Perfadex for Clinical Lung Procurement: Is It an Advance?

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Background. **Extensive laboratory experience suggested that low potassium dextran lung preservation solution (Perfadex; Medisan, Uppsala, Sweden) is superior to Euro-Collins (EC; Frusen, Hamburg, Germany), the clinical standard. The purpose of this study was to evaluate Perfadex in clinical lung transplantation.**

Methods. **A retrospective analysis of the outcome of 69 consecutive lung allografts retrieved and used for transplantation was made. Donor lungs were flushed with EC in 37 patients and Perfadex in 32 patients. The evaluation measurements were quantitative chest roentgenogram score (grade 0 to 4), graft oxygenation, duration of mechanical ventilation, length of intensive care treatment, and survival.**

Results. **The mean chest roentgenogram score was 1.55 and 1.81 for the EC group compared with 1.18 and 2.09 for the Perfadex group at 1 and 48 hours, respectively ($p = 0.1$ and 0.8, respectively). Arterial alveolar oxygen tension ratio was similar at 12 and 24 hours (0.61 vs 0.67; $p = 0.8$; and 0.64 vs 0.53; $p = 0.3$, respectively). The mean ventilation time was 71.2 ± 32.3 hours versus 81.9 ± 43.6 hours for the EC and Perfadex groups, respectively ($p = 0.4$). The mean intensive therapy unit stay was 3.1 ± 2.6 days for the EC group compared with 4.1 ± 3.9 days for the Perfadex group ($p = 0.4$). Death caused by primary organ failure was 5.1% for the EC group compared with 3.1% for the Perfadex group ($p = 0.8$).**

Conclusions. **There was no difference between Perfadex and EC in clinical lung preservation. This may reflect the difference between controlled laboratory environment and the real world of brain death lung injury. Further studies are required to investigate the impact of Perfadex in the long-term outcome of lung transplantation.**

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In recent years lung transplantation has become an effective therapy for patients with end-stage respiratory failure but is limited by severe scarcity of suitable donor organs and by still suboptimal preservation techniques that lead to various degrees of ischemic–reperfusion injury. Perioperative mortality is in the range of 10% to 20%, and reperfusion injury is one of the most frequent causes of early death after lung transplantation [1]. The incidence of reperfusion injury has been reported to range from 20% to 40% in different lung transplant programs [2]. Clinically this syndrome results in progressive hypoxemia, decreased pulmonary compliance, pulmonary edema, and increased pulmonary vascular resistance.

Donor lung preservation using a number of solutions that are prepared by modification of Euro-Collins (EC) (Frusen, Hamburg, Germany) preservation solution is the clinical standard in most lung transplantations [3]. The application of EC is associated with a high rate of reperfusion injury [3]. To improve the quality of pulmonary allograft preservation, alternative solutions have been developed. Perfadex (Medisan, Uppsala, Sweden) is a low-potassium solution with extracellular electrolyte composition that significantly reduces ischemic reperfusion and provides good functional results in terms of postischemic oxygenation (Table 1).

Experimental studies in vascular segments [4–5] or in isolated perfused lung or heart lung preparations [6] and transplantation experiments in canines and pigs have demonstrated the potential benefits of an extracellular-type low-potassium dextran (Perfadex) preservation solution for lung procurement when compared with the conventionally used EC solution or other solutions with high concentration of potassium [7–8]. The purpose of the present study was to determine whether the advantage of Perfadex as observed in the experimental setting could be confirmed in human lung preservation.

Material and Methods

Study Population

The study was conducted in a retrospective manner and included all donors considered for lung donation by the Freeman Hospital (Newcastle upon Tyne, UK) during the period between January 2000 and January 2002. Lung retransplantation recipients (n = 2), lungs retrieved by other preservative methods (n = 5), and lungs retrieved from live related lung donors (n = 2) were excluded from this study.

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Table 1. Composition of the Preservation Solutions

(Ad 1000 mL)	Euro-Collins	Perfadex
Na^+ (mmol/L)	10	138
K^+ (mmol/L)	115	6
CI^- (mmol)	15	142
Mg^{++} (mmol/L)	···	0.8
SO_4^{2-} (mmol/L)	···	0.8
Dextran (40 g)	···	50
HCO_3^- (mmol/L)	10	···
$H2PO_4^-$ (mmol/L)	15	0.8
HPO_4^{2-} (mmol/L)	42.5	···
Glucose (g)	35.7	0.91
Osmolarity (mOsm/L)	375	292

Donor Selection

As in other United Kingdom transplant centers, donor selection criteria at our center was liberalized to attract a larger donor pool. It has already been demonstrated that marginal heart and lung donors have been optimized with careful intensive care management and successful use for selected recipients. The criteria for selection of lung donors are widely established and approved by the United Kingdom Transplant Support Service Authority. They are summarized in Table 2.

