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ORIGINAL ARTICLE

Lung transplantation for cystic fibrosis: a single center experience of 100 consecutive cases†

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Abstract

OBJECTIVE: Lung transplantation is the ultimate treatment option for patients with end-stage cystic fibrosis (CF) lung disease. Despite poorer reports on survival benefit for CF patients undergoing lung transplantation, several centers, including ours were able to show a survival benefit. This study compares our center's experience with 100 consecutive recipients in two different eras.

METHODS: All CF patients who underwent lung transplantation at our center were included (1992–2009). Survival rates were calculated and compared between the earlier era (before 2000) and later era (since 2000).

RESULTS: CF patients constituted 35% of all transplantations performed at our institution. Mean age at transplantation was 27 years (range 12–52). Fifty-one percent of the patients were female. Waiting list time was lower in the earlier era compared to the later era ($p = 0.04$). Lobar transplantation was performed in 10 cases. Thirty-four percent of the cases required downsizing of the graft. In 33% of the cases, transplantations were done on cardiopulmonary bypass. There were no anastomotic complications. Total intensive care unit stay was significantly lower in the later era compared to earlier era ($p = 0.001$). The other parameters such as C-reactive protein at the time of transplantation, total cold ischemic time, and total operation time were comparable between the two eras. Overall 30-day mortality was 5%. The 30-day mortality was significantly lower in the second period ($p = 0.006$). In the earlier era, 3-month, 1-year, and 5-year survival were 85 ± 6%, 77 ± 8%, and 60 ± 9%, respectively, and in the later era improved to 96 ± 2%, 92 ± 3%, and 78 ± 5% ($p = 0.03$).

CONCLUSION: Improved results obtained in the early postoperative period since 2000 is most likely due to change in surgical management approach. Improved surgical outcome for CF patients can be obtained, especially in experienced transplant centers.

Keywords: Cystic fibrosis • Lung transplantation

INTRODUCTION

Lung transplantation is commonly performed for patients with end-stage cystic fibrosis (CF) lung disease. According to recent International Society for Heart and Lung Transplantation (ISHLT) Registry data, CF constitutes the third most common indication for lung transplantation [1]. Ultimately, it is the only treatment option which can restore patients with advanced CF lung disease toward normal respiratory health [2]. Good post-transplant outcome has been reported from transplant centers worldwide [2–4]. Despite of transplant-related and medical comorbidities, prolonged survival and good quality of life have been reported for CF recipients [4–7].

In our transplant program, CF is the most common indication constituting 35% of all lung transplantations performed. We subdivided our cohort into two groups (before year 2000 and since 2000). We have chosen year 2000 as a cut-off because since then we have changed our preservation solution, surgical approach (two separate anterolateral thoracotomies instead of clamshell incision), as well as routine induction therapy with basiliximab. We aim to compare era effect in this article. Era effect has also been shown in ISHLT registry as it shows the survival benefit among different eras [1]. This study analyzes particularly the surgical aspects of improved survival among our CF cohort.

METHODS

We conducted a retrospective cohort study assessing patients transplanted at our institution from 1992 to 2009, with follow-up through March 2010. We assessed all recipients with CF, including adult and pediatric cases, undergoing lung transplantation. A total of 100 patients underwent lung transplantation during the study period. For further comparison, we divided the whole

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cohort into two groups: operations performed before 2000 (early era) and those performed since 2000 (late era).

At our center, we follow the recently published ISHLT guidelines regarding referral and selection of lung-transplant candidates [8].

Organ preservation was performed with Euro-Collins solution (in the early era), thereafter with Perfadex® (Vitrolife, Sweden). Before antegrade flush, 500-μg prostaglandin E_1 was injected into the pulmonary artery in all cases. Harvesting of the donor lungs was undertaken en bloc after perfusion. Since 2000, we also use retrograde flush with Perfadex® at the time of the back-table preparation. The decision to perform size-reduced lung transplantation was made in the operating theater during implantation. Peripheral segmental wedge resections were undertaken with a commercially available stapler device. For lobar transplants, lobectomy was done on the back table. For bilateral sequential lung transplants, bilateral trans-sternal anterior thoracotomy (clamshell incision) or two separate anterolateral thoracotomies (since 2000) were performed. First, the bronchial anastomosis was done followed by venous (atrial cuff) and pulmonary artery anastomosis. The recipient's main bronchus was divided one ring proximal to the upper lobe bronchus branch. Bronchial arteries were ligated of the peri-bronchial tissue without electro-coagulation. All dissection on the bronchus was performed using 'minimal' or 'no touch' technique to keep the peri-bronchial tissue intact. The donor bronchus was cut back as close as possible to the origin of the upper lobe bronchus with special attention to the peri-bronchial tissue. Absorbable suture material polydioxanone was used. A continuous suture to the membranous wall (4/0) and end-to-end anastomosis with interrupted single stitches (3/0) to the cartilaginous part was performed [9].

