservation of lung architecture relative to control group which did not receive NO treatment [98]. As reported by other groups, significantly reduced pulmonary vascular resistance as well as improved oxygenation and prolonged survival were also observed in NO-treated group compared to control group [98], which indeed underscores the important detrimental contribution of neutrophils in the incidence of lung IRI after lung transplantation.

5.1.3. Nitric oxide gas in canine models of lung transplantation

The beneficial effect of gaseous NO in experimental lung transplantation has also been studied in dogs. In a canine model of single-lung DCD allotransplantation to investigate the impact of inhaled NO gas at the time of donor lung retrieval on graft function, lung allografts were flushed with modified Euro-Collins solution and preserved in the same solution at 1 °C for 21 hours after gaseous NO was administered in sequential concentration of 20 ppm, 40 ppm, 60 ppm and 80 ppm for 10 minutes per sequence prior to cardiac arrest [99]. Hemodynamics and arterial blood gas assessment during 6 hours of reperfusion at 37 °C showed significant decrease in pulmonary vascular resistance and wet-to-dry weight ratio, and marked increase in mean arterial oxygen tension in dogs that received NO-treated lung allografts (regardless of NO concentration) in comparison with control group without NO administration. Also, ROS production and MPO activity were significantly reduced in NO-treated allografts compared to control lungs [99], indicating that administration of gaseous NO at the time of donor lung retrieval improves allograft function, at least in part, by suppressing free radical production and neutrophil infiltration (Fig. 2). Following this empirical finding, another group also confirmed the salutary effect of NO inhalation in a similar canine model of single-lung DCD allotransplantation. In their study, Takashima et al. [99] reported that administration of 40 ppm of gaseous NO for the initial 1 hour during reperfusion after 3 hours of warm ischemia, and continuous NO administration during 6 hours of reperfusion greatly reduced pulmonary vascular resistance and MPO activity, improved oxygenation and prolonged recipient survival compared to control group without NO administration. Interestingly, no significant difference in these measurable parameters were observed between the groups that received 1 hour and 6 hours of NO during reperfusion [99,100]. This observation shows that not only does NO inhalation reduce lung IRI and prolong lung allograft function and recipient survival, but also points out that this benefit occurs during the early hours of reperfusion. In a canine model of living-donor double-lung allotransplantation to assess the effect of gaseous NO on early allograft function, continuous inhalation of 40 ppm of NO gas throughout 6 hours of reperfusion resulted in significantly higher oxygen tension, lower pulmonary artery pressure and pulmonary vascular resistance along with reduced wet-to-dry ratio and MPO activity, and thus culminating in increased recipient survival rate compared to control group that received nitrogen gas in the same manner as NO gas [101]. This report further attests the vasodilatory effect of gaseous NO in the pulmonary vasculature as well as its inhibitory effect on neutrophil activation and thereby attenuating IRI after lung transplantation.

5.1.4. Nitric oxide gas in human lung transplantation

Following the promising results from the preclinical studies discussed above, several human clinical trials were conducted in which inhalation of gaseous NO was shown to be indeed safe and beneficial in the treatment of complications arising from lung transplantation. For example, in a prospective non-randomized clinical trial involving 14 patients undergoing lung transplantation due to end-stage lung disease and pulmonary hypertension (indicator of PGD) with mean pulmonary artery pressure higher than 30 mmHg, inhalation of 20 ppm of gaseous NO resulted in significantly less incidence of acute allograft rejection in the first month after transplantation, with shorter hospital stay compared to 22 historical control subjects with matching age, diagnosis and disease severity, who underwent lung transplantation 2 years before this study [102]. This impressive clinical outcome corroborates the result of a previous prospective clinical dose-response study to assess the impact of low-dose NO gas on cardiopulmonary parameters in early lung allograft dysfunction after transplantation. In this clinical trial, inhalation of gaseous NO in sequential concentrations of 1 ppm, 4 ppm and 8 ppm by 8 patients, who had undergone single- or double-lung transplantation, markedly lowered their elevated mean pulmonary artery pressure and improved their arterial oxygen tension/fractional inspired oxygen ratio (PaO_2/FiO_2; indicator of PGD) in a dose-dependent manner [103]. This suggests that low-dose gaseous NO could provide therapeutic benefit in complications such as impaired gas exchange and pulmonary hypertension resulting from PGD after lung transplantation. In another clinical study, prolonged treatment of lung transplant recipients (who developed pulmonary hypertension) with low-dose gaseous NO (10 ppm) over 40–69 hours decreased pulmonary artery pressure, pulmonary vascular resistance and intrapulmonary shunt fraction (the main cause of hypoxemia) as well as mean arterial pressure and systemic vascular resistance without any side effects [104]. In addition, low-dose gaseous NO produced a stained improvement in oxygenation. Interestingly, high dose (80 ppm) produced the same salutary effect without affecting systemic hemodynamics [104,105]. These observations indicate that NO therapy could prevent PGD following lung transplantation.

