First Danish experience with ex vivo lung perfusion of donor lungs before transplantation

Ian Sune Iversen Henriksen[1], Hasse Møller-Sørensen[1], Christian Holdflod Møller[2], Mikhail Zemtsovski[1], Jens Christian Nilsson[1], Casper Tobias Seidelin[1], Michael Perch[3], Martin Iversen[3] & Daniel Steinbrüchel[2]

ABSTRACT

INTRODUCTION: The number of lung transplantations is limited by a general lack of donor organs. Ex vivo lung perfusion (EVLP) is a novel method to optimise and evaluate marginal donor lungs prior to transplantation. We describe our experiences with EVLP in Denmark during the first year after its introduction.

MATERIAL AND METHODS: The study was conducted by prospective registration of donor offers and lung transplantations in Denmark from 1 May 2012 to 30 April 2013. Donor lungs without any contraindications were transplanted in the traditional manner. Taken for EVLP were donor lungs that were otherwise considered transplantable, but failed to meet the usual criteria due to possible contusions or because they were from donors with sepsis or unable to pass the oxygenation test.

RESULTS: In the study period, seven of 33 Danish lung transplantations were made possible due to EVLP. One patient died of non-EVLP-related causes, but all other recipients were alive with normal graft function at the end of our registration period. All lungs showed an improved PaO_2/FiO_2 ratio from a median 23.1 kPa (8.8-38.9) within the donor to 58.8 kPa (34.9-76.5) (FiO_2 = 1.0) after EVLP, which corresponds to a 155% improved oxygenation. The median time to extubation, time in intensive care unit and the admission period were 1, 7 and 39 days, respectively.

CONCLUSION: In the first year after the introduction of EVLP in Denmark, seven pairs of donor lungs that previously would have been rejected have been transplanted as a result of their improved function. EVLP seems to be a safe way to increase the use of marginal donor lungs.

FUNDING: no funding was granted for the present paper.

TRIAL REGISTRATION: not relevant.

The first human lung transplantation was performed in 1963 in Mississippi, USA [1]. Since then the method has been widely used around the world.

Lung transplantation is offered to patients with end-stage lung disease in whom all other medical and surgical treatment options have been exhausted. The most common underlying diseases are cystic fibrosis, alpha-1-antitrypsin deficiency, idiopathic pulmonary fibrosis and chronic obstructive pulmonary disease. The number of lung transplantations is limited by a general lack of donor organs. Moreover, the lungs are only used in 20-30% of potential organ donations [2, 3]. Thus, the lungs are the organs with the lowest utilisation rate.

In Scandinavia, organ sharing and transplantation is coordinated through the collaborative initiative Scandiatransplant to ensure the best use of the organs available. The difficulty in using more donor lungs lies in the fact that not all lungs meet the strict criteria for transplantation.

The onset of brain death is associated with neurogenic pulmonary oedema and systemic inflammation. Studies of lungs that were assessed as being unsuitable for transplantation have shown that bronchopneumonia, diffuse alveolar damage and diffuse lung consolidation are the most common causes of rejection [4].

Several initiatives can increase the availability of donor lungs, for instance public information campaigns about organ donation, less restrictive donor criteria or introduction of donation from non-heart-beating donors.

Additionally, the usability of existing organs can be improved, which is the purpose of ex vivo lung perfusion (EVLP) technique.

The first successful transplantation with donor lungs that were initially considered unsuitable for transplantation was completed after treatment with EVLP in Lund, Sweden, in 2005 [5].

The method allows for optimisation of marginal donor lungs as well as for assessment of donor lung function.

In Denmark, lung transplantations are centralised at Rigshospitalet, Copenhagen, where the first procedure was performed in 1992 [6]. EVLP was implemented in 2012, and in the present paper we describe our experience with the first eight pairs of donor lungs treated with EVLP.

