Long-acting oral phosphodiesterase inhibition preconditions against reperfusion injury in an experimental lung transplantation model

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Objectives: Ischemia–reperfusion injury remains a devastating complication of lung transplantation. Phosphodiesterase inhibitors have been shown to precondition tissues against ischemia–reperfusion injury. Little is known, however, about the utility of phosphodiesterase inhibition in reperfusion injury after lung transplantation. We evaluated the long-acting phosphodiesterase-5 inhibitor, tadalafil, in an ex vivo lung transplant model.

Methods: New Zealand White rabbits (4 kg), were given oral tadalafil (n = 11) 24 hours before lung harvest and compared with rabbits given oral vehicle alone (n = 11). Lungs were recovered with Perfadex solution (Vitrolife, Kungsbacka, Sweden) and cold stored for 18 hours. After storage, lung blocks were reperfused with donor rabbit blood in an ex vivo apparatus. Pulmonary artery pressures were recorded with serial arterial and venous blood gas sampling and animals served as their own controls. Phosphodiesterase-5 and protein kinase G tissue activity assays confirmed drug effects. Luminol chemiluminescence assay was used to measure reactive oxygen species and levels of endothelial and inducible nitric oxide synthase were measured.

Results: Extended cold storage, followed by reperfusion produced a consistent reproducible decrease in oxygenation and increase in pulmonary pressure. Tadalafil-treated animals exhibited greater Pao_2 throughout the course of reperfusion ($P = .001$) Mean pulmonary artery pressure was lower in tadalafil-treated animals (22 vs 40 mm Hg; $P = .04$). Phosphodiesterase-5 activity was decreased (143 ± 8 vs 205 ± 32 mP; $P < .001$) with protein kinase G activity increased (25 ± 12 vs 12 ± 2.4 fU/μg; $P = .01$) in the experimental group confirming that oral pretreatment resulted in active phosphodiesterase inhibition in the lung tissue. Reactive oxygen species (as measured by luminol activity) were decreased in tadalafil-treated animals (7.8 ± 1.5 vs 10.2 ± 1.2 relative light units; $P = .003$).

Conclusions: Our experimental model demonstrates that oral donor pretreatment with a long-acting phosphodiesterase inhibitor is an effective strategy for improving pulmonary performance after reperfusion. Importantly, phosphodiesterase enzymes and their downstream effectors may play a critical role in reperfusion injury after lung transplantation.

Despite 20 years of successful lung transplantation, primary graft dysfunction (PGD) remains a significant and devastating cause of early postoperative respiratory failure.[1,2] Occurring in up to 20% of lung transplant recipients, PGD is characterized by the development of progressive hypoxemia, increased pulmonary pressures, and pulmonary edema.[3] Patients in whom PGD develops have increased rates of rejection and infection, longer intensive care unit and hospital lengths of stay, and greater short- and long-term mortality.[1,2,4-7]

Alterations in pulmonary vascular resistance, microvascular permeability, and gas exchange support the belief that injury in PGD is primarily caused by ischemia and reperfusion (IR).[8] Several studies have suggested an important role for nitric oxide (NO) signaling pathways mediated by secondary messengers such as cyclic guanosine monophosphate (GMP). Models of lung IR injury have demonstrated that reduced levels of cyclic GMP[9] and low levels of cyclic GMP after lung reperfusion have been associated with the development of pulmonary hypertension,[10] reduced oxygenation,[11] and increased microvascular permeability.[8,10]

The importance of NO signaling via cyclic GMP suggests an opportunity for preconditioning via modulation of this pathway. The phosphodiesterase (PDE) enzymes represent a class of 11 distinct isoenzymes responsible for hydrolysis of cyclic nucleotides.[12] Of these, PDE5 is perhaps the best known because of its high specificity for cyclic GMP and

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Abbreviations and Acronyms

eNOS	= endothelial nitric oxide synthase
GEE	= generalized estimating equation
GMP	= guanosine monophosphate
iNOS	= inducible nitric oxide synthase
IR	= ischemia and reperfusion
NO	= nitric oxide
NOS	= nitric oxide synthase
PA	= pulmonary artery
PAP	= pulmonary artery pressure
P_{CO_2}	= partial pressure of carbon dioxide
PDE	= phosphodiesterase
PGD	= primary graft dysfunction
PKG	= protein kinase G
P_{O_2}	= partial pressure of oxygen
RM-ANOVA	= repeated-measures analysis of variance
ROS	= reactive oxygen species

availability of specific Food and Drug Administration–approved inhibitors used primarily for the treatment of erectile dysfunction and pulmonary hypertension. Through augmentation of cyclic GMP levels, PDE inhibition may protect against the deleterious effects of IR injury after lung transplantation.