In a retrospective clinical study in which 15 lung transplant recipients inhaled 20–60 ppm of gaseous NO for 15–217 hours, the authors reported that NO therapy attenuated PGD by improving PaO_2/FiO_2 ratio within 1 hour of therapy, and reducing pulmonary artery pressure, with sustained improvement during prolonged treatment compared to 17 lung transplant recipients without NO therapy [106]. Remarkably, no systemic circulatory effects were recorded in NO-treated patients. Neither were any complications associated with NO therapy. Also, NO-treated patients had a significantly shorter post-operative mechanical ventilation time, with reduced mortality in comparison with their counterparts without NO administration [106]. In another clinical investigation to evaluate retrospectively the protective effect of coadministration of gaseous NO (10 ppm) and 400 mg pentoxifylline (an activator of endogenous NO production) after lung transplantation, coadministration of these two agents to 23 lung transplant recipients prophylactically during reperfusion resulted in a marked decrease in the incidence of PGD by reducing reimplantation edema, improving PaO_2/FiO_2 ratio, shortening post-operative mechanical ventilation time, and reducing 2-month mortality rate when compared to two historical

control groups (23 and 95 patients) [107]. This clinical report shows that prophylactic treatment with gaseous NO (and NO donor) is beneficial in the early post-operative course in lung transplant recipients. Likewise, inhalation of 40 ppm of NO gas followed by a gradual dose reduction before and after single- and double-lung transplantation resulted in markedly reduced mean pulmonary artery pressure, with improvement in arterial oxygenation and overall respiratory function, and no significant effect on systemic circulation. Also, duration of mechanical ventilation and mortality rate were significantly reduced [108]. To assess the effect NO inhalation on the endogenous NOS system, Cardella and associates [109] performed lung biopsy on lung transplant recipients who inhaled 20 ppm of gaseous NO or placebo (10 minutes after start of reperfusion) in a randomized phase II clinical trial. In this study, the authors collected lung tissues after warm and cold ischemia, 1 hour and 2 hours after the start of reperfusion, and reported that protein expression of constitutive NOS (eNOS and nNOS) increased significantly after 2 hour of reperfusion in NO-treated lung allografts but decreased in placebo group, while iNOS protein expression did not change significantly in both groups [109] (Fig. 2). Although the randomized phase II clinical trial did not report on the effect of NO inhalation in the lung transplant recipients, the upregulated expression of constitutive NOS proteins in the NO-treated lung allografts points to a possible interaction between gaseous NO molecules and the lung tissues.