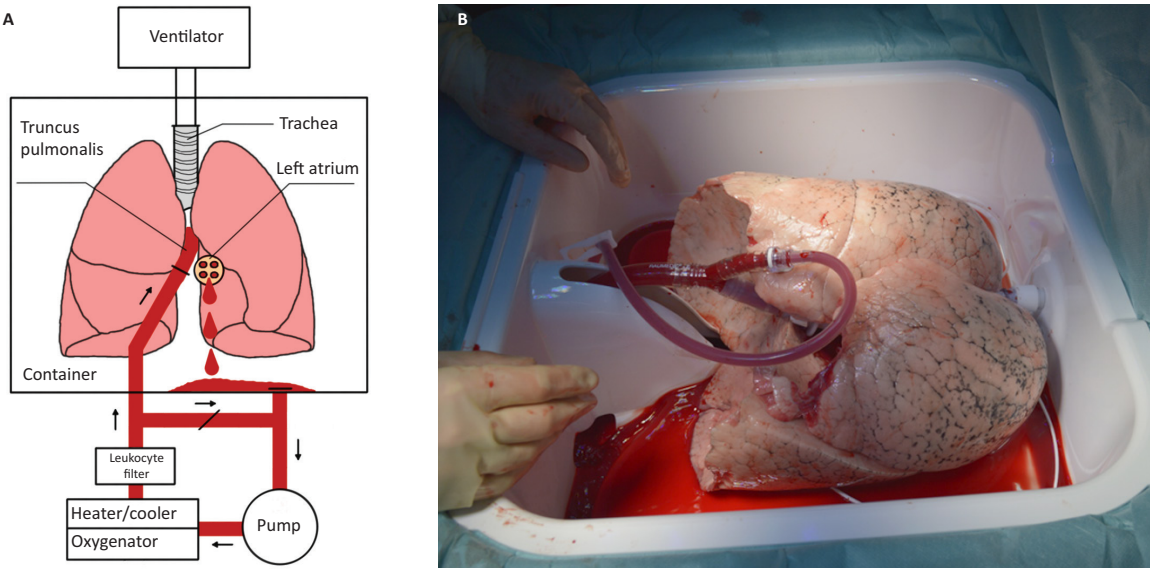
MATERIAL AND METHODS

This study was conducted by prospective registration of donor offers and lung transplantations in Denmark in the period from 1 May 2012 to 30 April 2013.

ORIGINAL ARTICLE

1) Department of Cardiothoracic Anaesthesiology, Rigshospitalet
2) Department of Cardiothoracic Surgery, Rigshospitalet
3) Department of Cardiology, The Lung Transplantation Unit, Rigshospitalet

Dan Med J 2014;61(3):A4809



Ex vivo lung perfusion. **A.** Graphical presentation. **B.** Clinical photo in which the lungs have just been connected and reconditioning commenced.

The following data were recorded:

- Donor and recipient characteristics
- Time from organ retrieval to EVLP and transplantation
- Total EVLP time
- PaO_2/FiO_2 ratio
- Pulmonary vascular resistance
- Lung compliance
- Time of mechanical ventilation, time in intensive care unit and total hospital stay after transplantation
- Complications after transplantation.

The contraindications for lung donation were:

- Age > 70 years (smokers > 60 years)
- Current hepatitis
- HIV infection
- Malignant tumours (depending on type)
- Sepsis
- Diabetes mellitus with microvascular complications or poor diabetes control
- Chronic obstructive pulmonary disease or asthma
- Significant lung infection (e.g. aspergillosis)
- Chest X-ray with infiltrate suspicious for tumours
- Lung contusion
- PaO_2 < 13 kPa at FiO_2 < 0.4 or PaO_2 < 40 kPa at FiO_2 = 1.0, both with positive end-expiratory pressure (PEEP) < 5 cmH_2O.

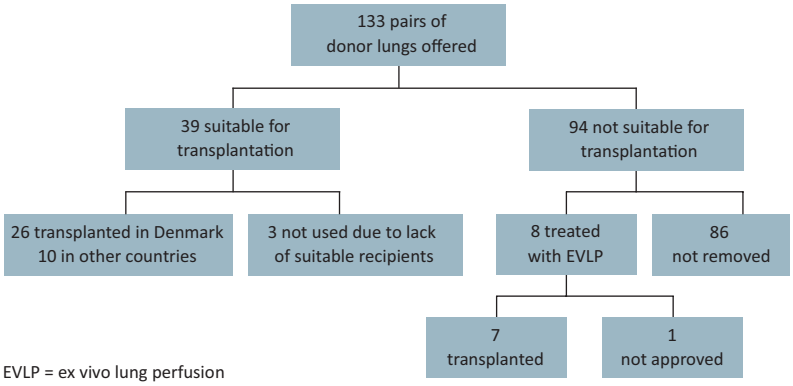
Donor lungs without any contraindications were transplanted in the traditional manner. EVLP was used in donor lungs that were otherwise considered transplantable, but failed to meet the usual criteria due to having possible contusions, being from donors with sepsis or being unable to pass the oxygenation test. With EVLP, the donor lungs are reconditioned and evaluated ex vivo.

