Portable normothermic ex-vivo lung perfusion, ventilation, and functional assessment with the Organ Care System on donor lung use for transplantation from extended-criteria donors (EXPAND): a single-arm, pivotal trial

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Summary

Background Donor lung use for transplantation is the lowest among solid organ tranplants because of several complex and multifactorial reasons; one area that could have a substantial role is the limited capabilities of cold ischaemic storage. The aim of the EXPAND trial was to evaluate the efficacy of normothermic portable Organ Care System (OCS) Lung perfusion and ventilation on donor lung use from extended-criteria donors and donors after circulatory death, which are rarely used.

Methods In this single-arm, pivotal trial done in eight institutions across the USA, Germany, and Belgium, lungs from extended-criteria donors were included if fulfilling one or more of the following criteria: a ratio of partial pressure of arterial oxygen (PaO_2) to fractional concentration of oxygen inspired air (FiO_2) in the donor lung of 300 mm Hg or less; expected ischaemic time longer than 6 h; donor age 55 years or older; or lungs from donors after circulatory death that were recruited and assessed using OCS Lung. Lungs were transplanted if they showed stability of OCS Lung variables, PaO_2:FiO_2 was more than 300 mm Hg, and they were accepted by the transplanting surgeon. Patients were adult bilateral lung transplant recipients. The primary efficacy endpoint was a composite of patient survival at day 30 post-transplant and absence of The International Society for Heart & Lung Tranplantation primary-graft dysfunction grade 3 (PGD3) within 72 h post-transplantation, with a prespecified objective performance goal of 65%. The primary analysis population was all transplanted recipients. This trial is registered with ClinicalTrials.gov, number NCT01963780, and is now complete.

Findings Between Jan 23, 2014, and Oct 23, 2016, 93 lung pairs were perfused, ventilated, and assessed on the OCS Lung. 12 lungs did not meet OCS transplantation criteria so 81 lungs were suitable for transplantation. Two lungs were excluded for logistical reasons, hence 79 (87%) of eligible lungs were transplanted. The primary endpoint was achieved in 43 (54%) of 79 patients and did not meet the objective performance goal. 35 (44%) of 79 patients had PGD3 within the initial 72 h. 78 (99%) of 79 patients had survived at 30 days post-transplant. The mean number of lung graft-related serious adverse events (respiratory failure and major pulmonary-related infection) was 0·3 events per patient (SD 0·5).

Interpretation Despite missing the objective primary endpoint, the portable OCS Lung resulted in 87% donor lung use for transplantation with excellent clinical outcomes. Many lungs declined by other transplant centres were successfully transplanted using this new technology, which implies its use has the potential to increase the number of lung transplants performed worldwide. Whether similar outcomes could be obtained if these lungs were preserved on ice is unknown and remains an area for future research.

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Introduction

Lung allografts are subject to a variety of insults related to brain death-induced inflammatory processes, infections, and acute lung injury. In addition, lung allografts from donors after circulatory death are subjected to the additional insult of warm ischaemia and lack of functional assessment of the allograft after the agonal phase. Cold ischaemic preservation of donor lungs increases the risk of time-dependent ischaemic injury, which compounds the insult on the lung allograft and limits the geographical retrieval distance. In addition, it does not allow ventilatory recruitment and has no assessment capabilities for the lung allografts. For decades, approximately 20%[1–2] of lungs donated by brain-dead donors and less than 5% from donors after circulatory death were used for transplantation,[3] leaving the vast majority of available lungs from these donors unused. This substantial underuse reduces access for

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Research in context

Evidence before this study

We reviewed relevant literature reporting transplant survival and graft function outcomes after lung transplantation using extended-criteria donor lungs. We searched PubMed for articles published in English from Jan 1, 2000, to Jan 1, 2019. Search terms included "lung transplantation", "donor lung", "extended-criteria donor", and "donation after circulatory death". The relevant references are included in the manuscript. Before the EXPAND trial, single-centre and multicentre studies have described the results of transplanting extended-criteria donor lungs after standard ice preservation, static ex-vivo lung perfusion systems, and the Organ Care System Lung. The quality of the available data was moderate because the majority of studies were single-centre studies. One multicentre prospective cohort analysis (UK DEVELOP) and one randomised controlled trial (INSPIRE) were available, and another prospective multicentre trial is in progress (NOVEL) with preliminary results available. Collectively, the review of the literature suggests underuse of donor lungs and increased morbidity for transplants using extended-criteria donor lungs.

Added value of this study

To our knowledge, the current study is the first multicentre international trial using a portable normothermic ex-vivo lung perfusion system for extended-criteria donor lungs. Despite not meeting the prespecified objective performance goal, we showed high use and survival with this strategy of lung preservation, which can be used as a new benchmark for future research.

Implications of all the available evidence

The EXPAND trial shows the safety and efficacy of using portable normothermic ex-vivo lung perfusion and ventilation for donor lungs from extended-criteria donors and donors after circulatory death, which has the potential to substantially expand the donor pool and increase the number of transplants done worldwide.

many patients to life-saving lung transplant procedures and results in 30% of patients on the waiting list either dying (15·6%) or being removed from the waiting list because of compromised health status (15%).[4] A few reports have shown acceptable clinical outcomes with the use of lungs for transplantation from extended-criteria donors and donors after circulatory death;[5–8] however, these reports are single-centre studies, using selective donor lung criteria and the overall global use of donor lungs remains low.

Static ex-vivo lung perfusion was developed to assess lungs and potentially recondition them or screen out those that are unsafe to transplant. Initial single-centre studies assessing static ex-vivo lung perfusion showed outcomes similar to standard cold storage preservation.[9,10] Results of subsequent multicentre trials using static ex-vivo lung perfusion showed that use of lungs assessed using this system ranged from 34% to 51%.[11–13] One limitation of static ex-vivo lung perfusion is that it leads to a mandatory and variable period of initial cold ischaemia and a delay in the ventilatory recruitment and assessment process.