Despite these exciting clinical outcomes with gaseous NO, there are a few conflicting reports. In a prospective clinical trial to investigate the role of gaseous NO in preventing IRI in lung transplant recipients, prophylactic administration of gaseous 20 ppm of NO to 28 lung transplant recipients during reperfusion followed by withdrawal for 15 minutes at 6 and 12 hours after reperfusion caused marked increase in pulmonary artery pressure and decrease in oxygenation index in 5 out of the 28 recipients who developed IRI, while the remaining 23 recipients had no IRI and no adverse events in the early post-operative course [110]. Meade et al. [110] also reported that there was no effect of gaseous NO on the outcome after lung transplantation. In their randomized, double-blinded, placebo-controlled clinical trial involving 84 lung transplant recipients, inhalation of 20 ppm of gaseous NO by 42 lung transplant recipients at 10 minutes after reperfusion produced no significant difference in hemodynamics, severity of IRI, immediate oxygenation, duration of mechanical ventilation and hospital stay, and 30-day mortality compared to 42 placebo-treated group [111]. Following these findings, Botha and colleagues [112] also observed a similar result in which 20 bilateral sequential lung transplant recipients were administered either 20 ppm gaseous NO or a standard anesthetic gas mixture (control group) during the first 30 minutes of reperfusion. Between both groups, there was no statistically significant difference in the effect of gaseous NO and the standard anesthetic gas mixture on the development of Grade II to III PGD, PaO_2/FiO_2 ratio, pulmonary neutrophil sequestration and the concentrations and levels of interleukin-8, nitrotyrosine (an oxidative stress marker) and MPO activity in epithelial lining fluid and bronchoalveolar lavage fluid during transplantation [112]. In the face of these refuting clinical findings, the therapeutic benefits of inhaled NO after clinical lung transplantation cannot be entirely ruled out, as NO is superior to other vasodilators, and its selectivity nature makes it suitable to target the pulmonary vasculature without significant adverse effects on systemic circulation. However, additional prospective randomized studies would be necessary to further demonstrate and standardize gaseous NO therapy against IRI and its associated complications after clinical lung transplantation.

5.2. Nitric oxide donors in lung transplantation

In addition to gaseous NO, several NO donor compounds such as nitroglycerine, nitroprusside, nicorandil, FK409, SIN-1, isosorbide mononitrate and isoamyl nitrate, have also been investigated and found to exhibit similar therapeutic benefits as gaseous NO in various animal models of lung transplantation. Following their administration, these pharmacologically active compounds spontaneously release NO or are metabolized to NO independent of its endogenous sources. Thus, they are exogenous sources of NO. Interestingly, NO donors exhibit different pharmacological properties that determine the type and degree of their effects on biological systems [113]. In addition, their experimental utilization has shed more light on the protective molecular mechanisms of NO in lung transplantation.

5.2.1. Nitric oxide donors in rat models of lung transplantation

Using an *in situ* isolated perfused rat model to investigate the effect of nitroglycerin on IRI, rat lungs were procured at varying intervals following cardiac death and reperfused at intervals with Earle's balanced salt solution (a physiological solution). In this study, the authors reported an increase in capillary filtration coefficient (Kfc) at all post-mortem ischemic times and decreases in the levels of cGMP and adenine nucleotides. However, addition of 0.1 mg/mL of nitroglycerin to the solution caused a substantial decrease in Kfc and increases in cGMP and adenine nucleotide levels compared to reperfused lungs without nitroglycerin supplementation [114]. This suggests that addition of nitroglycerin to preservation solutions may prevent capillary leak after reperfusion and thus, may improve DCD lung transplantation outcomes. The observed increase in cGMP level following nitroglycerin supplementation supports the established evidence that nitroglycerin is an organic nitrate that releases NO and intermediates intracellularly to directly stimulate cGMP production from GTP [81,115] (Fig. 2). In another rat model to specifically assess the effect of nitroglycerin during early post-ischemic period, donor lungs inflated with room air, were preserved in Perfadex solution at 10 ℃ and supplemented with 0.1 mg/mL of nitroglycerin followed by reventilation and reperfusion for 50 minutes. This resulted in significantly reduced flush-perfusion time, higher oxygenation capacity and reduced intrapulmonary edema, with markedly improved pulmonary vascular resistance and peak inspiratory pressures relative to control lungs without nitroglycerin treatment [116]. The result indicates that stimulation of the NO pathway by NO donors may enhance early functional outcome of lung allografts in clinical lung transplantation. Similar improvement in pulmonary function was obtained in an *ex vivo* rat lung perfusion model in which the donor lungs were flushed with and stored in nitroglycerin-supplemented extracellular-type Kyoto solution at 4 ℃ for 15 hours and then reperfused for 60 minutes [117]. Compared to control lungs, addition of nitroglycerin (0.44 mM) to the preservation solution also lowered shunt fractions substantially throughout reperfusion, reduced lung wet-to-dry weight ratio, maintained cGMP level in lung tissue, which decreased during preservation and reperfusion, and attenuated oxidative stressed-induced DNA damage evidenced by decreased expression of 8-hydroxy-2'-deoxyguanosine (8-OHdG) in alveolar epithelium, pulmonary endothelium and bronchial epithelium to levels comparable to fresh lungs, and thus improved post-reperfusion pulmonary function [117]. The antioxidant property of nitroglycerin has been reported in *in vivo* and *in vitro* models as well as in clinical studies of myocardial ischemia and reperfusion in which it scavenged ROS and decreased toxic metabolites [118–120], and therefore may have partly contributed to the attenuation of IRI in the *ex vivo* rat lung perfusion model. The study also confirmed previous rat models of lung transplantation, showing that addition of nitroglycerin to different preservation solutions attenuates lung IRI, improves pulmonary function and prolongs recipient survival after transplantation [121–124].