Lung donors were assessed on the basis of clinical history, radiologic appearance, duration of mechanical ventilation, and donor-oxygen tension. Donor-oxygen tension was determined during mechanical ventilation at an inspired oxygen tension of 1.0 and positive end-expiratory pressure of 5 cm H_2O. Fibro-optic bronchoscopy was used to assess the bronchial tree in every donor.

Donor Procurement

Before organ flushing, a bolus of 500 ug of epoprostenol sodium (Flolan; Wellcome, London, UK) was injected into the pulmonary artery to achieve vasodilatation of the pulmonary vessel bed. Then the aorta was cross-clamped, and flushing of both lungs through the pulmonary root was started. The preservation fluids used were EC, which was used in each donor procedure until March 2001, and Perfadex, which was introduced to our clinical program in April 2001 and was then used in each donor procurement procedure until the end of the study.

Table 2. General Criteria for Lung Donation in the United Kingdom

Meet criteria for brain death
Donor consent obtained
Age up to 60 years
ABO blood group compatibility
No active infection
No extracerebral malignant disease
No active chest infection
No history of asthma, chronic chest condition
Satisfactory operative assessment
Satisfactory radiologic assessment
Satisfactory oxygenation
$Pa_{O_2} > 300$ mm Hg or $PY_{O_2} > 300$ mm Hg (P_{IO_2} 100% 5 positive end-expiratory pressure), or both

The preservation fluid was used in a volume of 60 mL/kg, infusion pressure of 10 to 15 cm H_2O and temperature of 4° to 6°C. Ventilation was continued with 100% oxygen until flushing was complete. Retrograde perfusion of 1,000 mL through the pulmonary veins was performed only in the Perfadex group. Explantation of the lung block was carried out in the deflated state. Then the retrieved lungs were kept inflated at a pressure of 25% to 75% of the maximum lung volume capacity. Ischemic times were defined as the interval from donor cross-clamping to reperfusion and were recorded for each lung.

Previously described standard techniques were used for single and double lung transplantation. Recipients underwent standard pulmonary function testing before transplantation and determination of left and right ventricular ejection fractions by noninvasive examination. Cardiopulmonary bypass was used for all double lung and heart–lung procedures. Cardiopulmonary bypass was used in single lung procedures only when hemodynamic, technical, or other intraoperative factors made it necessary.

Assessment of Allograft Function

Chest radiographs were obtained at 0 and 24 hours after the operation. A semiquantitative scale was used to assess the degree of pulmonary allograft injury, with scoring as follows: 0 = no abnormal findings; 1 = perihilar infiltrate; 2 = infiltrate localized to a limited lung field; 3 = diffuse moderate interstitial and alveolar infiltrate; 4 = diffuse severe interstitial and alveolar infiltrate. Each lung was graded independently, and a mean score was calculated.

Arterial blood gases were obtained at multiple intervals after transplantation and used to calculate the arterial and alveolar oxygen tension ratio ($_{a/A}$ O_2 ratio) and the Pa_{O_2}/Fi_{O_2} ratio. The alveolar oxygen tension (PA_{O_2}) was calculated as follows: $PA_{O_2} = (760 - P_{H_2}O)\ Fi_{O_2} - 1.25\ PaCO_2$, where $P_{H_2}O$ is the water vapor partial pressure, assumed to be 47 mm Hg at 37°C, Fi_{O_2} is the inspired fraction of oxygen, and $PaCO_2$ is the arterial partial pressure of carbon dioxide.

Time of intubation, length of stay in the intensive care unit, and patient survival at 30 days after transplantation were recorded.

Statistical Analysis

Statistical computations were carried out with SPSS software (Windows 7.5; SPSS, Inc, Chicago, IL).

Results are expressed as mean ± standard deviation. Comparisons between patient characteristics mean allograft ischemic times, perioperative blood transfusion requirements, a/A O_2 ratios, and Pa_{O_2}/Fi_{O_2} ratios in the two groups were carried out with the unpaired *t* test.