The system used in Denmark is the Vivoline LS1 (Vivoline Medical AB, Lund, Sweden), which consists of a pump, an oxygenator, a heater/cooler, a leukocyte filter, temperature and pressure gauges as well as a container in which the lungs are placed under sterile conditions. There is also a control screen for operating the system and access to connect a ventilator.

The procedure is divided into the following phases: priming of the system, connecting the lungs, reconditioning and evaluation.

FIGURE 1

Donor offers and lung transplantations in Denmark from 1 May 2012 to 30 April 2013.



EVLP = ex vivo lung perfusion

Priming

The system is primed with 2,000 ml of Steen Solution (albumin, dextran and electrolytes), 2 units of packed red cells diluted with saline-adenine-glucose-mannitol solution (SAG-M), 10,000 IU heparin and 100 mg of meropenem. Next, blood gas is measured. The target values are pH 7.35-7.45, base excess ± 3 and haematocrit 10-15%. If needed additional buffer (Addex Tham) and/or SAG-M are added.

Connecting

A sterile plastic tube is inserted into the truncus pulmonalis and then connected to the EVLP circuit. Another plastic tube is inserted into the trachea and then connected to the ventilator. The left atrium is left open so that the reconditioning fluid flows directly out into the container for recirculation. β

Reconditioning

The reconditioning process is started with low flow of perfusion. The lungs are heated slowly from a few °C, and the perfusion flow is increased when 25 °C is reached. Lung-protective ventilation is initiated at 32 °C, and at 36 °C blood gases are obtained in order to assess whether the evaluation phase can begin. The aim is a PCO_2 < 6 kPa and a PO_2 > 40 kPa at FiO_2 = 0.5. Defects in the lungs that allow for air leakages are stabled and recruiting manoeuvres are performed to alleviate atelectasises. A bronchoscopy is performed if required.

Evaluation

The oxygenator is used to deoxygenate the perfusate, allowing for assessment of the lungs' oxygenation capability, and blood gases are measured at FiO_2 = 1.0 and 0.21. The lungs are approved if PCO_2 < 6 kPa and if PO_2 > 50 kPa at FiO_2 = 1.0 or PO_2 > 13 kPa at FiO_2 = 0.21. A collapse test is performed to evaluate possible oedema of the lung tissue. A normal non-oedematous lung deflates and becomes globally atelectatic when the ventilator is disconnected while oedematous areas remain unchanged.

If the lungs cannot be approved, reconditioning and evaluation are repeated. Lungs that meet the criteria mentioned above are accepted for transplantation and re-cooled until transplantation.

Trial registration: not relevant.

RESULTS

During the study period, a total of 133 pairs of donor lungs were offered, 91 from Denmark and 42 from the other Nordic countries. A total of 36 were transplanted in the conventional manner, 89 were not used and eight underwent EVLP of which seven were transplanted after EVLP (**Figure 1**). Donor and recipient characteristics are shown in **Table 1** and **Table 2**.

TABLE 1

Donor characteristics.

	Sex	Blood type	Cause of death	Time from removal to, h:min. EVLP	Time from removal to, h:min. transplantation	Total time of EVLP, h:min.
No. 1	Female	0 positive	SAH	3:54	9:47	1:16
No. 2	Male	0 positive	SAH	3:19	12:39	2:47
No. 3	Male	A positive	Stroke	4:14	12:15	2:26
No. 4	Female	B negative	Multi-trauma	4:13	Not approved	2:22
No. 5	Female	A positive	SAH	5:51	14:27	3:18
No. 6	Male	A positive	Asystolia	4:50	17:31	4:25
No. 7	Male	A positive	Head trauma	2:37	14:12	2:25
No. 8	Male	0 positive	SAH	4:49	12:06	2:02
Median (range)	–	–	–	4:14 (02:37-05:51)	12:39 (09:47-17:31)	2:26 (01:16-04:25)

EVLP = ex vivo lung perfusion; SAH = subarachnoid haemorrhage.

TABLE 2

Recipient characteristics.

	Diagnosis	Ventilator, days	ICU, days	Hospital, days	Complications
No. 1	Pulmonary hypertension	1	3	17	–
No. 2	Lung fibrosis	1	2	23	–
No. 3	Lung fibrosis	8	27	70	Renal failure, dialysis
No. 4	Alpha-1-antitrypsin deficiency	1	6	32	Perforated ulcer
No. 5	Chronic obstructive pulmonary disease	22	65	111	Pneumonia, renal failure, dialysis
No. 6	Cystic fibrosis	1	9	104	Diarrhoea, lung cavitations due to Mycobacterium abscessus, death
No. 7	Cystic fibrosis	3	7	39, admitted	–
Median (range)	–	1 (1-22)	7 (2-65)	39 (17-111)	–

ICU = intensive care unit.