Portable ex-vivo lung perfusion with the Organ Care System (OCS) Lung (TransMedics, Inc, Andover, Massaschusetts, MA, USA) allows for the initiation of perfusion and ventilation of the donor lungs from the time of retrieval at the donor site until they are ready to be transplanted into the recipient. It limits the risk of the obligatory ischaemic injury, enables early initiation of ventilatory recruitment manoeuvres, and enables assessment of the function of lung allografts throughout the preservation period.[14–17]

We designed the multicentre OCS Lung EXPAND trial to evaluate the efficacy of using portable ex-vivo lung perfusion with OCS Lung on donor lung use and post-transplant outcomes after transplantation of extended-criteria donor lungs from brain-death donors, and donors after circulatory death, which are seldomly used for transplantation.

Methods

Study design

The EXPAND trial was a single-arm, pivotal trial done at eight leading academic transplant institutions: six in the USA, one in Germany, and one in Belgium. The trial was done in accordance with the Harmonised Good Clinical Practice Guidelines.[18] Each site obtained the appropriate institutional review board approval, ethics committee approval, or both.

Participants

All participants gave written informed consent. Donor lungs were included if they had one or more of the following extended criteria: a ratio of partial pressure of arterial oxygen (PaO_2) to fractional concentration of oxygen (FiO_2) of 300 mm Hg or less; expected total ischaemic time of less than 6 h; donation after circulatory death; and donor older than 55 years. Published literature suggests that these criteria represent a minority of transplants performed in the USA with cold ischaemic storage.[3,19–21]

Donor exclusion criteria were presence of moderate-to-severe traumatic lung injury with air or blood leak; presence of confirmed active pneumonia or persistent pooling of purulent secretions on repeated bronchoscopic evaluations, if they had a history of active pulmonary disease; transfusions exceeding 10 units of packed red blood cells; ABO incompatibility with the recipient; or a tobacco history of more than 20 packs per year.

Eligible transplant recipients were 18 years of age or older and undergoing a bilateral lung transplantation.

Recipients were excluded if they had a previous solid organ or bone marrow transplant; were getting a single-lung transplant; or had diagnosis of chronic kidney disease or were on renal replacement therapy.

After perfusion and assessment on the OCS Lung, donor lungs had to satisfy all of the following conditions to be eligible for transplantation: stability of physiological variables, including pulmonary vascular resistance, pulmonary artery pressure, and peak airway pressure, with no increase of greater than 20% while on OCS compared with baseline; a PaO_2 to FiO_2 ratio of 300 mm Hg or more at the end of OCS Lung perfusion; and confirmation by the transplanting surgeon of clinical suitability for transplant.

Procedures

After examination in the donor chest and acceptance for inclusion in the EXPAND trial, donor lungs were flushed antegrade with 4 L followed by a 1–2 L retrograde flush using cold-buffered OCS Lung Solution[16] plus 50 mg nitroglycerin. The lungs were connected to the OCS Lung, gradually warmed to 37°C, and ventilated at 6 mL/kg ideal bodyweight, 10 breaths per min, and positive end-expiratory pressure of 5 cm H_2O. The perfusate consisted of three units of packed red blood cells (about a total of 900 mL), 1·5 L of OCS Lung Solution, and target haematocrit of 15–25%. The ratio of PaO_2 to FiO_2 was assessed in the donor's body and at the end of the OCS Lung perfusion. Lung perfusion haemodynamic parameters were assessed at baseline, within 30 min of OCS Lung perfusion (initial OCS assessment), and at the recipient hospital before acceptance (final OCS assessment). If the lung was accepted for transplantation, standard bilateral lung transplantation was done in all recipients using centre-specific protocols. The OCS Lung and transplantation procedures have previously been described in detail.[15,16]

We collected information on patients' hospital course and their follow-up at 6 and 12 months after transplantation. Post-transplant functional assessments at days 0–30 included PGD grading, mechanical support time, intentive care unit stay, standard post-transplant diagnostics, and adverse events. At 6 and 12 months, we collected information related to patient status, lung quality, and adverse events.

Outcomes

The primary efficacy endpoint was a composite of patient survival at day 30 post-transplant and absence of 2005 International Society for Heart and Lung Transplantation (ISHLT) primary graft dysfunction grade 3 (PGD3) within 72 h after transplantation.[22] PGD grading in the EXPAND trial used the same caveats as used by the INSPIRE trial,[16] which are defined in the 2005 ISHLT consensus statement.[22] Grading at individual study sites was done by the principal investigator or co-principal investigator. All PGD entries were adjudicated by an independent medical monitor experienced in lung transplantation and PGD grading.

The secondary endpoints were incidence of PGD3 72 h after transplantation, and PGD 2 or 3 at the same timepoint. Additional, non-statistical endpoints were duration of initial post-transplant invasive mechanical ventilation; length of initial post-transplant intensive care unit stay; length of initial post-transplant hospital stay; PGD scores at baseline, 24 h, 48 h, and 72 h after tranplantation; the proportion of donor lungs that were accepted; patient survival at 30 days, 6 months, and 12 months; and overall incidence of all described phenotypes of chronic lung allograft dysfunction at 6 months and 12 months after transplant, collectively named in the protocol as bronchiolitis obliterans syndrome.

The primary safety endpoint was the mean number of lung-graft-related serious adverse events within 30 days post-transplant. These serious adverse events were prespecified to include biopsy-proven moderate-to-severe acute rejection, respiratory failure necessitating prolonged ventilation or reintubation, bronchial anastomotic complications, and major lung-related infection. Multiple occurrences of same events in one patient were counted once.

