# Effects of exogenous surfactant instillation in clinical lung transplantation: A prospective, randomized trial

Martin Strüber, MD,[a] Stefan Fischer, MD, MSc,[a] Jost Niedermeyer, MD,[b] Gregor Warnecke, MD,[a] Bernhard Gohrbandt, MD,[a] Adelheid Görler, MD,[a] Andre R. Simon, MD,[a] Axel Haverich, MD,[a] and Jens M. Hohlfeld, MD[b]

**Objective:** Despite the introduction of low potassium–based preservation strategies for clinical lung transplantation, relevant early graft dysfunction occurs in up to 20% of cases after lung transplantation. This was found to be frequently associated with postreperfusion surfactant dysfunction. We performed a randomized, prospective study investigating the effect of exogenous surfactant instillation into human donor lungs on posttransplant surfactant function and on clinical outcome.

**Methods:** Exogenous surfactant was instilled into 15 donor lungs before retrieval via bronchoscopy. Bronchoalveolar lavage fluids were taken before instillation as well as 24 hours after transplantation. Surfactant function, phospholipids, and protein content in bronchoalveolar lavage fluids were assessed and clinical data prospectively recorded. Pulmonary function testing was performed 4 weeks after lung transplantation. Additionally, the best forced expiratory volume in 1 second was determined within the first year after lung transplantation. The control group consisted of 14 patients receiving donor lungs without surfactant instillation in randomized order. Pulmonary function test results were further compared with those of 154 consecutive recipients of bilateral lung transplants, which were not involved in the study (historical control).

**Results:** No deaths occurred during the first year after lung transplantation. Surfactant function in donor lungs was within normal ranges before harvest. In the control group, surfactant function was markedly impaired after reperfusion. This was significantly improved by surfactant substitution. Protein content of the bronchoalveolar lavage fluid in the surfactant group was significantly lower, indicating less leakage through the alveolocapillary membrane. Forced expiratory volume in 1 second after 4 weeks was significantly higher in the surfactant group than in either control group ($P = .034$ and .01, respectively). Interestingly, the best forced expiratory volume in 1 second during the first year after lung transplantation was significantly higher in both control groups compared with forced expiratory volume measured in examinations 4 weeks after lung transplantation ($P = .01$). The best forced expiratory volumes in 1 second of control patients were comparable with those in surfactant lungs 4 weeks after transplant.

**Conclusions:** This study indicates a protective effect of exogenous surfactant instillation to donor lungs before retrieval on post–lung transplantation surfactant function and on early clinical outcome. This approach may help to improve the outcome after lung transplantation in the future.

From the Hannover Thoracic Transplant Program, Division of Thoracic and Cardiovascular Surgery[a] and the Department of Respiratory Medicine,[b] Hannover Medical School, Hannover, Germany.

Received for publication April 11, 2006; revisions received Dec 10, 2006; accepted for publication Dec 14, 2006.

Address for reprints: Martin Strüber, MD, Director, Hannover Thoracic Transplant Program, Division of Thoracic and Cardiovascular Surgery, Hannover Medical School, Carl Neuberg Strasse 1, 30625 Hannover, Germany (E-mail: strueber.martin@mh-hannover.de).

J Thorac Cardiovasc Surg 2007;133:1620-5

0022-5223/$32.00



doi:10.1016/j.jtcvs.2006.12.057

TX

One of the major obstacles in clinical lung transplantation is the occurrence of reperfusion injury, which may lead to life-threatening primary graft dysfunction. The importance of this issue initiated an enormous effort in research related to experimental lung transplantation. The majority of investigations focused on the improvement of pulmonary preservation. With the introduction of

**Abbreviations and Acronyms**
BAL = bronchoalveolar lavage
BALF = bronchoalveolar lavage fluid
$FEV_1$ = forced expiratory volume in 1 second
$\gamma_{min}$ = minimal surface tension
LPD = low-potassium dextran
SA/LA = small-to-large aggregates ratio

Euro-Collins flush perfusion, a worldwide standard was announced. However, although ischemic times were limited to 6 hours only, the initial graft function remained unreliable and unpredictable. One of the findings was impairment of surfactant function after reperfusion, a unique feature in pulmonary preservation and transplantation. In experimental studies, substitution of exogenous surfactant was used to prevent primary graft dysfunction.

