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LETTER TO THE EDITORS

The potential role of *ex vivo* lung perfusion for the diagnosis of infection before lung transplantation

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Dear Sirs,

It has been shown that normothermic *ex vivo* lung perfusion (EVLP) is a safe and feasible strategy to increase the pool of transplantable organs [1,2,3]. Cypel *et al.* [4] have demonstrated that EVLP is a reliable platform to evaluate and to recondition the lungs before transplantation. It has been shown that edematous lungs can reach the criteria for transplantation, once after normothermic controlled perfusion.

Although there is no evidence of usefulness of EVLP in the reconditioning of infected lungs, we present a case in which EVLP allowed to detect an undiagnosed pneumonia in the donor.

A 43-year-old female patient dying from pneumococcal meningitis became available as donor. She had been on mechanical ventilation for 6 days and presented a positive sputum for *Enterococcus* spp. White blood cell counts were normal and no fever episodes were reported during her ICU stay. No further investigations had been performed (i.e., blood culture, C-reactive protein, erythrocyte sedimentation rate, and procalcitonin) to detect a potential infection. However, the patient was on a prophylactic therapy with a large-spectrum antibiotic since admission to ICU. The best blood–gas analysis showed a pO_2/FiO_2 ratio of 213 with appropriated ventilation, but chest X-ray and CT scan (performed the same day of donation) were negative for any infiltration or consolidation. Bronchoscopy before retrieval showed a small amount of secretions, and consequently, broncoalveolar lavage (BAL) was not performed. At direct surgical inspection, the lungs appeared heavy and edematous. Poor function was therefore thought to be related to the increase in extravascular lung water. Since July 2011, an EVLP program for rejected or marginal lungs is active in our center and the graft was retrieved to be reconditioned and eventually transplanted.

After 2 h of cold storage, cannulation of left atrium, pulmonary artery, and trachea was performed. The lungs were then connected to a circuit of 2.0 l of acellular solution (Steen® Solution), with the addition of antibiotics (imipenem/cilastatin 500 mg/500 mg), steroids, and heparin. Forty percent of the ideal flow was reached in 1 h. Lungs were gradually rewarmed and ventilation was started when the temperature of perfusate reached 32 °C, according to the Toronto technique [4].

During EVLP, despite the stable left atrial and pulmonary pressures (5 and 10–13 mmHg, respectively) with an improvement of gas exchange at the end of perfusion (from 417 to 543 mmHg), lungs became more and more edematous with foamy fluid coming out from the trachea. At the same time, lung mechanics got worse at every single assessment (dynamic compliance dropped from 67.5 ml/cmH_2O at first hour to 38.6 ml/cmH_2O after 4 h of perfusion).

First-hour bronchoscopy showed a small amount of fluid secretions in the airway, which increased after 3 h. The first lungs X-ray looked normal, but after 3 h of perfusion, a clear consolidation in the right lower lobe became evident (Fig. 1). Despite a good gas exchange, lungs were not considered for transplantation because of the results of bronchoscopy, lung mechanics, and infiltrates at the X-ray. Biopsies taken from right lower lobe (RLL) at the end of perfusion confirmed the presence of focal organizing pneumonia among a normal alveolar walls and spots of edema and fibrosis. Histology from other areas of lungs appeared normal (Fig. 1). BAL and RLL tissue cultures resulted positive for the same *Enterococcus* isolated from patient's sputum.

Pulmonary edema is one of the main causes of graft refusal for lung transplantation. In this scenario, EVLP plays a major role to improve pulmonary function, reducing wet-to-dry ratio of lung parenchyma [5].

This case is unique because EVLP allowed a significant improvement of gas exchange, probably decreasing pulmonary edema, but at the same time, it showed an unknown infection.