Statistical analysis

The primary analysis population consisted of all recipients of transplants in the trial, for which all outcomes were analysed. The primary hypothesis was that the true proportion of the transplant recipients with a composite of patient survival at day 30 after transplantation and without PGD3 at any timepoint up to 72 h was greater than the prespecified objective performance goal (OPG) of 0·65 (65%). This OPG was established before study initiation and was based on the only published data available for PGD3 within the initial 72 h post-tranplant of 30% (95% CI 28·2–33·3) for standard-criteria donor lungs.[23] No published data were available on expected PGD3 rates within the initial 72 h, including the expected rate at time zero (ie, just after transplantion), for patients who received lungs from extended-criteria donors, donors after circulatory death, or non-ideal donors. Therefore, the expected PGD3 incidence for such organs was not known. The 65% goal for the composite was derived from an assumption of 30% PGD3 incidence and 5% mortality risk at 30 days. The primary effectiveness endpoint was summarised using counts and percentages and an exact 95% CI for the true percentage based on the binomial distribution. A one-sided exact binomial test at 0·05 significance level was done to test the null hypothesis. Secondary effectiveness endpoints were summarised using counts and percentages and a 95% CI for the true percentage based on normal approximation. To comply with the US Food and Drug Administration requirement, the OCS INSPIRE control group was used as a comparator for

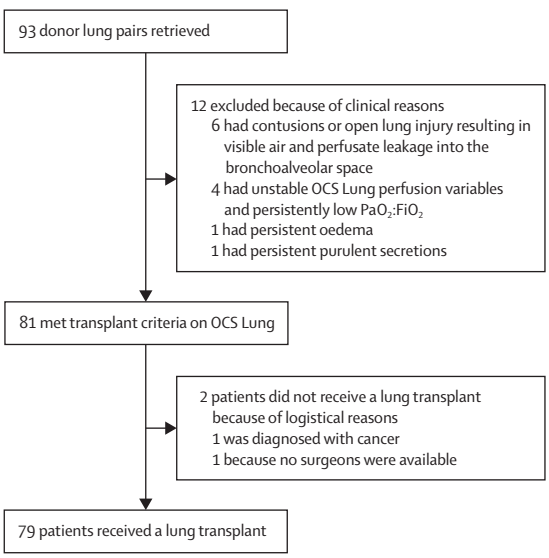

Figure 1: **Trial profile**
PaO_2:FiO_2=ratio of partial pressure of arterial oxygen to fractional concentration of oxygen inspired air. OCS=Organ Care System.

benchmarking the results for survival, bronchiolitis obliterans syndrome incidence, and safety endpoints.

Safety was analysed by assessing the frequency of lung-graft-related serious adverse events. The outcomes were summarised using descriptive statistics, specifically the mean (SD), median (range), and 95% CI for the mean based on the *t* test distribution. Sample size was determined on the basis of the primary effectiveness endpoint. The calculation assumed a one-sided exact binomial test (α=0·05, OPG of 0·65, true survival rate for OCS of 0·8, and power of 80%). The required minimum sample size was 55 transplanted recipients.

All analyses were done using SAS, version 9.4. This trial is registered with ClinicalTrials.gov, number NCT01963780.

Role of the funding source

The funder of the trial led the design of the study protocol in collaboration with senior investigators, and was responsible for data collection and generating the final study report. All authors were responsible for clinical data interpretation and writing of this manuscript. GL, DVR, MAV, and AA had full access to all the data from the study. The funder assisted the authors in drafting and reviewing figures, tables, corresponding descriptions, and provided some text suggestions, to ensure accuracy of the data presented. At the specific request of the authors, the funder provided additional analyses of the trial data to help address reviewers' comments. All authors approved the final manuscript and had final responsibility for the decision to submit for publication.

	Participants (n=79)
Donors	
One inclusion criterion	
Age ≥55 years	22 (28%)
DCD	16 (20%)
Expected cross-clamp time >6 h	11 (14%)
PaO_2:FiO_2 ≤300 mm Hg	9 (11%)
Two inclusion criteria	
DCD and expected cross-clamp time >6 h	6 (8%)
PaO_2:FiO_2 ≤300 mm Hg and expected cross-clamp time >6 h	5 (6%)
PaO_2:FiO_2 ≤300 mm Hg and age ≥55 years	3 (4%)
DCD and age ≥55 years	3 (4%)
DCD and PaO_2:FiO_2 ≤300 mm Hg	1 (1%)
Expected cross-clamp time >6 h and age ≥55 years	1 (1%)
Three inclusion criteria	
PaO_2:FiO_2 ≤300 mm Hg, expected cross-clamp time >6 h, and age ≥55 years	2 (3%)
Total number of donors according to inclusion criteria	
DCD	26 (33%)
Donor age ≥55 years	31 (39%)
Expected cross-clamp time >6 h	25 (32%)
PaO_2:FiO_2 ≤300 mm Hg	20 (25%)
Donors with multiple criteria	21 (27%)
Recipients	
Age, years	55·56 (10·6)
Sex	
Female	33 (42%)
Male	46 (58%)
Body-mass index, kg/m²	24·49 (4·6)
Lung allocation score*	42·0 (13·5)
Primary diagnosis	
Chronic obstructive pulmonary disease or emphysema	27 (34%)
Idiopathic pulmonary fibrosis	18 (23%)
Cystic fibrosis	12 (15%)
Non-specific interstitial pneumonia	5 (6%)
Bronchiectasis	4 (5%)
Sarcoidosis	2 (3%)
Secondary pulmonary hypertension	22 (28%)
Other	11 (14%)

Data are n (%) or mean (SD). PaO_2:FiO_2=ratio of partial pressure of arterial oxygen to fractional concentration of oxygen inspired air. DCD=donor after circulatory death. *Measured only in 70 patients.

