

# Lung Transplantation in Cystic Fibrosis: Perioperative Mortality

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**OBJECTIVE:** To determine the incidence and causes of perioperative mortality following lung transplant for cystic fibrosis.

**PATIENTS AND METHODS:** We analyzed the cases of 57 patients. Fifty-five patients received double lung transplants, 1 received a heart-double lung transplant, and 1 received a combined double lung and liver transplant. Information related to the organ donor, recipient, lung graft, and early postoperative period was gathered. Perioperative mortality was defined as death resulting from anesthesia or surgery regardless of how many days had passed. The Kaplan-Meier method was used to analyze survival. A Cox logistic regression model was used to determine variables affecting mortality.

**RESULTS:** Survival was 83.7% at 1 year after transplantation, 77.3% at 2 years, and 66.9% at 5 years. Five (8.7%) patients died as a result of anesthesia or surgery. A ratio of PaO<sub>2</sub> to inspired oxygen fraction (FiO<sub>2</sub>) less than 200 mm Hg in the early postoperative period was observed in 8 (14%) patients. Primary graft failure occurred in 4 patients, due to pneumonia in 2 and to biventricular dysfunction in 2. Three of those patients died. Two patients with PaO<sub>2</sub>/FiO<sub>2</sub> greater than 200 mm Hg died after surgery, 1 from septic shock due to *Pseudomonas cepacia* and the other from massive cerebral infarction.

PaO<sub>2</sub>/FiO<sub>2</sub> upon admission to the recovery care unit was the only variable significantly associated with perioperative mortality in the logistic regression model ( $P=0.0034$ ).

**CONCLUSIONS:** The only factor significantly related to perioperative mortality in patients receiving transplants for cystic fibrosis was PaO<sub>2</sub>/FiO<sub>2</sub> upon admission to the recovery unit.

**Key words:** Cystic fibrosis. Lung transplant. Perioperative mortality.

Fibrosis quística y trasplante pulmonar. Mortalidad perioperatoria

**OBJETIVO:** Conocer la incidencia y las causas de mortalidad perioperatoria en el trasplante pulmonar por fibrosis quística.

**PACIENTES Y MÉTODOS:** Se ha analizado a 57 pacientes. Se realizaron 55 trasplantes bipulmonares, uno cardiobipulmonar y uno hepatobipulmonar. Se recogieron una serie de datos del donante, del receptor, del injerto pulmonar y del postoperatorio inmediato. Se definió la mortalidad perioperatoria cuando el fallecimiento aconteció como consecuencia del acto anestésico-quirúrgico, independientemente de los días transcurridos. Para determinar qué variables la condicionaron se utilizó el modelo de regresión logística de Cox. La supervivencia se calculó mediante el método de Kaplan-Meier.

**RESULTADOS:** La supervivencia fue del 83,7% al año del trasplante, del 77,3% a los 2 años y del 66,9% a los 5 años. Cinco pacientes (8,7%) fallecieron en el perioperatorio. En 8 (14%) se objetivó un cociente de presión arterial de oxígeno (PaO<sub>2</sub>)/fracción inspiratoria de oxígeno (FiO<sub>2</sub>) inspirado < 200 mmHg en el perioperatorio inmediato y 4 se catalogaron como fracaso primario del injerto, 2 por una neumonía y 2 por disfunción biventricular; 3 de estos pacientes fallecieron en el perioperatorio, uno por un shock séptico por *Pseudomonas cepacia* y otro por un infarto cerebral masivo.

Mediante el análisis de regresión logística, el cociente PaO<sub>2</sub>/FiO<sub>2</sub> al ingresar en la unidad de reanimación fue la única variable que condicionó significativamente la mortalidad perioperatoria ( $p = 0,0034$ ).

**CONCLUSIONES:** El cociente PaO<sub>2</sub>/FiO<sub>2</sub> al ingresar en la unidad de reanimación fue la única variable que condicionó significativamente la mortalidad perioperatoria en los pacientes trasplantados por fibrosis quística.

**Palabras clave:** Fibrosis quística. Trasplante pulmonar. Mortalidad perioperatoria.

## Introduction

A better understanding of cystic fibrosis has improved the prognosis considerably for patients with

this disease, bringing their life expectancy to somewhat over 30 years.<sup>1</sup> However, the course of disease is marked by serious and irreversible deterioration in lung function leading to severe respiratory insufficiency, which is the most common cause of death for cystic fibrosis patients. Lung transplantation has become the treatment of choice at this stage,<sup>2</sup> given its 5-year survival rate of around 60%<sup>3-5</sup> and a perioperative mortality rate ranging from 0% to 10%.<sup>3-8</sup>

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Although many risk factors for mortality have been studied, they have usually been assessed with regard to lung transplantation in all types of patients.<sup>6</sup> Therefore, we aimed to study perioperative mortality and risk factors in a group of patients with cystic fibrosis who received lung transplants.