Despite a large-spectrum antibiotic prophylactic therapy in the donor and the addition of imipenem/cilastatin to the perfusate, all the clinical and instrumental findings confirmed the presence of pneumonia. The use of antibiotics during perfusion suggests that the infection was not

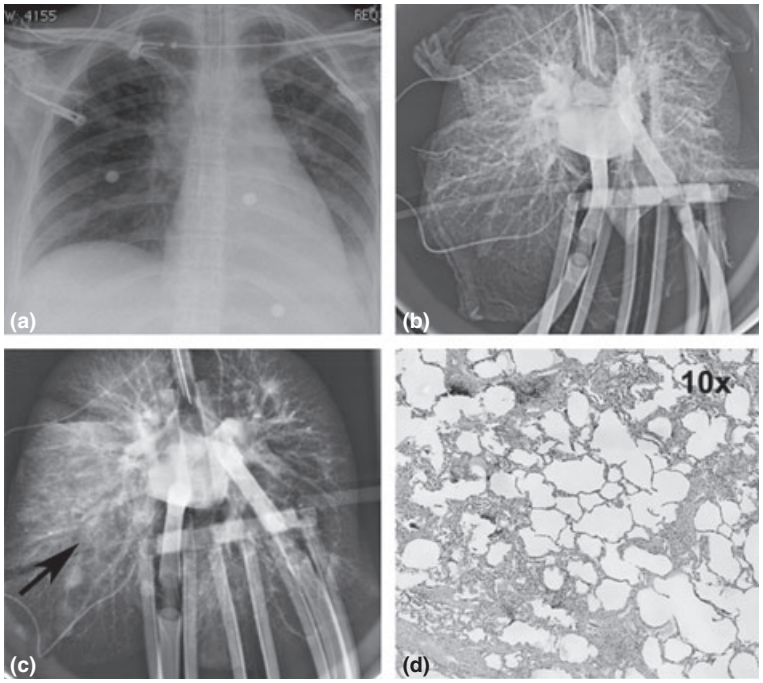

Figure 1 (a) Chest X-ray in the donor (day of retrieval). (b) Lung X-ray after 1 h of *ex vivo* lung perfusion (EVLP). (c) Lung X-ray after 3 h of EVLP (the arrow shows RLL consolidation). (d) Histology of RLL after 4 h of EVLP.

related to EVLP procedure. One can speculate that a subclinical pneumonia was already present in the donor and during the time of perfusion became evident. Moreover, the role of antibiotics in the Steen Solution is not completely evaluated. Antimicrobic activity is dose and time dependent. According to the Toronto protocol, during perfusion, a certain amount of Steen Solution is replaced and no extra-dose of antibiotics is provided. Antibiotic concentration may be reduced at the end of the EVLP procedure. Moreover, antibiotic effect is also dependent on the duration of perfusion that, according to the same protocol, can last up to 6 h. This time seems to be too short to get a therapeutic effect of the antibiotics that plays only a prophylactic role in the perfusate. Unfortunately, perfusion solution was not cultured, but this appears irrelevant for the diagnosis, being the *Enterococcus* isolated both in the BAL during EVLP and in the lung parenchyma. In fact, histological evaluation of lung parenchyma, microbiological sampling of lung tissue, and BAL were highly suggestive for an organizing pneumonia due to Enterobacter spp. The same microorganism was isolated in donor's sputum. Clinical significance of positive sputum in the donor is a debated topic, and it can decrease the suitability of lungs for transplantation [6].

As far as the gas exchange, oxygenation alone appeared to be an unreliable parameter for transplantation suitability. In this case, the graft gained optimal gas exchange, even if it was clear that those lungs could not be clinically used not only because of pneumonia but also for poor lung mechanics. For these reasons, also the left graft was not considered suitable for transplantation.

Ex vivo lung perfusion again confirmed its importance in the evolution of lung transplantation from an uncontrolled to a multilevel quality controlled procedure and its potential role as a therapeutic platform. Speculations and experimental trials on the use of antibiotic delivery during EVLP are on the way [7,8], and the use of such a platform to obtain lung sterilization is an interesting methodology to increase the lung pool.

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Conflict of interest

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