Table 1: **Risk factors of lung donors and baseline characteristics of recipients**

Results

Between Jan 23, 2014, and Oct 23, 2016, 93 lung pairs from extended-criteria donors and donors after circulatory death were retrieved and assessed on the OCS Lung; 61 (66%) of these were from brain-death donors and 32 (34%) were from donors after circulatory death. 81 (87%) of 93 donor lungs met the prespecified clinical

	PaO_2/FiO_2≤300 mm Hg	Expected cross-clamp time >6 h	Donor after circulatory death	Donor age ≥55 years	All donors
Sex					
Female	5/20 (25%)	7/25 (28%)	9/26 (35%)	17/31 (55%)	33/79 (42%)
Male	15/20 (75%)	18/25 (72%)	17/26 (65%)	14/31 (45%)	46/79 (58%)
PaO_2:FiO_2, mm Hg	239 (46·5; 135–295)	378 (122; 190–624)	407 (81; 250–624)	398 (106; 144–663)	378 (110; 135–663)
Total cross-clamp time, min	603 (88; 452–800)	643 (124; 432–864)	608 (146; 359–899)	603 (134; 353–1047)	609 (127; 353–1047)
Age, years	42 (16; 17–68)	38 (14; 17–62)	40 (14; 17–69)	63 (6; 55–76)	47 (16; 17–76)
Abnormal findings on inspection and palpation	6/20 (30%)	3/25 (12%)	7/26 (27%)	15/30 (50%)	25/78 (32%)
Abnormal imaging findings	15/20 (75%)	18/24 (75%)	15/26 (58%)	21/31 (68%)	51/78 (65%)

Data are n/N (%) or mean (SD; range). PaO_2:FiO_2=ratio of partial pressure of arterial oxygen to fractional concentration of oxygen in inspired air.

Table 2: **Baseline characteristics of donors stratified by inclusion criteria**

transplantation criteria and 12 (13%) donor lungs were excluded because they did not meet the prespecified criteria after OCS Lung assessment (figure 1). Of the remaining 81 donor lungs that were suitable for transplantation, two were not transplanted solely because of logistical reasons (one recipient was diagnosed with lung cancer on the day of transplantation and the surgical team was not available to do the transplant for the second patient). Therefore, 79 transplants were completed in this trial (donor lung use of 87% [79 of 91 lung pairs, excluding the two lung pairs because of logistical reasons, or 81 of 93 lung pairs]; figure 1).

Donor and recipient demographics and risk factors for the transplanted organs and recipients are shown in tables 1 and 2. Donor risk factors were further increased in 21 (27%) of 79 transplanted lungs who met two or three inclusion criteria. To independently validate the previous refusal status of the donor lungs in the EXPAND trial, we obtained the match run data from the United Network for Organ Sharing-Organ Procurement and Transplantation Network (UNOS-OPTN) on the 66 US donor lungs perfused on OCS Lung. These 66 donor lung pairs were refused by other transplant centres a mean of 35 times (range 0–197) before donor lung acceptance in the EXPAND trial centre. The EXPAND trial recipients represented an appropriate real-world mix of lung transplant recipients, including high-risk factors and characteristics. Mean lung allocation score was 42·0 (SD 13·5). 18 (23%) recipients were diagnosed with idiopathic pulmonary fibrosis and 22 (28%) with secondary pulmonary hypertension. The transplant procedure was done on cardiopulmonary bypass in 38 (48%) of 79 transplanted recipients.

Mean ischaemic times for the first and second implanted donor lungs were 2·6 h (SD 2·0) and 3·9 h (1·6), respectively, despite a total out-of-body time of 8·5 h (2·1) and 10·2 h (2·1) for first and second lungs, respectively (figure 2). The transplanted donor lungs' perfusion and ventilation variables at initial and final assessments on the OCS Lung showed a slight improvement over the course of OCS Lung perfusion and ventilation. Similarly, the ratio

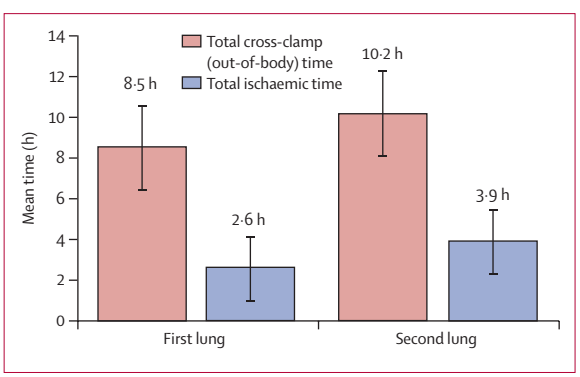

Figure 2: **Total cross-clamp time and ischaemic time of donor lungs**
Total cross-clamp or out-of-body time is the total time from donor aortic cross-clamp application until the pulmonary artery clamp is released in the recipient after transplantation. Total ischaemic time is the time the donor lungs were not perfused with oxygenated blood-based perfusion. Error bars show SD.