Comparisons of mean chest radiographic scores, death, duration of ventilation, and other postoperative events

Table 3. Comparison for the Patient Variables Between Patients in Both Groups

Variable	EC Group (n = 37)	Perfadex Group (n = 32)	*p* Value
Age	28 ± 14	36 ± 15	0.09
Gender			
Male (%)	21 (56%)	19 (57%)	0.9
Female (%)	16 (44%)	13 (43%)	0.9
Recipient pathology			
Cystic fibrosis	21	19	0.9
Chronic obstructive airways disease	7	6	0.9
Cryptogenic fibrosing alveolitis	2	1	0.9
Surgical procedure			
Double lung transplantation	27	24	0.8
Heart-lung transplantation	3	3	0.9
Single lung transplantation	7	5	0.9
Left ventricular ejection fraction prior to operation (%)	60 ± 11	63 ± 6	0.8
Donor criteria			
Donor age	38 ± 13	37 ± 12	0.9
Donor Pao_2	411 ± 42	431 ± 122	0.8
Donor ventilation (hours)	69 ± 13	66 ± 11	0.8
Cardiopulmonary bypass (%)	32 (86%)	28 (87%)	0.9
Use of nitric oxide during the perioperative period	23/37 (62%)	21/32 (65%)	0.8
Ischemic time (min)	293 ± 47	317 ± 36	0.4

were also analyzed using the Mann–Whitney *U* test or unpaired *t* test where applicable.

Results

Recipient and Donor Characteristics

Comparison of recipient-related and donor-related characteristics between EC (n = 37 donors) and Perfadex (n = 32 donors) is detailed in Table 3. There were no significant differences in donors or recipients demographics. All cystic fibrosis patients received double lung transplantation. For chronic obstructive airway disease, 3 patients from each group received double lung transplantation. Three patients from each group underwent heart lung transplantation. The details of the recipients and type of operation in both groups are also described in Table 3.

Postoperative Allograft Function

RADIOLOGIC ASSESSMENT. Mean chest roentgenogram scores for both groups were compared at 1, 24, and 48 hours after transplantation. Immediately after the operation, the EC group had a mean chest roentgenogram score of 1.55 ± 0.63 in comparison with 1.18 ± 0.79 for the Perfadex group ($p = 0.1$). At 24 hours, scores remained 1.73 ± 0.36 in the EC group and 1.50 ± 0.34 in the Perfadex group ($p = 0.7$). Similar chest roentgenogram scores were seen up to 48 hours after operation ($p = 0.8$; Fig 1).

GRAFT OXYGENATION. The Po_2/Fio_2 ratio was similar in both groups at various stages after transplantation. Po_2/Fio_2 was 267 ± 78 versus 298 ± 88 ($p = 0.08$) and 244 ± 51 versus 266 ± 59 for EC and Perfadex patients, respectively ($p = 0.9$ at 12 and 24 hours posttransplantation, respectively; Fig 2). The average arterial and alveolar oxygen tension ratio was also similar between recipients in EC and Perfadex patients at 1, 12, 24, and 48 hours after operation at 0.46, 0.61, 0.64, and 0.55 ratios versus 0.52, 0.67, 0.53, and 0.57 ratios for the EC and Perfadex groups, respectively ($p = 0.2$, 0.8, 0.4, and 0.7, respectively). Extracorporeal life support was not required for any patient in this study.

POSTOPERATIVE STAY. Mean duration of intubation was also similar in both groups (71.2 ± 32.2 hours in the EC group compared with 81.9 ± 43.6 hours in the Perfadex patients ($p = 0.5$; Fig 3). The prevalence of patients treated with pulsed steroid because of proven or suspected rejection during the first 3 weeks after transplantation was 27 of 39

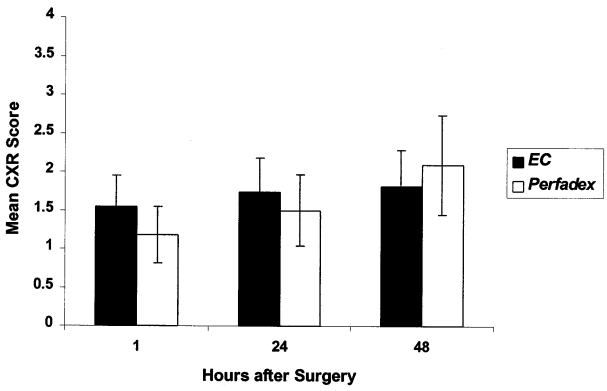

*Fig 1. Mean chest roentgenogram scores (*Mean CXR Score*) at 1, 24, and 48 hours after operation. (*EC = *Euro-Collins; Frusen, Hamburg, Germany.) (Perfadex; Medisan, Uppsala, Sweden.)*