Minanoto and colleagues [125] also noted in a rat model of isogeneic single-lung transplantation that early administration of 0.1 mg/mL of nitroglycerin during flushing and 6 hours of preservation in modified Euro-Collins solution at 4 ℃ followed by *ex vivo* flushing with normal saline, caused a decrease in vascular tone as well as pulmonary artery pressure and pulmonary vascular resistance in lung isografts, and improved gas exchange and recipient survival after lung transplantation. Interestingly, administration of nitroglycerin to grafts immediately before transplantation, did not produce the post-transplantation benefits

of early nitroglycerin treatment. Surprisingly, the result of late nitroglycerin treatment was similar to control group, which did not receive nitroglycerin administration [125], suggesting that early treatments of donor lungs during procurement and preservation creates sufficient priming and protective internal environment against IRI after transplantation. Mechanistically, the vascular response of the isografts to early treatment with nitroglycerin was reported to be via downregulated expression of endothelin-1 (ET-1; a potent vasoconstrictor) mRNA and protein [125] (Fig. 2). This was confirmed by a later study of normothermic *ex vivo* perfusion of transplantation-declined human lungs obtained from DCD. In this *ex vivo* study, the authors reported significantly higher levels of ET-1 and Big ET-1 (the precursor of ET-1) in the perfusates at 1 and 4 hours of *ex vivo* perfusion in comparison with control lungs from bilateral transplantation with good early outcomes [126]. This result may imply that perfusate ET-1 and Big ET-1 could serve as biomarkers of lung allograft function during *ex vivo* lung perfusion and following clinical lung transplantation. Besides its role in promoting vasoconstriction, it is worth noting that ET-1 also increases vascular permeability, stimulates neutrophil accumulation, and promotes coagulation, which have been reported in animals and humans with pulmonary hypertension and also observed in lung allografts after transplantation [127–133]. NO is known to prevent adherence of neutrophils and platelets to vascular endothelium, and thereby decreasing leukocytes extravasation into lung parenchyma. This action inhibits cytokine production and thereby prevents vascular permeability. Considering that both ET-1 and NO are in reciprocal balance to regulate vascular tone, including pulmonary vasomotor tone, the observation that nitroglycerine suppresses ET-1 mRNA and protein expression suggests that the vasodilatory effect of NO may be via inhibition of ET-1 production (Fig. 2). On the whole, supplementation of preservation solutions attenuates lung IRI, improves lung allograft quality and function, reduces post-transplant complications, and prolongs recipient survival after transplantation.