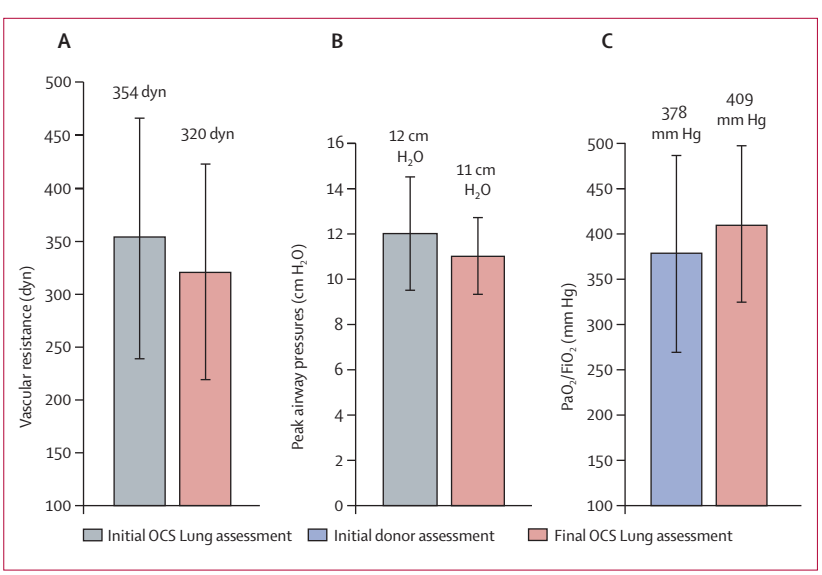

Figure 3: **OCS Lung perfusion and ventilation parameters (A, B) and donor lung PaO_2:FiO_2 assessment (C)**
Data are mean values. Error bar show SD. OCS=Organ Care system. PaO_2:FiO_2=ratio of partial pressure of arterial oxygen to fractional concentration of oxygen in inspired air.

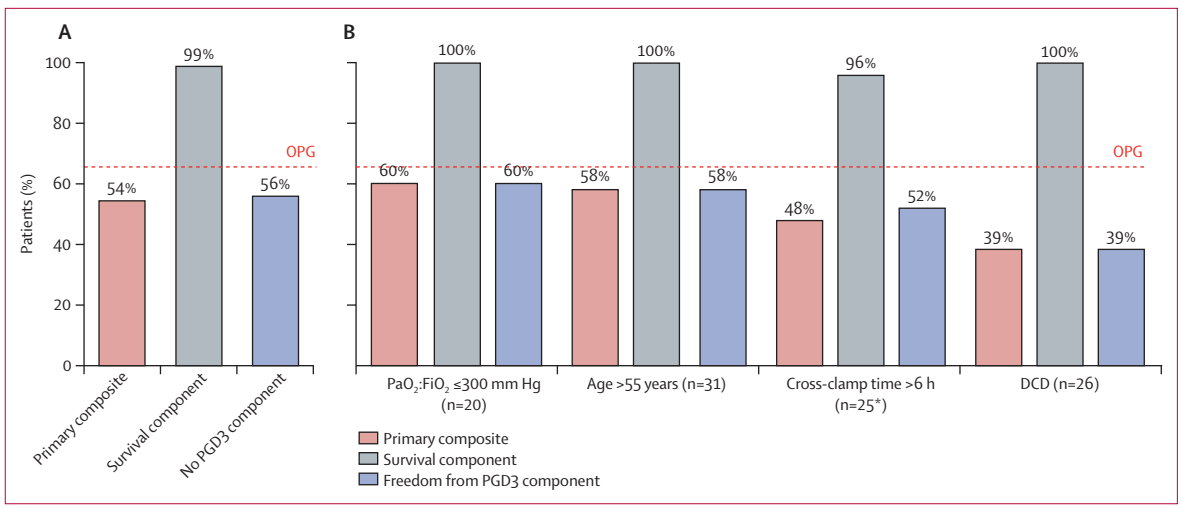

Figure 4: **EXPAND trial primary efficacy composite endpoint**
(A) Overall. (B) Stratified by donor criteria. DCD=donors after circulatory death. OPG=objective performance goal. PGD3=primary graft dysfunction grade 3. PaO_2:FiO_2=ratio of partial pressure of arterial oxygen to fractional concentration of oxygen in inspired air. *14 (56%) of the 25 donors had additional criteria including six (24%) donors who were also DCD.

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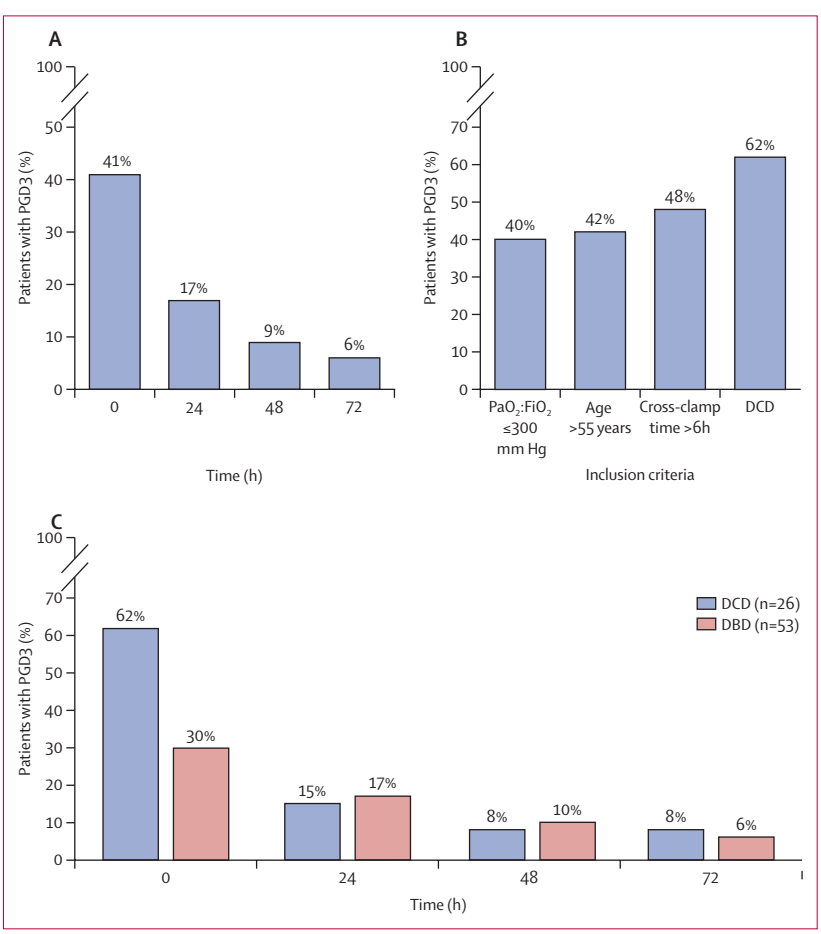

