Commentary

What is the role of surfactant and inhaled nitric oxide in lung transplantation?

Martin Strüber

Staff Surgeon, Hannover Thoracic Transplant Program, Division of Thoracic and Cardiovascular Surgery, Hannover Medical School, Germany

Correspondence: Martin Strüber, strueber@thg.mh-hannover.de

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Abstract

Although numerous studies over the past 40 years have addressed this problem, initial graft failure is still a key question in clinical lung transplantation. As a possible tool to avoid and treat initial graft failure after lung transplantation, laboratory evidence and clinical reports currently emphasize the role of substitution therapy of surfactant combined with inhaled nitric oxide.

Keywords lung transplantation, nitric oxide, reperfusion injury, surfactant

The case report by Della Rocca and coworkers published in this issue of *Critical Care* [1] describes the occurrence of severe reperfusion injury after lung transplantation and successful treatment using a combination of inhaled nitric oxide (iNO) and surfactant instillation. What is the role of surfactant in management of initially impaired graft function after lung transplantation, and do these findings apply to other forms of lung injury?

Ischaemia/reperfusion injury leading to initial graft failure is a major cause of early mortality after lung transplantation. In addition, this problem led to the exclusion of most organ donors from lung harvesting, because acceptance criteria selected only optimal grafts. A shortage of suitable lung grafts became the rate-limiting step to lung transplantation [2]. Numerous studies were performed to avoid or ameliorate ischaemia/reperfusion injury. As early as 1991, Novick and coworkers [3] reported on alterations in surface activity of surfactant in experimental lung transplantation. Subsequent work [4] revealed an increase in serum protein associated with an increased small aggregate/large aggregate ratio in lavage of transplanted lungs. This finding led to the hypothesis that leakage of plasma protein into the alveolar space may inhibit surface-active large surfactant aggregates. In order to deal with this problem, two courses of action were considered. One is to substitute surface-active surfactant, and the other is to prevent plasma protein leakage into the alveolar space. In 1995 we were the first to report successful clinical treatment of reperfusion injury in a lung transplant recipient by administration of exogenous surfactant [5], followed by a review of six consecutive patients with established severe ischaemia/reperfusion injury [6]. Because a prospective clinical trial of surfactant substitution in lung transplantation is not available, these clinical observations are supported only by animal studies [7].

Methods to prevent ischaemia/reperfusion injury and pulmonary oedema were the subject of numerous studies. The use of iNO as a means to ameliorate such injury by reduction in pulmonary vascular resistance, leucocyte sequestration in the lung and improvement in gas exchange emerged from laboratory investigations [8]. Therefore, many lung transplant programmes use iNO routinely during early reperfusion of the lung. Bearing in mind that the concept of ischaemia/reperfusion injury in clinical transplantation also embodies the state of the donor lung before harvesting and the quality of preservation, the method of lung procurement must be considered.

Antegrade cold flush perfusion using cold Euro-Collins solution became the standard method of lung procurement 10–15 years ago [9]. Euro-Collins is a solution of intracellular ion composition that was originally developed for kidney preservation. Deleterious effects of this solution on the

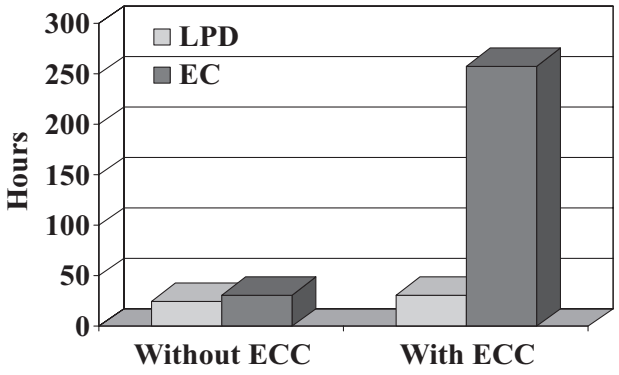
iNO = inhaled nitric oxide; LPD = low potassium dextran.

surfactant system were frequently reported [10]. Experimentally, it was shown that a preservation solution composed of extracellular ions might improve early graft function, particularly when dextran was added as an oncotic agent. The so-called low potassium dextran (LPD) solution improved surfactant function in an ischaemia/reperfusion model in minipigs by preventing plasma leakage [11]. A further improvement in graft function and better maintenance of the small aggregate/large aggregate ratio was found when the LPD solution was flushed retrograde through the graft [12]. Therefore, many major lung transplant centres abandoned the Euro-Collins technique and started to use LPD or other extracellular solutions instead. A lesser incidence as well as lesser severity of ischaemia/reperfusion injury and a reduction in requirement for early retransplantation have been reported [13,14].

The case reported by Della Rocca and coworkers [1] represents a typical report of severe reperfusion injury in a graft preserved in Euro-Collins solution, with an ischaemic time of 6 hours or more. In our experience, Euro-Collins preserved lungs are especially prone to reperfusion injury when extracorporeal circulation is used during the procedure. We observed a prolonged ventilation period in such patients after lung transplantation as a result of reperfusion injury, and we therefore changed the perfusion solution from Euro-Collins to LPD (Fig. 1). According to the case report [1], extracorporeal circulation was instituted when right heart failure occurred after implantation of the left lung and clamping of the contralateral pulmonary artery, despite iNO and prostaglandin E_1 treatment. However, it does not indicate for how long the first transplanted lung was reperfused when the pulmonary artery was clamped. Increased pulmonary vascular resistance is a common phenomenon in early reperfusion. For this reason, many surgeons prefer to transplant the right lung first, and to employ a prolonged reperfusion time after implantation of the first lung before clamping the contralateral pulmonary artery.

There are case reports and small studies of the successful use of iNO and surfactant replacement in adult respiratory distress syndrome patients. However, both therapeutic strategies failed to show efficacy in prospective randomized trials, so what justification is there for the use of these approaches in lung transplantation? A body of evidence has been established that indicates that surfactant function after lung transplantation is reduced in all cases. However, after an uncomplicated lung transplant procedure, lung function starts to improve following completion of surgery and is usually best 3–6 months after transplantation. In the cases of graft failure, brain death and infection of the donor lung, reduced surfactant function is aggravated by preservation of the graft, ischaemia and reperfusion. Therefore, substitution of surfactant may bridge the patient to recovery of the graft. The combination of iNO and surfactant proved to be successful in experimental severe reperfusion injury [15], strengthening the hypothesis that this combination prevents intrapulmonary shunt more effectively than does either intervention alone, and that it reduces inactivation of surfactant substitutes.

Figure 1



Ventilation time in 54 patients after lung transplantation with and without use of extracorporeal circulation (ECC). In 28 recipients the lungs were preserved with Euro-Collins (EC) solution. The remaining grafts were perfused with low potassium dextran (LPD) solution.

In summary, we emphasize that surfactant function should be considered when a preservation method is selected for lung procurement. In addition, combined iNO and surfactant replacement may be effective in graft failure after lung transplantation, and should be used before indications for extracorporeal membrane oxygenation or retransplantation are considered. This interesting approach was successful in the experimental setting of acute lung injury and needs to be verified in clinical indications other than lung transplantation.

Competing interests

None declared.

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