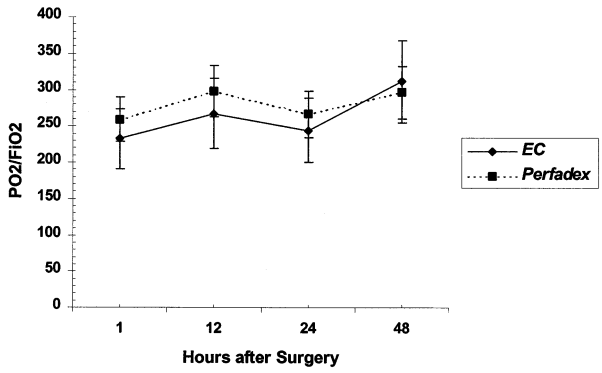

Fig 2. Po_2/Fio_2 for Euro-Collins (EC; Frusen, Hamburg, Germany) and Perfadex (Medisan, Uppsala, Sweden) groups at different hours after operation.

(70%) for the EC group compared with 25 of 32 (78%) for the Perfadex group ($p = 0.4$).

Similarly the mean length of stay in the intensive care unit was not statistically different (19 ± 2.65 days for patients in the EC group and 22 ± 3.95 days for patients in the Perfadex group; $p = 0.6$).

Survival and Cause of Death

Two patients died from the EC group (2 of 37; 5.1%) compared with 1 patient from the Perfadex group (1 of 32; 3.1%) caused by primary graft failure within the immediate postoperative stage ($p = 0.8$). The overall 30-day hospital mortality rate was 4 of 37 (10.8%) in the EC patients and 3 of 32 (9.3%) in the Perfadex patients. This difference did not reach statistical significance ($p = 0.88$).

One patient from the EC group died on postoperative day 67 caused by persistent bronchopleural fistula. Another patient from the same group died at day 29 from postoperative sepsis. Two patients from the Perfadex group died on postoperative days 15 and 74. The first patient died because of heart failure after a heart–lung transplantation procedure, and the second patient died from multiorgan failure. Two patients from the Perfadex group required ventilation on postoperative days 8 and 47 due to acute respiratory insufficiency caused by acute severe lung rejection. Both patients were treated successfully with antirejection therapy and discharged from the hospital.

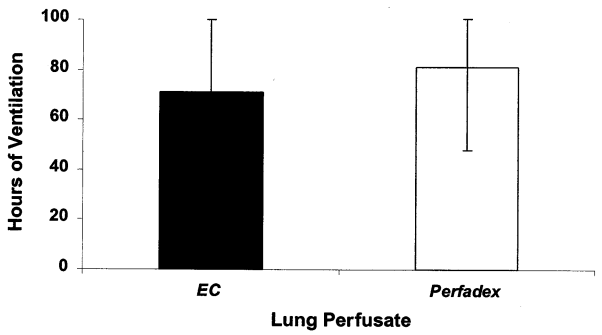

Fig 3. Hours of ventilation in the Euro-Collins (EC; Frusen, Hamburg, Germany) and Perfadex (Medisan, Uppsala, Sweden) groups.

Comment

Lung transplantation is an effective treatment for many types of end-stage pulmonary disease. Compared with initial results, improved outcome was mainly related to optimized immunosuppression regimens and modified protocols for pulmonary preservation. However, early graft dysfunction remains a continuing problem, resulting from multifactorial lung injury starting within the donor and continuing through harvesting, organ storage, implantation and postischemic reperfusion. Reperfusion injury is a common complication of lung transplantation. In approximately 15% to 20% of patients, reperfusion injury leads to graft failure, and in even a higher percentage of patients, the amelioration of reperfusion injury leads to less disturbed graft function [9].

Currently, modified EC is the most widely used for clinical lung preservation solution [10]. However, high potassium concentration of EC is believed to cause severe pulmonary vasoconstriction followed by edema formation [11]. Moreover, an indirect effect on the perivascular smooth muscle cells by an impaired endothelial effect nitric oxide synthesis may play a role in the altered relaxation capacity of the transplant vasculature, resulting in an increase of vascular resistance [4, 11]. Therefore many experimental studies were conducted to modify EC solution in order to improve the quality of lung graft and to extend the ischemic time. Solutions with extracellular ion composition as low potassium dextran solution (Perfadex) were thought to be superior to EC with regard to preservation of endothelial function [12].