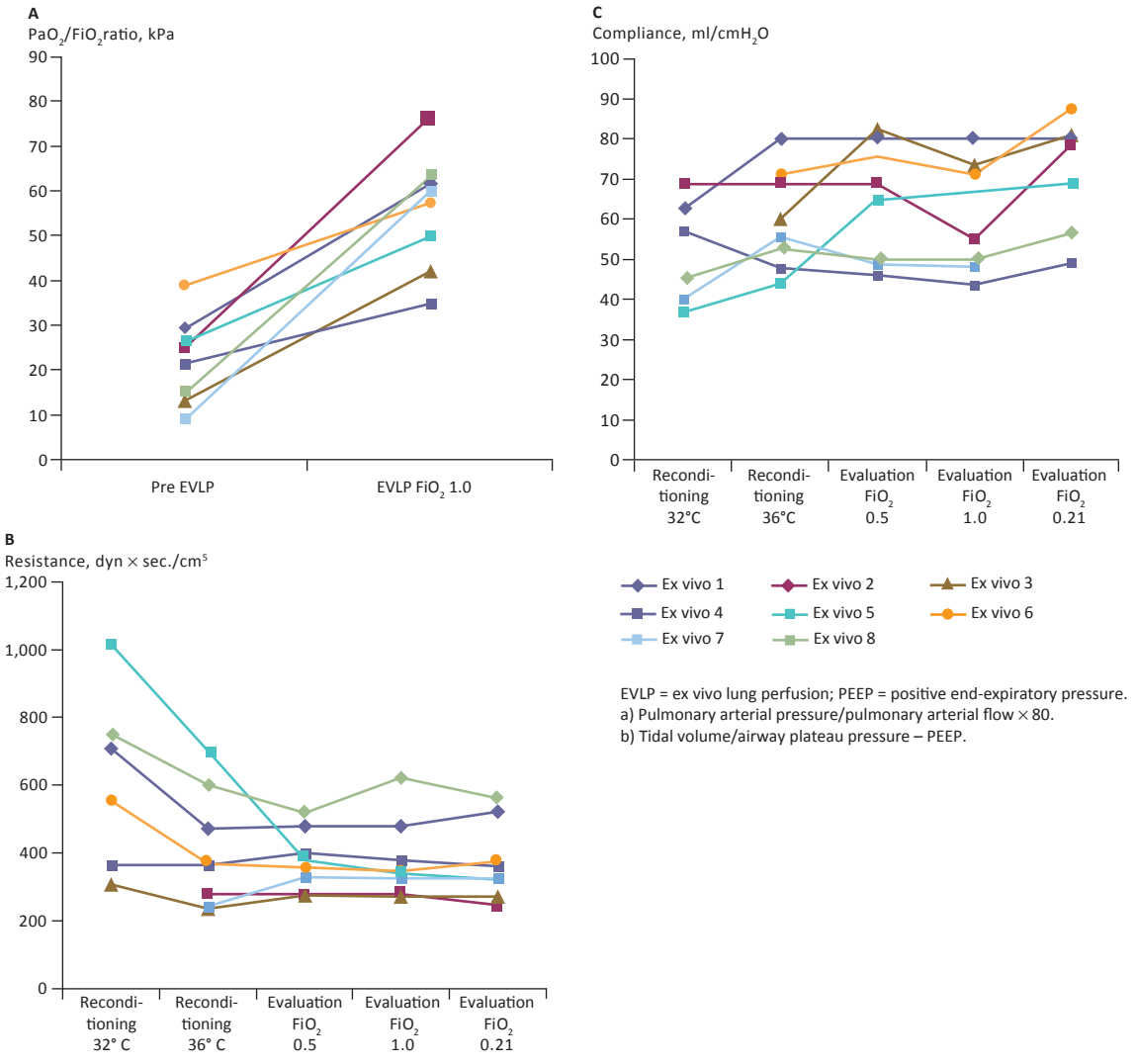
The median PaO_2/FiO_2 ratio was 23.1 kPa (8.8-38.9) before the lungs were removed from the donors. All lungs improved their PaO_2/FiO_2 ratio during EVLP to a median value of 58.8 kPa (34.9-76.5) (FiO_2 = 1.0), which corresponds to a 155% improved oxygenation (**Figure 2**A).

