• 系統編號	RN9704-0393		
• 計畫中文名稱	吸入性氧氣濃度、一氧化氮及肺內皮素阻斷劑對於豬左肺自體移植後局部通氣及血流的影響		
• 計畫英文名稱	The Effect of Inhaled Oxygen, Nitric Oxide and Endothelin Blockers on Ventilation and Perfusion Matching Post Lung Transplantation		
• 主管機關	行政院國家科學委員會	• 計畫編號	NSC95-2314-B016-042
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• 研究人員	張宏 Chang, Hung		
• 中文關鍵字	缺血及再充血肺損傷;肺臟移植;局部肺血流及通氣;肺部氣體交換;單側肺部通氣及呼吸;一氧化氮及肺血管內皮素阻斷劑		
• 英文關鍵字	Lung transplantation; Pulmonary gas exchange; Ischemia-reperfusion lung injury; Inhaled oxygen; Cytokine; Regional blood flow distribution; Nitric oxide; Endothelin blocker		
• 中文摘要	有 10 ~ 20%肺臟移植後的患者，面臨肺移植體衰竭而呈現動脈低血氧及氣體交換急劇變差的現象。肺移植時充血及再充血機轉所造成的肺損傷被認為是造成肺移植體衰竭的主要原因。亦是胸腔外科及加護病房醫生照顧此種病患揮之不去的夢魘，過去少數且結果矛盾的研究顯示移植後的肺血流減少且肺血管阻力增加，但是肺移植缺血及再充血造成氣體交換變差的機轉仍不是很清楚。有效率的氣體交換端視局部肺血流及通氣的分佈完全吻合，過去的研究顯示肺局部血流及通氣的分佈受到重力、肺容積變化及缺氧性肺血管收縮等因素影響。最近的研究用高解析度螢光顆粒球標記局部肺血流及通氣，發現肺血管及支氣管的分叉構造才是主要決定肺血流及通氣的因素。這新發現對於肺血流分佈過去的認知提出嚴重的質疑。吸入性一氧化氮及低潮汐高吐氣末正壓呼吸對於改善及保護肺移植後缺血及再充血肺損傷有助益，但是氣體交換改善的機轉依然不清楚。我們假設移植肺及存留肺局部肺血流分佈不同並且局部通氣及血流吻合於存留肺較移植肺有效率。移植肺以 100%氧氣通氣呼吸比以 21%氧氣通氣於缺血及再充血後能維持較佳的肺功能，但是也有研究顯示 50%及 100%氧氣的供給較呼吸大氣中的含氧會造成更嚴重的肺損傷。吸入高濃度的氧氣會造成脂質過度氧化，肺容積及氣道壓力喪失減少。吸入氧分壓對於肺移植缺血再充血後局部通氣及灌流吻合的影響，至今尚未被仔細研究過。如何以適度的氧氣照護病患而不致引發肺損傷亦無定論。一氧化氮於血管內皮經內皮一氧化氮外生成?使用氧氣催化生成。一氧化氮是很重要的缺氧性肺血管收縮反應的調控管制因素。須要大於 50%一氧化氮外生?的表現使能維持正常肺血管的彈性。吐出的一氧化氮是上呼吸道上皮產量而非血管內皮的標記。吸煙經證實能改變肺血管的結構及內皮功能使一氧化氮生成減少。血管內皮素具有很強的血管收縮作用，藉由刺激血管平滑肌內皮上血管內皮素 A、B 受體執行作用。缺氧能刺激內皮素的產生及釋放。一氧化氮是血管內皮素的拮抗者，二者之間的平衡能決定肺血管阻力的調控。為了檢驗及證實此假說，於此連續二年的計畫中，我們以高解析度螢光顆粒球及多項惰氣排除技術研究肺移植後局部血流及通氣血流吻合的變化。高解析度螢光顆粒球技術具有估算肺小區域血流及通氣量大小，預估局部氧分壓及建立三度空間局部血流、通氣、氧分壓視覺圖像的優點。在此二年計畫我們建立豬缺血再充血的動物模式合併本實驗透室特有偵測局部肺血流及通氣分佈的技術，將探討缺血及再充血在局部血流及通氣變化上所扮演的角色；並且評估吸入性一氧化氮及呼吸機運用保護策略如何改進肺缺血及再充血肺損傷後氣體交換的機 3 轉。實驗的目的包括：甲、評估肺移植後缺血及再充血肺損傷造成存留肺及缺血肺局部血流及通氣血流吻合的變化。乙、探討吸入性氧氣濃度改善缺血再充血肺損傷氣體交換局部肺血流變化的機轉。丙、評估一氧化氮及肺血管內皮素對於移植後缺血及再充血肺損傷於肺局部血流及通氣血流吻合的影響。丁、建立豬的肺移植後缺血及再充血損傷的動物模式。完成此二年計畫可以使我們對於肺移植後因缺血及再充血造成氣體交換變差的機轉更為明瞭，並且所得到的知識及經驗更可幫助臨床醫生妥善治療及處理此類病患。		

• 英文摘要	Lung transplantation has become the main therapy for end-stage lung disease. Despite high successful rate of lung transplantation, 10-20% of patients developed immediate graft failure and complication with gas exchange abnormalities as well as severe arterial hypoxemia. Acute graft failure resulting from ischemia-reperfusion injury after lung transplantation is still life-threatening problem for the recipients and a challenge problem encountered by thoracic surgeon and critical care specialists. Effective pulmonary gas exchange depends on perfect ventilation and perfusion matching. Regional pulmonary blood flow distribution is