We were able to demonstrate a beneficial effect of surfactant substitution on graft function in recipients with severe experimental reperfusion injury.[1] A quantum leap in lung preservation was achieved with the introduction of low-potassium dextran (LPD) solution for flush preservation. A significant improvement of postoperative graft function was reported in clinical[2,3] and experimental studies, and better surfactant function was shown.[4] The purpose of this study was twofold: The first question addressed was whether the improvements of surfactant function resulting from LPD solution could be verified in clinical lung transplantation. The second aim was to define whether substitution of exogenous surfactant to the donor at the time of lung retrieval has an impact on surfactant function beyond the reperfusion period. The latter question was to be answered by laboratory assessment of surfactant composition and function and not by the early clinical course. Owing to the high variability of lung recipients and the high costs of exogenous surfactant, such a study would have been seriously underpowered and not feasible.

## Patients and Methods

In a prospective, monocenter, randomized, investigator-initiated trial, 30 donor lungs for elective double lung transplantation were assessed by standard criteria before retrieval. All donors were evaluated consecutively and those with severe neurologic pulmonary edema were excluded from this study. On acceptance of the graft, randomization was performed and a bronchoalveolar lavage (BAL) was obtained from the right middle lobe. In the control group (n = 14), lungs were flushed antegradely via the pulmonary artery with LPD solution (4-6 L) at 8°C within 10 minutes while mechanical ventilation was continued. Lungs were excised en bloc and stored at a mild inflated state in cold (4°C) preservation solution. In the surfactant group (n = 15), a bovine surfactant preparation (Alveofact; Thomae, Germany) was instilled bronchoscopically (100 mg/kg body weight of the donor) and distributed in aliquots of 2 to 3 mL to all segments of both lungs. Thereafter, preservation and harvesting were conducted as described for the control group. One double lung graft was not transplanted and was excluded from the study for severe infiltrations found ex situ in both lower lobes. Bilateral sequential lung transplantation was carried out in all recipients via anterolateral minithoracotomies as we described previously.[5] In 12 recipients, the transplant procedure was carried out with the support of cardiopulmonary bypass. Use of cardiopulmonary bypass was statistically comparable in the surfactant and control groups ($P = .91$). After transplantation, recipients were transferred to the intensive care unit and their lungs were mechanically ventilated in a pressure-controlled mode. BAL was obtained 18 to 24 hours after graft reperfusion.

**TABLE 1. Patient characteristics**

| | Recipients | |
|---|---|---|
| | Surfactant | Control |
| Height (cm) | 169 ± 7.2 | 169 ± 9.6 |
| Age (y) | 34 ± 11 | 41 ± 13 |
| Female/male | 9/6 | 8/6 |
| Total lung capacity (L) | 5.6 ± 0.9 | 5.7 ± 0.8 |
| Diagnosis | | |
| Emphysema | 5 | 4 |
| Cystic fibrosis | 5 | 5 |
| Fibrosis | 2 | 2 |
| Other | 3 | 3 |

### Donor Characteristics

The main causes of deaths in the group of organ donors were subarachnoidal bleeding (31%) and head injury (28%). The mean donor age was 34.6 ± 11.2 years (range, 14-53 years). There were 17 male and 12 female donors, which were mechanically ventilated for 77 ± 65 hours (15-240 hours) before multiorgan donation. The ischemia time ranged from 210 to 640 minutes with a mean of 392 ± 42 minutes. There was no significant difference in these demographics between the surfactant and the control groups. Gender was not statistically different between the surfactant group (8 female donors of 15) compared with the control group (6 female donors of 14).

### Recipient Characteristics

Recipient age, gender, and diagnosis are shown in Table 1. All patients were candidates for elective pulmonary transplantation. None was receiving mechanical or noninvasive ventilatory support before transplant. Informed consent for the study was obtained from each recipient. This trial was approved by the local ethics committee of the Hannover Medical School. Patient insurance for the trial was supplied.

The immunosuppressive protocol in all study and historical control patients consisted of a triple drug regimen of cyclosporine A (trough levels 250-350 ng/mL for the first 6 months after lung transplantation and 200-300 ng/mL thereafter), mycophenolic acid (2-3 g/day according to body weight), and prednisone (starting with 1 mg/kg body weight, followed by a taper regimen to a target dose of 0.1 mg/kg body weight over 3 weeks). No immunosuppressive induction therapy was administered. Acute rejection was