5.2.2. Nitric oxide donors in rabbit models of lung transplantation

In an isolated, ventilated, whole-blood-perfusion rabbit lung model, lungs were retrieved *en bloc*, flushed and preserved in an inflated state in Euro-Collins solution for 18 hours at 4 ºC followed by reperfusion at a physiologic flow rate of 60 mL/min for 30 minutes with nitroprusside infusion at 0.2, 1.0 and 5.0 μg/kg/min through the pulmonary artery during reperfusion. Compared to control lungs without nitroprusside supplementation, nitroprusside infusion markedly decreased pulmonary artery pressure and pulmonary vascular resistance in a dose-dependent manner, with additional substantial improvements in wet-to-dry lung weight ratio, arteriovenous oxygen gradient and dynamic airway compliance without significant systemic hypotension [134]. This shows that direct intravascular infusion with NO donors during reperfusion ameliorates IRI immediately after lung transplantation. Although the authors did not measure endogenous NO level in their model, nitroprusside is a short-acting, non-selective, and direct NO donor that releases NO into the vascular smooth muscle cell without requiring enzymatic conversion, leading to dilation of all blood vessels. Thus, nitroprusside increases endogenous NO level and thus activates NO/cGMP signaling pathway that leads to vasodilation (Fig. 2). In another rabbit model of IRI in buffer-perfused rabbit lungs in which warm ischemic time lasted for 150 min and anoxic ventilation and a positive intravascular pressure were maintained throughout the ischemic period and followed by 30 min of reperfusion, aerosol delivery of 0.126 μmol of nitroprusside over 5 min into alveoli at 5 min after the onset of ischemia significantly lowered pulmonary artery pressure elevation and capillary leakage response, and preserved physiological gas exchange conditions after reperfusion, leading to less lung edema formation in comparison with control lungs without nitroprusside treatment [135]. A similar isolated buffer-perfused rabbit lung model with longer ischemic time of 180–210 min, with the same dose and route of administration of nitroprusside but delivered at either 5 min after the onset of ischemia or 10 min prior to reperfusion, reduced precapillary elevation of vascular resistance, Kfc and preserved normal pulmonary hemodynamics and microvascular integrity. Interestingly, nitroprusside administration at the onset of reperfusion was less effective [136]. Esme et al. [137] also reported in a rabbit model of *in situ* normothermic ischemic lung that administration of nitroglycerin during flush perfusion and reperfusion markedly improved arterial oxygenation, decreased neutrophil level in bronchoalveolar lavage fluid, with lower tissue histopathological lesion scores and higher nitrate level when compared to control lungs without nitroglycerin treatment. Interestingly, administration of nitroglycerin during flush perfusion period alone did not produce these beneficial effects [137], demonstrating that nitroprusside administration during *in situ* flush perfusion and reperfusion is more protective against lung IRI than other treatment modalities. L-arginine (20 mg/kg; NO precursor) and pentoxifylline (50 mg; enhancer of endogenous NO production [138] added to lactated Ringer solution just before reperfusion after 4–48 h preservation of lungs at 10 ºC, preserved endothelium functional integrity and reduced IRI in a rabbit model of lung transplantation [139]. Taken together, administration of nitric oxide donors protects against IRI and preserves allograft function after lung transplantation.

5.2.3. Nitric oxide donors in canine models of lung transplantation

In canine model of single-lung allotransplantation, addition of 10 mg/L of nitroprusside during flush perfusion in one experimental group, followed by storage of the inflated lung allografts in modified Euro-Collins solution at 1 ºC for 21 hours, and then bolus injection (0.2 mg/kg) in recipient animals prior to reperfusion as well as continuous infusion at a rate of 0.1 mg/kg/hr during a 6-hour reperfusion period in another experimental group showed amelioration of IRI and preserved lung allograft function in both nitroprusside-treated groups [140,141]. This was characterized by markedly improved respiratory gas exchange and pulmonary hemodynamics, lower wet-to-dry weight ratio and reduced neutrophil accumulation compared to control group without nitroprusside supplementation. Interestingly, no significant difference was observed between both nitroprusside-treated groups [140,141], indicating that both treatment modalities are effective in limiting IRI after lung allotransplantation. In another study by the same authors, replacing nitroprusside with pentoxifylline using the same experimental protocol produced the same salutary effects, with significantly decreased neutrophil adhesion to endothelium as well as reduced protein levels and neutrophil concentration in bronchoalveolar lavage fluid [142]. Akin to this finding, Yamashita and associates [143] also reported in another canine model of single-lung allotransplantation that nicorandil enhances allograft preservation, improves gas exchange and prevents allograft dysfunction after transplantation. In their investigation, they used the same protocol and treatment modalities in which supplementation of flush solution with 24 mg/L of nicorandil, and intravenous administration (0.5 mg/kg) to recipient dogs at the onset of reperfusion followed by continuous infusion (0.74 mg/kg/hr) during 6 hours of reperfusion and assessment period. Considering that nicorandil is an opener of adenosine triphosphate-sensitive potassium (K_{ATP}) channel in addition to being a generator of endogenous NO, intravenous administration of glibenclamide (3.0 mg/kg; a specific K_{ATP} channel blocker) 15 minutes prior to donor lung flush and before nicorandil administration, as well as to recipients (1.0 mg/kg) 15 minutes before nicorandil bolus injection and also infused during reperfusion at a rate of 0.3 mg/kg/hr, abrogated the therapeutic effects of nicorandil [143]. This observation provides another mechanism of protection, which shows that NO reduces lung allograft IRI partly by activating and opening K_{ATP} channels (Fig. 2). K_{ATP} channels regulate pulmonary vascular tone, and their inhibition has been recently found to induce and increase hypoxic pulmonary vasoconstriction in murine endotoxemic lungs [144], implying that activation of K_{ATP} channels favors pulmonary vasodilation. Besides activating K_{ATP} channels in lung allografts, nicorandil may have also activated NO-sGC-cGMP signaling pathway, as was