determined by gravity, innate pulmonary artery branching structure, lung volume and hypoxic pulmonary vasoconstriction. Lung inflated with 100% oxygen had significantly better lung function after reperfusion than lungs preserved with room air. In contrast, others have found that lungs expanded with 50 and 100% FIO2 did significantly worse than lungs preserved with room air. High inspired oxygen fraction is associated with more lipid peroxidation, greater loss of lung volume and airway pressure during storage. The effect of inhaled O2 on regional VA／Q distribution post lung transplant has not been studied and the appropriate concentration of inhaled oxygen during ischemia-reperfusion lung injury still in controversial. In the vascular endothelium the production is catalyzed predominantly by endothelial NO synthase (eNOS) using molecular oxygen. eNOS derived NO is an important modulator of HPV. More than 50% of eNOS expression is required to maintain normal pulmonary vascular tone. Attempts to quantify NO produced in the vascular endothelium have been done by measuring exhaled NO. Exhaled NO provides a marker of airway epithelial production, but not vascular endothelial generation. Use of L-NAME for inhibition of eNOS reduces shunt during one lung ventilation. Diminished synthesis of NO may contribute to the alterations in structure and endothelial function of pulmonary vessels in cigarette smoking. ET is a potent vasoconstrictor and acts by stimulating ETA and ETB receptors on smooth muscle and endothelium. Hypoxia also stimulates production and release of endothelin-1 (ET) from the endothelium. Another modulator counteracting the vasoconstrictor role of ET is NO, the principal modulator of endothelium-dependent vasodilation in the pulmonary circulation. Balance between ET and NO may provide much (but not all) of the mechanisms for characteristic regional different pulmonary vascular resistance response. 5 In this two year proposal, we using high-resolutional fluorescent microsphere and multiple inert gas elimination technique to assess the effect of ischemia-reperfusion and inhaled oxygen on the regional distribution of ventilation, perfusion and ventilation-perfusion matching post lung transplant. In addition, study the effect of nitric oxide and endothelin blocker on regional pulmonary perfusion and VA／Q changes. In completing this study, we can understand the patho-physiology of impaired gas exchange during ischemia-reperfusion lung injury and help to shed light on improving care of patient post lung transplantation.