Tadalafil (Cialis; Lilly ICOS, Indianapolis, Ind) is a selective PDE5 inhibitor that was approved for the treatment of erectile dysfunction in 2003. Tadalafil is distinct from other commonly used selective PDE5 inhibitors (ie, sildenafil or vardenafil) in that it possesses a substantially longer half-life (17.5 hours).[13-15] Tadalafil is furthermore readily bioavailable when administered orally, reaching peak levels approximately 2 hours after administration. Because of these pharmacokinetic properties, tadalafil is a potentially attractive agent for donor preconditioning before lung transplantation.

Although much research has focused on treatment of IR at the recipient level, few studies have investigated donor preconditioning as a means to prevent IR injury after transplantation. Further, to our knowledge, no study has investigated the use of oral tadalafil as a preconditioning agent. Given the potential therapeutic role for PDE inhibition in PGD, we hypothesized that pretreatment with a long-acting oral selective PDE5 inhibitor will reduce reperfusion injury and graft dysfunction in an ex vivo experimental model of lung transplantation.

METHODS

Model

We conducted these experiments with an ex vivo lung reperfusion model whereby rabbit lungs are externally ventilated and perfused with donor rabbit blood. The experiment used male New Zealand White rabbits (Myrtle's Rabbitry Inc, Thompson Station, Tenn) weighing 3 to 4 kg. All studies were approved by the Animal Care and Use Committee at the Johns Hopkins University.

Experimental Protocol

Protocol in brief. A total of 26 rabbits were arbitrarily divided into 2 experimental groups and underwent en bloc heart–lung harvest followed by 18 hours of cold storage. These heart–lung blocks were reperfused (18 hours after harvest) with donor rabbit blood for 180 minutes while physiologic data were recorded.

Experimental Groups

Thirteen animals (experimental group) received 1 mg of oral tadalafil (Toronto Research Chemicals, Inc, North York, Ontario, Canada) dissolved in 0.5 mL of dimethyl sulfoxide (JHU Core Store; Sigma Chemical Co, St Louis, Mo) 6 hours before lung harvest (24 hours before reperfusion). The second set of 13 rabbits (control group) received 1 mL of oral dimethyl sulfoxide only administered in an identical time frame. Four animals were excluded owing to technical complications relating to surgery. In all 4 cases, a pulmonary artery (PA) injury occurred during harvest (see procedure below) and when it became clear that PA perfusion was compromised, the experiment was aborted with no additional data collected. The final study population thus comprised 22 subjects (11 experimental and 11 controls).

Heart–Lung Block Harvest

Experimental rabbits were anesthetized with intramuscular injection of ketamine (35 mg/kg) and xylazine (6.5 mg/kg) with intravenous acepromazine (5 mg/kg) given as needed for additional sedation. A tracheotomy was performed for endotracheal intubation and mechanical ventilation (forced expiratory volume in 1 second 100%) was initiated (Harvard ventilator apparatus, model 665; Harvard Apparatus Co, Holliston, Mass). Through a midline incision and medium sternotomy, the chest was entered and the superior and inferior venae cavae, aorta, and PA were isolated. Intravenous heparin (1000 U/kg) was given, and 30 μg of prostaglandin E_1 was administered directly into the PA. The PA was cannulated via a right ventriculotomy. An incision was made within the left ventricle for venting, and cold (4°C) Perfadex solution (Vitrolife, Kungsbacka, Sweden) was run by gravity drainage into the lungs through the PA cannula. The superior and inferior venae cavae and aorta were ligated and a left atrial cannula was placed through the left ventricle. After placement of cannulas, cold ice slush was placed surrounding the heart–lung block, and this block was excised from within the mediastinum. The lungs were inflated, and the block was placed within a bag of Perfadex solution and cold stored (4°C) for 18 hours.

Perfusion Pump System

After cold storage, the heart–lung block was suspended by the trachea and ventilated at 10 mL/kg, 30 breaths/min, at 100% forced expiratory volume in 1 second. Two donor rabbits were heparinized (1000 U/kg) and exsanguinated to obtain approximately 300 mL of whole blood. All animals were perfused for 180 minutes with this donor blood using a Sarns 5000 roller head pump (Sarns, Inc, Ann Arbor, Mich). Arterial blood removed from the left atrial cannula was collected in a reservoir and deoxygenated to achieve a P_{O_2} and P_{CO_2} of 60 mm Hg (simulating venous blood). Venous blood was then pumped into the PA cannula for reperfusion.

Hemodynamic Measurements

Physiologic measurements were recorded initially and then every 15 minutes for the full 180 minutes of perfusion. Pressure transducers recorded pressures for fluid-filled lines including PA and left atrial pressures. Arterial and venous blood sampes were collected every 15 minutes for blood gas sampling (arterial blood gas analyzer, model 348, Chiron Diagnostics, Norwood, Mass).

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