Figure 5: **EXPAND trial incidence of primary graft dysfunction grade 3**
(A) At each timepoint post-transplant. (B) Within initial 72 h post-transplant stratified by donor criteria. (C) At each timepoint post-transplant stratified by donors after circulatory death (DCD) and brain-death donors (DBD). PGD3=primary graft dysfunction grade 3. PaO_2:FiO_2=ratio of partial pressure of arterial oxygen to fractional concentration of oxygen in inspired air.

of PaO_2 to FiO_2 showed improvements at the end of preservation on OCS compared with the initial values in the donor's chest (figure 3).

The primary effectiveness composite endpoint of patient survival at day 30 post-transplant and no PGD3 within the initial 72 h was achieved in 43 (54%) of 79 patients and did not meet the prespecified OPG of 65% (figure 4A). The primary clinical driver for missing the OPG was the relatively high proportion of patients with PGD3 (35 [44%] of 79 patients) within the initial 72 h. Nevertheless, patient survival at day 30 post-transplant occurred in 78 (99%) of 79 patients, and was similar for all donor inclusion criteria (figure 4B). Detailed analysis of the incidence of PGD3 at each timepoint (figure 5A) and stratified by donor inclusion criteria (figure 5B) showed PGD3 was disproportionately high at baseline and in lungs from donors after circulatory death (figure 5C).

At 72 h post-tranplantation, the proportion of patients with PGD3 was five (6%) of 79, and of PGD3 or PGD2 was 13 (16%). These results are similar to those observed for the INSPIRE control group,[16] in which standard-criteria donor lungs were used (5·5% and 10·9%, respectively).

Patient survival in the EXPAND trial occurred in 78 (99%) of 79 patients at 30 days, 74 (94%) at 6 months, and 72 (91%) at 12 months (figure 6). These survival results were similar to those of the INSPIRE trial control group[16] and UNOS-OPTN[4] benchmarks for standard-donor-criteria lung transplants. Bronchiolitis obliterans syndrome diagnosis occurred in none (0%) of 79 patients at 6 months and one (1%) of 79 at 12 months in the EXPAND trial, versus three (2%) of 168 patients at 6 months and seven (4%) of 162 at 12 months in the INSPIRE control group (appendix p 3).

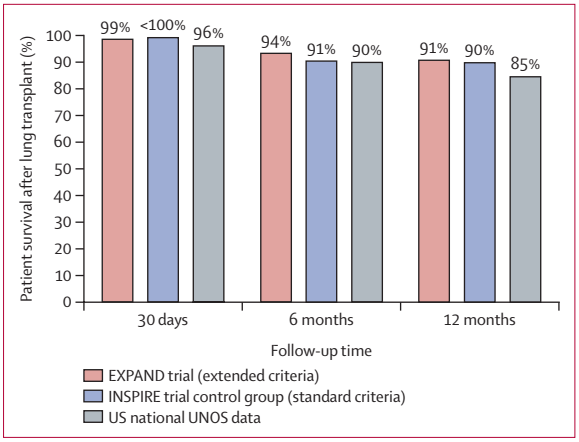

Figure 6: **Patient survival after lung transplant**
Data from the EXPAND trial (extended-criteria donors), INSPIRE control group (standard-criteria donors), and US national average (data from United Network for Organ Sharing [UNOS]).

	OCS Lung EXPAND trial (extended-criteria lungs; n=79)	OCS Lung INSPIRE trial control group (standard-criteria lungs; n=184)
Number of lung-graft-related serious adverse events up to the 30-day follow-up after transplantation (at most one per type)*		
Mean (SD)	0·3 (0·5)	0·3 (0·5)
Median (range)	0 (0–2·0)	0 (0–2·0)
95% CI of the mean	(0·1–0·4)	(0·2–0·4)
Type of lung-graft-related serious adverse events		
Acute rejection	0	4 (2%)
Respiratory failure†	12 (15%)	16 (9%)
Bronchial anastomotic complication	0	4 (2%)
Major pulmonary-related infection	7 (9%)	29 (16%)

Data are n (%) unless stated otherwise. OCS=Organ Care System. *Multiple occurrences of the same category of events in one patient are counted once only. †Need for reintubation, the inability to discontinue ventilator support within 4 days post-transplant, or tracheostomy.

Table 3: **Number of lung-graft-related serious adverse events during the first 30 days post-transplantation in the EXPAND trial and in the control group of the INSPIRE trial**

The EXPAND trial primary safety endpoint of 30-day mean lung-graft-related serious adverse events per patient was 0·3 events (SD 0·5), which was similar to that reported in the INSPIRE trial for standard-criteria donor lungs (table 3). Comparing individual types of serious adverse events, the EXPAND trial results were similar to those from the INSPIRE trial for acute rejection, bronchial anastomotic, and major pulmonary infection. However, the EXPAND trial reported a slightly higher proportion of patients with respiratory failure requiring reintubation or prolonged ventilation.