For several of the lungs, pulmonary vascular resistance was higher early in the reconditioning phase, but then decreased and remained unchanged during the evaluation (Figure 2B).

Lung compliance was unchanged during reconditioning and evaluation (Figure 2C).

One pair of donor lungs (no. 4) did not pass the collapse test. Its total weight was 947 g prior to EVLP and

FIGURE 2



The donor lungs' oxygenation capability, pulmonary vascular resistance and lung compliance.
A. The donor lungs' oxygenation capability (PaO_2/FiO_2 ratio) when still in donor and during EVLP.
B. Pulmonary vascular resistance[a] during reconditioning and evaluation.
C. Lung compliance[b] during reconditioning and evaluation.

EVLP = ex vivo lung perfusion; PEEP = positive end-expiratory pressure.
a) Pulmonary arterial pressure/pulmonary arterial flow × 80.
b) Tidal volume/airway plateau pressure – PEEP.

1,333 g afterwards. The fact that they failed the collapse test and the weight gain was taken as indications of substantial pulmonary oedema. Furthermore, massive amounts of bilateral oedema fluid were observed by bronchoscopy and the pair of lungs was rejected even though its PaO_2/FiO_2 ratio improved during EVLP and the right lung met the oxygenation criteria.

The remaining seven pairs fulfilled the oxygenation criteria, passed the collapse test and were subsequently transplanted successfully.

One recipient (no. 6) died 104 days after the transplantation due to severe gastrointestinal complications combined with infection with Mycobacterium abscessus, which formed cavitations in the lungs and led to pulmonary failure. The patient was colonised before transplantation, which is known to be associated with an increased mortality after transplantation. The patient's death is not considered to be EVLP-related.

At the end of the registration period (30 April 2013), all other recipients were still alive with good graft function and without signs of rejection. With the exception of the last patient transplanted, all had been discharged.

DISCUSSION

We here present the experience from the first year with EVLP in Denmark. Seven pairs of lungs that would normally be deemed unsuitable because they failed to meet the usual criteria for transplantation were used for transplantation after EVLP. Thus, seven out of 33 (21%) Danish lung transplantations in the period were made possible as a result of EVLP. Studies from international centres have reported similar results ranging from 20%

to 30% [7, 8], but some variation is expected, as all the data sets are relatively small. It is expected that EVLP will increase the availability of usable donor lungs by approximately 25% in Denmark.

The PaO_2/FiO_2 ratio was improved for all lungs during EVLP, which is in line with what has been shown in other studies [9, 10]. The PaO_2/FiO_2 ratio is used for functional evaluation in order to compare the lungs' oxygenation capability at different levels of FiO_2. However, the relationship between PaO_2 and FiO_2 is not linear, which explains the different levels of approval at various FiO_2 [11].

The oxygenation capability is not the only criterion used for the assessment of donor lungs during EVLP. Adverse changes in airway pressure or lung compliance have been found to be early signs of lung injury, and an increase in airway pressure or a decrease in lung compliance of more than 15% over 2 hours has been suggested as an exclusion criterion for transplantation [12]. In our study, no lungs showed signs of deterioration using these variables.

The Danish experience with the use of EVLP is limited by the short period of time and the small number of lungs that have been treated, but international studies with longer observation periods and larger numbers indicate that the results after EVLP are not inferior to those recorded after conventional lung transplantation. We still lack a large randomised study to clarify this area, but several multicentre studies are underway and preliminary interim results are promising [13].

A Canadian non-randomised study comparing the one-year survival rate after transplantation of EVLP-treated (20 patients) and conventionally treated lungs (116 patients) found no significant difference – the rates being 80% and 84%, respectively. A 10% 30-day mortality was reported in the EVLP group (two patients), but both patients died of non-EVLP related causes [14].

In a Swedish study, which was also non-randomised, six transplantations after EVLP were evaluated and the Swedish investigators found a three-month survival rate of 100%. Subsequently, two patients died, one due to sepsis and one due to rejection. The four other recipients were still alive 24 months after transplantation [9].

In our study, we found the median time to extubation, time in intensive care unit and duration of overall hospital stay after transplantation to be 1, 7 and 39 days, respectively.

The largest study to date (50 transplantations after EVLP) found median times to be 2, 4 and 20 days, respectively. They found no significant differences compared with lungs transplanted traditionally [8].

The reasons for the improved function following EVLP is still not clear, but it is believed that the hyperoncotic reconditioning fluid helps to mobilise and remove excess interstitial and alveolar fluid. Furthermore, alleviation of atelectasis can be of importance [15].