### Patients and Methods

From March 1993 through June 2004, 57 patients diagnosed with cystic fibrosis received transplants at the thoracic surgery department of Hospital Universitario La Fe in Valencia, Spain. Fifty-five procedures were sequential double-lung transplants. One was a heart-lung transplant and the last was a liver-lung transplant.

Donor variables gathered were sex, age, cause of brain death, days intubated, PaO<sub>2</sub> with an inspired oxygen fraction (FiO<sub>2</sub>) of 100% and a positive end-expiratory pressure of 5 cm H<sub>2</sub>O. Recipient characteristics recorded were sex, body mass index (BMI), and right and left ventricular ejection fractions (RVEF and LVEF, respectively). Lung graft characteristics collected were use or not of a second, retrograde perfusion at the bench and duration of ischemia in minutes. The variable related to surgical technique was the use or not of extracorporeal circulation. Variables describing the early postoperative period were PaO<sub>2</sub>/FiO<sub>2</sub> upon admission to the recovery unit and at 24, 48, and 72 hours after implantation, presence or not of primary graft failure, and need for reoperation.

Primary graft failure was considered to be present when PaO<sub>2</sub>/FiO<sub>2</sub> was less than 200 mm Hg in the first 72 hours after implantation or when assisted ventilation was needed longer than 5 days and no observable causes other than lung dysfunction could account for the need.

BMI was considered normal in the range of 18.5 to 24.9 kg/m<sup>2</sup>.<sup>9</sup> The cut point for defining RVEF and LVEF was 45%.<sup>10</sup>

Perioperative death was defined as exitus caused by the anesthetic or surgical procedure, regardless of the number of days that had passed.

Survival was analyzed using the Kaplan-Meier method. Logistic regression models were constructed to determine which variables influenced perioperative mortality. When a variable was entered into regression, the Fisher exact test was used because of the small sample size.

### Results

Twenty-seven donors were men and 30 were women. The mean (SD) age was 26.6 (11) years (range, 7-48). The cause of death was head injury for 32, cerebrovascular accident for 22, and other for 3. Mean duration of intubation was 2.4 (1.9) days (range, 1-9). The mean PaO<sub>2</sub> with an FiO<sub>2</sub> of 100% and a positive end-expiratory pressure of 5 cm H<sub>2</sub>O was 480.1 (79.1) mm Hg (range, 357-640).

Of the 57 transplanted patients, 33 were men and 24 were women. The mean age was 21.3 (8) years (range, 9-56). The mean BMI was 17.7 (2.9) kg/m<sup>2</sup> (range, 10.9-24.5); 35 patients had a BMI less than 18.5 kg/m<sup>2</sup> and the others were within the normal range. The mean RVEF was 36.5% (6%) (range, 25%-60%) and 54 patients had values less than 45%; the mean LVEF was

TABLE  
Patients With a Ratio of PaO<sub>2</sub> to Inspired Oxygen Fraction  
Less Than 200 mm Hg\*

Patient	PaO <sub>2</sub> /FiO <sub>2</sub> , mm Hg	Cause	Intubation, h	Postoperative Death
9	198	PGF	23	No
16	165	PGF	54	No
24	186	PGF	96	No
26	190	Pneumonia	144	No
32	70	FHT	72	Yes
40	98.5	FHT	24	Yes
46	96	Pneumonia	96	No
55	40.8	PGF	24	Yes

\*PGF indicates primary lung graft failure; and EHF, early hemodynamic failure.

56.2% (7.2%) (range, 40%-75%) and 4 patients had values under 45%.

A second, retrograde perfusion was performed at the bench on 39 occasions. Ischemic time was 210.5 (55.6) minutes (range, 60-380) for the first graft and 314.1 (63.8) minutes (range, 150-500) for the second.

Extracorporeal circulation was needed during transplantation for 27 patients (for both grafts in 11 cases and for the second lung in 16 cases). Four patients had to undergo a second intervention due to hemothorax.

In 8 patients (14%) the PaO<sub>2</sub>/FiO<sub>2</sub> index was less than 200 mm Hg in the early postoperative period; 4 of them were classified as cases of primary graft failure, 2 due to pneumonia and 2 due to biventricular dysfunction. Three of those patients died in the perioperative period (Table).

Survival was 83.7% at the end of the first post-transplant year, 77.3% at the end of the second, and 66.9% at the end of the fifth. In total, 5 patients (8.7%) died in the perioperative period. Three were the aforementioned cases with primary graft failure. One of the 2 remaining patients died from septic shock due to *Pseudomonas cepacia* infection. The fifth died from a massive cerebrovascular accident 34 days after the transplant. Both had a PaO<sub>2</sub>/FiO<sub>2</sub> index less than 200 mm Hg.