reported to protect against IRI in isolated rat lungs [145]. At the subcellular level, NO was found to directly activate mitochondrial K_{ATP} channels and contributed to cardioprotection [146]. Although this has not been investigated in lung transplantation, it is possible that nicorandil and endogenous NO may have activated mitochondrial K_{ATP} channels in the lung allografts, and thereby contributing to attenuating IRI after lung transplantation.

The therapeutic impact of NO donors in canine lung transplantation was further studied using FK409, an organic NO donor which spontaneously releases NO. In a canine model of orthotopic single-lung allotransplantation, 5 μg/kg/min of FK409 was intravenously infusion 30 minutes before ischemia until the onset of ischemia in donor dogs, followed by preservation of lung allografts in Euro-Collins solutions at 4 ºC for 8 hours, and then FK409 administration from 15 minutes before reperfusion until 45 minutes after reperfusion. Compared to control lung allografts which did not receive FK409 treatment, FK409-treated allografts functioned adequately after reperfusion as revealed by pulmonary perfusion and ventilation scintigraphy [147]. This suggests good pulmonary hemodynamics and blood-gas exchange, leading to prolonged post-transplant survival. Histopathologically, FK409 markedly reduced alveolar damage, which was increased with severe interstitial, alveolar and alveolar-septal edema in control lung allografts [147]. Also, serum NO level in FK409-treated group significantly increased at the end of ischemia and reperfusion, which corresponded with markedly decreased serum ET-1 level in comparison with control group [147]. This observation further highlights the vasodilatory property of NO and its beneficial effect after lung transplantation. Collectively, NO donors improve lung allograft function and prolong recipient survival in canine models of lung allotransplantation via mechanisms including activation and opening of K_{ATP} channels and inhibition of ET-1 activity (Fig. 2).

5.2.4. Nitric oxide donors in porcine models of lung transplantation

Besides rat, rabbit and canine models, the effect of nitric oxide donors in lung transplantation has also been studied experimentally in pigs. Using a porcine model of DCD single-lung transplantation, lung allografts were ventilated with 100% oxygen and flushed with Perfadex solution 90 minutes after cardiac arrest and then preserved in an inflated state in Ringer's solution at 4 ºC for 18 hours. Continuous infusion of nitroglycerin at an increased stepwise rate of 0.3, 0.4 and 2.4 mg/kg/min in the reperfusion circuit and at a rate of 2.0 μg/kg/min in recipient pigs starting 5 minutes prior to reperfusion preserved pulmonary gas exchange, which was significantly impaired in control lungs that were flushed and retrieved immediately after cardiac arrest [148]. However, neutrophil count and protein concentration in bronchoalveolar lavage fluid as well as histological changes were unchanged compared to control group [148]. This result demonstrates that administration of nitric oxide donors in the early phase and during reperfusion improves DCD lung allograft function following prolonged preservation. Along the same train of evidence, Clark and colleagues [149] also showed in another porcine model of DCD single-lung allotransplantation that after flushing and preservation of lung allografts in modified Euro-Collins solution for 18 hours, intravenous infusion of 0.02 mg/kg/h of SIN-1 (NO donor which spontaneously releases NO) during reperfusion significantly lowered pulmonary vascular resistance, improved oxygenation and attenuated neutrophil sequestration relative to control allografts without SIN-1 infusion. In the same study, pentoxifylline infusion at 2 mg/kg/h also produced the same result as SIN-1, with superior oxygenation and a further decrease in ROS production [149]. Similarly, administration of nitroprusside attenuated IRI and improved porcine allograft function. In their study of single-lung allotransplantation in pigs, Kukkonen et al. [150] observed that continuous infusion of nitroprusside at a rate of 9.0 μg/kg/min markedly lowered pulmonary vascular resistance, however, with a 44% decline in systemic vascular resistance compared to control group that received equal amount of vehicle [150]. The observation that nitroprusside caused such a substantial decline in systemic vascular resistance suggests that the infusion rate was too high and may have mediated prolonged systemic vasodilation. Interestingly, lower infusion rates of 1.0 and 3.0 μg/kg/min did not have significant effect on pulmonary hemodynamics. In summary, infusion of NO donors during reperfusion improves allograft function in porcine models of lung allotransplantation.