Discussion

To our knowledge, the EXPAND trial is the first multicentre prospective international trial to evaluate a blood-based normothermic portable ex-vivo lung perfusion system—OCS Lung—to improve donor lung use from currently underused donor groups. This trial showed that 87% of donor lungs from extended-criteria donors and donors after circulatory death, perfused and assessed with OCS Lung System, could be used. 1-year survival for patients transplanted with these lungs was 91%. The proportion of patients who had PGD3 within 72 h (including baseline) was 44%.

For decades, donor lung use for transplantation has been limited to approximately 20% of existing donors, which is the lowest reported use for solid organ transplants. This fact also undermines lung transplantation numbers and survival while on the waiting list. Reasons for this international problem are complex and multifactorial; however, one area that could have a major role is the limited capability for intervening during cold ischaemic storage, such as absence of ventilatory recruitment, optimisation, and lung assessment. The OCS Lung represents a change in lung preservation for transplantation from a static state to a dynamic environment, which enables new capabilities, including optimisation and functional assessment of donor lungs from donor to recipient, while also reducing the risk of ischaemic injury. The EXPAND trial prospectively targeted donor inclusion criteria that represent a minority of lung transplants, with 21 (27%) of 79 transplanted lungs having two or more risk factors. The use status of the donor lungs used in EXPAND was independently validated by the UNOS-OPTN match run data for US donors, showing that lungs were rejected for transplantation by US transplant centres an average of 35 times before donor lung acceptance in the EXPAND trial centre. To our knowledge, the 87% use obtained with the EXPAND trial is the highest reported use from a prospective, multicentre, ex-vivo lung perfusion trial. The promising use of 86% in the single-centre trial with static ex-vivo lung perfusion reported by Cypel and colleagues[9,10] has not been achieved in multicentre trials with static ex-vivo lung perfusion systems. In the DEVELOP-UK trial, five UK centres used a static ex-vivo lung perfusion platform (Vivoline LS1; Vivoline Medical AB, Lund, Sweden) and Toronto and Lund's based perfusion protocols,[11] resulting in 34% use. The NOVEL extension trial[12] was a multicentre trial using the XVIVO perfusion system (XPS; XVIVO Perfusion AB, Goteborg, Sweden) for extended-criteria donor lungs. Despite using better quality lung donors than the EXPAND trial (appendix pp 1, 2), the NOVEL trial[13] reported a 51% use rate.

The EXPAND trial reported that 44% of recipients had PGD3 within the initial 72 h post-transplantation from extended-criteria donor lungs and donor lungs after circulatory death compared with 28·8% reported in the control group of the INSPIRE trial of standard-criteria donors lungs. This higher than expected finding for PGD3 is the main reason why EXPAND did not meet the

OPG for the composite primary endpoint of 65%. Importantly, the OPG for the EXPAND trial was set using published proportions of PGD3 in mostly standard-criteria donor lungs[23] and in the absence of this information for extended-criteria donors and donors after circulatory death and, particularly, those exposed to ex-vivo lung perfusion. Since the EXPAND trial started, emerging data reported higher than predicted proportions of PGD3 within 72 h after ex-vivo lung perfusion for extended-criteria donor lungs. In the DEVELOP-UK trial[11] the proportion of recipients with PGD3 at baseline was 88·9% compared with 41% in the EXPAND trial and, at 72 h, the proportions were 27·8% and 6%, respectively.

The disproportionate increase of PGD3 from donors after circulatory death compared with brain-death donor lungs was also reported by Whitson and colleagues[12] in the NOVEL extension trial, in which PGD3 in lungs from donors after circulatory death at 24 h occurred in 50% compared with 15% in EXPAND, and at 72 h occurred in 25% compared with 8%, respectively. This observed higher prevalence of PGD3 in lungs from donors after circulatory death could be attributed to warm ischaemic injury during the agonal phase before retrieval. In this case, using a portable oxygenated-blood-based ex-vivo lung perfusion strategy might have attentuated the ischaemic injury on the donor allograft and expedited the assessment and recruitment phase compared with static ex-vivo lung perfusion, in which donor lungs require a period of cold ischaemia from retrieval until reaching the transplant centre for evaluation. Another potential contributing clinical factor for the high observed PGD3 prevalence could be that 38 (48%) of 79 recipients in the EXPAND trial were transplanted on cardiopulmonary bypass, which is a known risk factor for PGD3 development.[23] Future considerations should be given to the use of intraoperative manoeuvres to reduce PGD risk, such as off-pump or extracorporeal membrane oxygenation strategies, when appropriate.[24–26]

Despite the higher than expected proportion of patients with PGD3 at baseline and in donors after circulatory death that resolved by 72 h after transplant, EXPAND results showed short-term and long-term patient survival higher than 90%, which was similar to the results from the INSPIRE trial of standard-criteria donor lungs and to the US UNOS-OPTN national average for lung transplantation. In addition, the EXPAND trial reported a slightly lower occurrence of major pulmonary infection, acute rejection, and bronchial anstomotic complications than the INSPIRE trial. In addition, the early occurrence of all phenotypes of chronic lung allograft dysfunction was lower than in the INSPIRE trial during the 1-year follow-up, despite the relatively higher than anticipated prevalence of PGD3 in the initial 72 h post-transplant. This result could suggest that the PGD3 observed in the EXPAND trial after portable ex-vivo lung perfusion with OCS Lung might be of a different phenotype and its long-term effect might be different to the one observed historically with cold ischaemic storage. For example, several studies have shown alterations in the donor and recipient inflammatory profile after ex-vivo lung perfusion, which might affect the subsequent development and effect of PGD. Additional long-term bronchiolitis obliterans syndrome and survival follow-up of the EXPAND trial patients, as well as expanding the number of patients in the postmarket setting, would be crucial to further investigate this observation.