Logistic regression analysis indicated that the PaO<sub>2</sub>/FiO<sub>2</sub> index upon admission to the recovery unit was the only variable that was significantly related to perioperative mortality ( $P=.0034$ ), given that 3 of the 8 patients whose PaO<sub>2</sub>/FiO<sub>2</sub> index was less than 200 mm Hg died (Fisher exact test,  $P=.0165$ ).

### Discussion

Although lung transplantation for patients with certain diseases has been called into question, this treatment has become established as an appropriate option in cystic fibrosis given that perioperative mortality rates are acceptable.<sup>2</sup>

Both survival figures and perioperative mortality rates in our series are within the range reported by the Registry of the International Society for Heart and Lung Transplantation<sup>3</sup> and for other surgical case series.<sup>4-8</sup> Perioperative mortality after a lung transplant may be

related to a large number of factors. However, the literature treats this outcome from the point of view of lung transplantation in general<sup>6</sup> and until now no studies have looked exclusively at cystic fibrosis patients who receive transplants.

Five of our patients (8.7%) died in the perioperative period. None of the donor, graft preservation, recipient, or transplant procedure variables significantly affected perioperative mortality. The only relevant factor was the PaO<sub>2</sub>/FiO<sub>2</sub> index on the first postoperative day. That index is known to be a predictor of early outcome in the transplanted patient.<sup>6,11,12</sup> Of the 8 patients with a PaO<sub>2</sub>/FiO<sub>2</sub> index less than 200 mm Hg, 3 died within the perioperative period. In contrast, only 2 among the 49 whose index was 200 mm Hg or greater died—1 due to sepsis and 1 due to cerebral infarction.

The PaO<sub>2</sub>/FiO<sub>2</sub> index, agreed upon as a criterion for defining adult respiratory distress syndrome,<sup>13</sup> is used by various authors as an indicator of primary graft failure,<sup>14-17</sup> although its value may change for other reasons.<sup>18</sup>

Four patients in our series experienced primary graft failure. One died within 24 hours of the transplant procedure and the other 3 patients were extubated after periods that ranged from 23 to 96 hours, illustrating the problems of defining this clinical picture and determining its incidence accurately.<sup>19</sup> Two distinct clinical situations are probably involved. Some patients can be extubated early, such that primary graft failure probably arises in relation to increased hydrostatic pressure after the first lung is transplanted and obliged to handle the entire cardiac output, given that the contralateral pulmonary artery is clamped for transplantation of the second lung.<sup>20</sup> Other patients, however, must remain intubated for longer periods, probably because of ischemia-reperfusion injuries resulting from the interaction of potent mediators and various types of cells,<sup>21</sup> and these lesions lead to death in a substantial number of patients.

Two of our 4 patients with poor oxygen exchange developed pneumonia and required ventilatory support for longer than 72 hours. In the 2 remaining patients who had a PaO<sub>2</sub>/FiO<sub>2</sub> index under 200 mm Hg, early hemodynamic failure was observed and both died. Heart failure has been postulated as a possible cause of perioperative mortality in these patients.<sup>7</sup>

Pulmonary hypertension is not uncommon in patients with cystic fibrosis. The 94.7% incidence of RVEF of less than 45% observed in our series was somewhat higher than reported for other series.<sup>10</sup> This observation would explain the need to use extracorporeal circulation more often in lung transplants in cystic fibrosis than in other diseases (in 47.36% in our experience). The incidence of pulmonary hypertension, which is around 30% in cystic fibrosis patients scheduled for transplants, has been found to be a risk factor for death while on waiting lists. Some authors therefore believe that these patients should be given priority. The problem is, however, that pulmonary hypertension is subclinical

in a large percentage of these patients and isotopic ventriculography does not detect it. Some authors therefore call for careful echocardiography and, upon observation of the slightest anomaly, right cardiac catheterization.<sup>24</sup>

The 2 patients in our series who died from heart failure, however, had no history of pulmonary hypertension and in both cases both ejection fraction and echocardiographic findings were normal. Some authors have observed that severe hemodynamic alterations are not uncommon after lung transplantation and have suggested that such alterations tend to increase risk of death; moreover, they have been related to certain markers of inflammation, such as interleukins, which would also be products of ischemic-reperfusion injury.<sup>25</sup>

In conclusion, lung transplantation has become accepted as a treatment for advanced stage cystic fibrosis, based on outcomes achieved, although such consensus has not been reached for other diseases. We have found no preoperative factor that increases risk of death. Only a PaO<sub>2</sub>/FiO<sub>2</sub> index under 200 mm Hg in the first few hours after transplantation affected perioperative mortality.

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