5.3. Role of inducible nitric oxide synthase in lung transplantation

As mentioned in Section 5.0, inducible nitric oxide synthase (iNOS) is a pathological isoform of NOS, and its expression has been shown to be upregulated in lung IRI and contributes to acute graft rejection following lung transplantation. Therefore, inhibition of iNOS expression is emerging as an attractive therapeutic approach for prevention of IRI and acute allograft rejection after lung transplantation. In a study to investigate the role of iNOS in acute lung allograft rejection, intraperitoneal administration of 200 mg/kg of aminoguanidine (a selective iNOS inhibitor) every 6 hours for 6–12 days in recipient rats after lung allotransplantation significantly reduced acute allograft rejection as observed histologically and radiographically compared to saline-treated control group [151,152]. iNOS inhibition also resulted in reduced NO production and prolonged recipient survival without inducing immunological tolerance when compared to control group [151,152]. It is important to note that iNOS is an important immunomodulation molecule in allograft rejection, and overproduction of NO can induce cytotoxicity via its reaction with superoxide to produce peroxynitrite, a toxic reactive nitrogen species [153]. Therefore, the observation that iNOS inhibition reduced NO production and suppressed early lung allograft rejection suggests that NO produced by iNOS during early lung allograft rejection may serve as a sensitive biomarker that indicates the functional status of the lung allograft while mediating early graft rejection. In a similar rat model of acute lung allograft rejection, upregulated expression of iNOS mRNA and protein in transplanted lung along with increased influx of inflammatory cells and NO production (as seen in increased levels of serum nitrate and nitrite) was observed [154,155]. However, iNOS inhibition with 250 mg/kg aminoguanidine (administered subcutaneously) every 12 hours beginning immediately after transplantation until post-operative day 5 (day of sacrifice) resulted in significant downregulation of lung allograft iNOS mRNA and protein expression, reduction in NO production and improvement in histological rejection scores, and thus preventing allograft rejection [154,155]. In addition, iNOS inhibition also preserved allograft function, which was impaired in the control group. These results further support experimental evidence showing that iNOS-derived NO could be used as an excellent diagnostic indicator of early graft rejection, and that iNOS could be an important therapeutic target for the prevention of acute allograft rejection after lung allotransplantation.

6. Conclusion

Lung transplantation has become a routine clinical practice and the only therapeutic option for patients suffering from a variety of end-stage pulmonary diseases. However, despite significant success achieved in this field, including improvement in surgical techniques and modification of preservation solutions, PGD and other post-transplant complications arising from IRI continue to increase morbidity and mortality rates after transplantation, and thereby limiting the success of these important life-saving undertakings. Among the factors that contribute to IRI after lung transplantation is the significant decrease in endogenous NO production, which suggests that NO pathway can be a potential therapeutic target, whose activation might be beneficial in attenuating IRI after lung transplantation. Bearing this in mind, there has been several preclinical studies and clinical evidence showing that direct administration of gaseous NO to lung donors prior to donor lung procurement, or to recipients, or administered indirectly by supplementing preservation solutions with NO donor compounds attenuates IRI,

improves graft quality and function and prolongs recipient survival without causing any unfavorable systemic hemodynamic changes. Therefore, these empirical findings suggest that NO should be routinely used in clinical lung transplantation. Additionally, high expression levels of iNOS along with its increased NO production, has been consistently associated with increased incidence of IRI, PGD, post-transplant morbidity and mortality in experimental and clinical lung transplantation. Therefore, iNOS-derived NO may be considered a potential and reliable diagnostic biomarker for allograft rejection after lung transplantation.

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Declaration of Competing Interest

The author declares that there is no conflict of interest.

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