Some of the lungs considered suitable for transplantation after EVLP could possibly have been transplanted in a conventional manner with satisfactory results if the oxygenation criterion had been lowered. A randomised clinical trial on these marginal donor lungs could clarify this, but ethical considerations run counter to conducting such a study. So far, EVLP has primarily been used for reconditioning and evaluation after arrival at the centre where the transplantation is carried out. Recently, a mobile EVLP system has been introduced on the market, so the procedure can begin immediately after the lungs have been removed from the donor. This approach minimises the time of cold ischaemia to which the lungs are otherwise exposed with the current preservation and transportation procedure. In the first study that evaluated the system, 12 pairs of donor lungs were included and the authors found no worsening of the PaO_2/FiO_2 ratio during transportation. A randomised trial has been initiated to compare standard cold preservation with EVLP during transportation [13].

CONCLUSION

EVLP was introduced in Denmark in May 2012 and seven pairs of donor lungs that would have previously been rejected have since been transplanted as a result of their improved function after EVLP. Our results and several international studies suggest that lungs treated with EVLP have similar outcomes after transplantation as lungs transplanted in a conventional manner. The method seems to be safe and a way to increase the utilisation of potential donor lungs, thereby reducing the discrepancy between the supply of and the need for donor lungs.

CORRESPONDENCE: *Hasse Møller-Sørensen*, Anæstesiafdelingen, Hjertecentret, Rigshospitalet, Blegdamsvej 9, 2100 Copenhagen Ø, Denmark. E-mail: hassedk@gmail.com

ACCEPTED: 13 January 2014

CONFLICTS OF INTEREST: Disclosure forms provided by the authors are available with the full text of this article at www.danmedj.dk.

LITERATURE

1. Hardy JD, Webb WR, Dalton ML et al. Lung Homotransplantation in Man. JAMA 1963;186:1065-74.
2. www.scandiatransplant.org/data/sctp_figures_2012_4Q.pdf (1 Jan 2014).
3. http://srtr.transplant.hrsa.gov/annual_reports/2011/default.aspx (1 Jan 2014).
4. Kutsogiannis DJ, Pagliarello G, Doig C et al. Medical management to optimize donor organ potential: review of the literature. Can J Anesth 2006;53:820-30.
5. Steen S, Ingemansson R, Eriksson L et al. First human transplantation of a nonacceptable donor lung after reconditioning ex vivo. Ann Thorac Surg 2007;83:2191-5.
6. Hjertecentrets transplantationsgruppe. Thoraxtransplantation – Rigshospitalet 1990-2002. Ugeskr Læger 2003;165:4736-40.
7. Lindstedt S, Hlebowicz J, Koul B et al. Comparative outcome of double lung transplantation using conventional donor lungs and non-acceptable donor lungs reconditioned ex vivo. Interact Cardiovasc Thorac Surg 2011;12:162-5.
8. Cypel M, Yeung JC, Machuca T et al. Experience with the first 50 ex vivo lung perfusions in clinical transplantation. J Thorac Cardiovasc Surg 2012;144:1200-7.

9. Ingemansson R, Eyjolfsson A, Mared L et al. Clinical transplantation of initially rejected donor lungs after reconditioning ex vivo. Ann Thorac Surg 2009;87:255-60.
10. Medeiros IL, Pêgo-Fernandes PM, Mariani AW et al. Histologic and functional evaluation of lungs reconditioned by ex vivo lung perfusion. J Heart Lung Transplant 2012;31:305-9.
11. Aboab J, Louis B, Jonson B et al. Relation between PaO_2/FIO_2 ratio and FIO_2: a mathematical description. Intensive Care Med 2006;32:1494-7.
12. Yeung JC, Cypel M, Machuca TN et al. Physiologic assessment of the ex vivo donor lung for transplantation. J Heart Lung Transplant 2012;31: 1120-6.
13. Warnecke G, Moradiellos J, Tudorache I et al. Normothermic perfusion of donor lungs for preservation and assessment with the Organ Care System Lung before bilateral transplantation: a pilot study of 12 patients. Lancet 2012;380:1851-8.
14. Cypel M, Yeung JC, Liu M. Normothermic ex vivo lung perfusion in clinical lung transplantation. N Engl J Med 2011;364:1431-40.
15. Wierup P, Haraldsson Å, Nilsson F et al. Ex vivo evaluation of nonacceptable donor lungs. Ann Thorac Surg 2006;81:460-6.