A previous study demonstrated that preservation of type II pneumocytes with Perfadex revealed less cytotoxicity and improved cellular metabolic activity when compared with EC solution [13]. In animal transplant experiments, using Perfadex as a flushing solution, a good transplant function was observed for preservation time up to 24 hours [12]. Experimentally comparing Perfadex to EC, a significantly better graft function was achieved after the use of cardiopulmonary bypass [13–15]. Also in a bovine model of orthotopic single lung transplantation after 18 hours of cold ischemic storage, Sakamaki and colleagues [16] reported a significant reduction of lipid perioxidation and ischemic–reperfusion injury after the use of Perfadex when compared with the effects of EC. In clinical lung procurement, Thabut and colleagues [17] reported better lung preservation outcome with extracellular-type solutions (Cambridge or Celsior) in comparison with an intracellular type of solution (EC; University of Wisconsin).

The initial two studies [18–19] to assess the impact of Perfadex in clinical lung procurement reported improved early survival and reduction in the incidence of reperfusion injury in favor of lung allografts preserved by Perfadex. However, both reports shared the disadvan-

tages of study design that both groups did not match exactly in terms of patient selection, type of procedure or era of transplantation. In addition, the previous two studies did not take into consideration the general recent improvement in the early outcome of lung transplantation caused by improvement of the learning curve, refinement of the operative technique, increased understanding of the pathophysiology of reperfusion injury, recent changes in clinical practice including controlled reperfusion, and routine using of nitric oxide during the postoperative period. All these factors may change the interpretation for the outcome of new lung preservative solutions. Fischer and associates [20] recently reported improved oxygenation (measured by Po_2/Fio_2) in human lung allografts preserved by Perfadex with an average ischemic time of 348 minutes compared with EC preserved allografts for shorter ischemic periods. None of the previous studies investigated the radiologic appearance or the changes in alveolar arterial oxygen tension ratio for the recipients in either side.

The present study represents an assessment of two different generation lung perfusates used during the same era by a single institution, which included radiologic appearance and detailed graft oxygenation. During the period of this study the criteria of donor lungs, standards for procurement of the graft, surgical procedure, anesthesia, postoperative care, and immunosuppression regimen protocol remained unchanged. The waiting list of our center as a large European lung transplant program is characterized by a high number of patients waiting more than 3 years until a donor organ is available, while becoming a borderline transplant candidate caused by deteriorated physical status and high incidence of prior thoracic operation. These recipients were not excluded from the study. Therefore this study offered a strong assessment for the outcome of lung procurement using EC and Perfadex in a population of poor and borderline lung transplant recipients.

Unlike the previous reports, we could not demonstrate the expected benefits in the outcome of lung procurement Perfadex compared with EC. One of the reasons behind the discrepancy between experimental and clinical work in lung preservation is because of the large variety of experimental models that have been used to assess the efficacy of lung preservative solutions, and none of these animal models used to assess this outcome were actually brain stem death animal models. This underlines the necessity of standardizing not only the type of models used in lung preservation research but also the criteria by which lung preservation is analyzed and reported in the literature.

The retrospective nature of our analysis represents the limitation in our study. However, the study population and type of procedure were similar in each group. In evaluation of the graft oxygenation and radiologic score, we did not analyze the outcome in each group according to the procedure they have had (heart lung, double lung, or single lung transplantation procedure). However, the number of single lung transplantation procedures is equal in both groups. The percentage of use of cardiopulmonary bypass in both groups was also identical. Another limitation in our study was the relatively short ischemic time, which may undermine the influence of lung preservatives in the early allograft function. Further studies may be required to investigate the potential role of Perfadex in clinical lung procurement for extended ischemic periods.

In conclusion, the initial results for clinical lung procurement using Perfadex are comparable with our results of lung procurement using EC solution in terms of early graft function, graft oxygenation, survival and intensive therapy unit staying. Our study did not demonstrate any real advantage in clinical lung procurement using low potassium dextran solution of Perfadex over the EC. Further studies are required to demonstrate the midterm and long-term benefits of the low potassium contents of the Perfadex in the procurement of borderline human lung allografts.

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