One of the limitations of the EXPAND trial was the single-arm design, chosen because of the ethical and patient safety challenges of allowing extended-criteria donor lungs to be randomly assigned to cold storage. Importantly, the single-arm design avoids any potential donor selection bias based on presence or absence of the OCS Lung at the donor centre after randomisation. Thus, we do not know how recipients who might have received lungs from extended-criteria donors and donors after circulatory death after cold ischaemic storage would have responded after transplant. Indeed, some of these extended-criteria donor lungs might well have been transplanted successfully without ex-vivo lung perfusion. However, many donor lungs in the EXPAND trial had multiple extended criteria, increasing the recipient's risk when being transplanted directly. Portable ex-vivo lung perfusion provides an extra safety tool to screen out donor lungs that might not do well after transplantation. Some centres now successfully use lung transplants from donors after circulatory death without ex-vivo lung perfusion as reported by the ISHLT registry;[27] however, these centres use strict selection criteria to maintain good clinical outcomes. It would be ethically and clinically challenging to accept lungs from donors after circulatory death with average cross-clamp times of 10 h and from donors older than 55 years or with a low initial PaO_2:FiO_2 ratio. These are the types of donor lungs that were placed on the OCS Lung for recruitment and functional assessment before final acceptance, and used successfully in the EXPAND trial. It was agreed that the best alternative was to use INSPIRE standard-criteria donor lung transplants as a comparator group for benchmarking.

Moreover, the use of lungs from donors after circulatory death in the USA remains low (2–4%),[8] despite positive reports from ISHLT registry data, and higher use of lungs from donors after circulatory or brain death (eg, 25–50%) in some European countries (Belgium, Spain, the Netherlands, the UK) and Australia. There is considerable variability in the process and procedures between countries, organ procurement organisation, and transplant centre protocols for the donors after circulatory death. Levvey and colleagues[28] showed an almost three-times difference in 1-year mortality associated with the continent where the lung transplant was done. The results of the EXPAND trial provide evidence that portable normothermic ex-vivo lung perfusion with OCS

Lung provides a standard reproducible platform that could enable safe and broader use of lungs from donors after circulatory death that currently go unused, because of the system's ex-vivo ventilatory optimisation and functional assessment capabilities.

Another issue is the inherent limitation of the overall ex-vivo lung perfusion strategy because it is associated with open air leak and severe lung contusions. For example, of the 12 donor lungs that were rejected for transplantation after OCS Lung assessment, six were rejected because of open air leak from either lung contusion or surgical laceration during retrieval, resulting in perfusate leak into the broncho-alveolar tree creating bloody froth and compromising oxygenation capacity of the donor lung. Open air leak and lung contusion remain a contraindication for OCS Lung and represents an area of potential research using novel modalities[29–31] to potentially further increase the use of these donor lungs for transplantation. Moreover, the study protocol described bronchiolitis obliterans syndrome rather than chronic lung allograft dysfunction as a prespecified secondary study outcome. Thus, FEV_1 values were reviewed for presence or absence of bronchiolitis obliterans syndrome without differentiating between restrictive allograft syndrome, bronchiolitis obliterans syndrome, or chronic lung allograft dysfunction.

As with many medical innovative technologies, the OCS Lung adds new costs over cold static storage. This cost could be well justified by the high number of donor lungs used that would have gone unused for transplantation and reduction of costs on the waiting list for patients who would potentially be transplanted sooner with increased donor lung use. In addition, given the portable nature of the OCS Lung system, it eliminates the need for all the costs associated with dedicated laminar flow operating room space for lung instrumentation, additional ventilator equipment, delayed decision making on the suitability of the lung graft for transplantation, and dedicated personnel costs associated with static ex-vivo lung perfusion systems.

In conclusion, the use of OCS Lung resulted in 87% of donor lungs being used, safely, from seldomly used lungs from extended-criteria donors and donors after circulatory death, with excellent survival outcomes up to 1 year of follow-up, few lung-graft-related serious adverse events, and a low prevalence of bronchiolitis obliterans syndrome post-transplantation. The ability to optimise, functionally assess, and safely use more lungs from these extended-criteria donors has the potential to substantially increase the number of viable donor lungs for transplantation globally. Longer follow-up of EXPAND trial patients is underway to assess the long-term survival and prevalence of bronchiolitis obliterans syndrome. In addition, a prospective OCS Thoracic Organ Perfusion registry has been developed to further expand prospective clinical evidence with the OCS Lung technology in the postmarket setting. Advances in portable ex-vivo lung perfusion technology, along with evolving strategies for reducing PGD, could usher a new era in lung transplantation marked by greater use and improved quality of lung allografts.

Contributors

GL, DVR, MH, MV, and AA had access to the entire clinical study report for the EXPAND trial. GL and DVR reviewed the data, wrote the manuscript, designed the figures and tables, and did the literature search for the manuscript. All authors participated in the data collection and reviewed the final data analysis from the OCS Lung EXPAND trial. All authors reviewed and approved the final version of the manuscript for submission.

Declaration of interests

GL reports grants from United Therapeutics and Maquet, and grants and non-financial support from Transmedics, during the conduct of the study. MIH reports personal fees from TransMedics, outside of the submitted work. GW reports a non-financial research grant from and travel reimbursement (to attend investigators meetings) from TransMedics, during the conduct of the study. MAS reports non-financial support from TransMedics, during the conduct of the study. MAD reports grants from TransMedics, during the conduct of the study, and grants from XVIVO, outside of the submitted work. AA reports other support from TransMedics, outside of the submitted work. DVR, MAV, MH, SH, AH, JCM, and JK declare no competing interests.

Data sharing

All data from the EXPAND trial will remain confidential and will not be shared until the last patient completes the 5-year follow-up endpoint in 2021.

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