The decision to perform the operation with or without the use of cardiopulmonary bypass (CPB) or extracorporeal membrane oxygenation (ECMO) was made according to the hemodynamic and gas-exchange status, including one-lung ventilation, temporary clamping of the ipsilateral pulmonary artery, and/or after transplantation of one side.

According to our standard protocol, patients received induction therapy (anti-thymocyte globulin or basiliximab since 2000) and triple immunosuppressive therapy, including cyclosporine, azathioprine or mycophenolate mofetil (since 1997), and prednisone described elsewhere [10]. Anti-infective prophylaxis was used according to our center's protocol [10].

In general, CF recipients underwent sinus surgery post-transplant followed by regular nasal care [11].

Post-transplant management at our center includes routine surveillance bronchoscopies with trans-bronchial biopsies and bronchoalveolar lavage during the first 6 months after transplant and regular outpatient clinic follow-up visits as previously described [3].

Statistical analysis

Descriptive statistics was used, and data are expressed as mean ± standard deviation. The statistical analysis was performed with SPSS 15.0 for Windows. Actuarial survival rates were calculated by Kaplan–Meier method and compared with Breslow (Generalized Wilcoxon) test. To test for univariate differences in categorical variables, we used the Fisher's exact test. The Mann–Whitney *U*-test was used to compare continuous variables between the groups. A p value less than 0.05 (2-tailed) is considered significant. The University Hospital Zurich's Research Ethics Committee granted approval for this retrospective study.

RESULTS

During the study period, we performed lung transplantation in 286 patients. Of these recipients, 100 (35%) had CF and were included in this study. The other indications for lung transplantation in our center are shown in Fig. 1. The mean age was 27 years (range 12–52). Eleven of the recipients were younger than 18 years of age. There were 51 female and 49 male recipients. The mean follow-up of our cohort was 59.5 months and the median follow-up was 50.1 (range 3–193.5) months. All patients but one underwent bilateral sequential lung transplantation. This one patient had concomitant congenital heart disease and underwent heart–lung transplantation. Twenty-one patients had a pneumothorax prior to transplantation. Two patients underwent pre-transplant bronchial arterial embolization due to massive hemoptysis. Two recipients were chronically infected with Burkholderia Cepacia Complex (BCC; undefined genomovar). Size reduction was achieved by lobar transplantation (n = 10) and anatomic or non-anatomic resections (n = 44). On the right side, the middle lobe was the most commonly resected lobe (n = 21), followed by lingula resection (n = 17) on the left. Otherwise, downsizing was achieved by right upper lobectomy (n = 8), left upper lobectomy (n = 6), left lower lobectomy (n = 1), and non-anatomic wedge resections (n = 11), respectively (more than 1 size reductions might have been performed in one recipient). Other than one middle lobectomy, all size reductions and all of the lobar transplantations were done in the late era. Age and sex distribution was comparable between the two eras. However, recipients in the late era had longer waiting list times and older donors were utilized (Table 1). Nevertheless, intensive care unit (ICU) stay was significantly shorter in the late era. The other donor variables were comparable between the two eras. We used ECMO more frequently in the late era (30 vs 3 recipients). Two recipients in the late era were on mechanical ventilation and ECMO, and two patients were on mechanical ventilation before transplantation. Postoperative ECMO was needed in two cases.

Re-transplantation was performed in three recipients due to chronic graft failure and in one due to primary graft dysfunction (PGD). All re-transplantations were done in the late era.

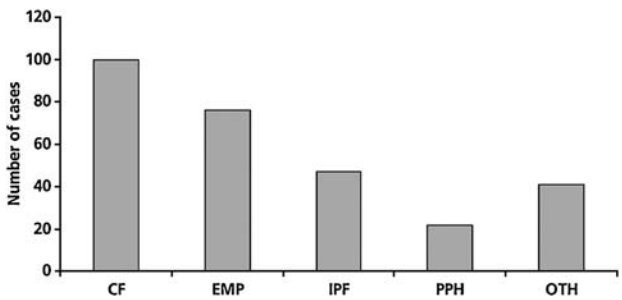

Figure 1: The number of transplants for CF and for other end-stage lung disease performed in Zurich Lung Transplant Program between 1992 and 2009 (N = 286). CF: cystic fibrosis (N = 100); EMP: emphysema (N = 76); IPF: idiopathic pulmonary fibrosis (N = 47); PPH: primary pulmonary hypertension (N = 22); and OTH: other (N = 41).

Table 1: Characteristics for cystic fibrosis lung-transplant recipients stratified by era

	Early era	Late era	*p* value
N	27	73	
Age (years)	27.8 ± 9.4	27 ± 8.4	0.8
Female (*N*)	17	34	0.2
Height (cm)	166.4 ± 9.9	162.4 ± 9.7	0.03
Weight (kg)	47.2 ± 7.9	47.5 ± 9.4	0.5
BMI (kg/m^2)	16.9 ± 1.2	17.7 ± 3.1	0.1
Waiting list time (days)	111.1 ± 95.8	181.5 ± 175.8	0.04
CRP at Tx (mg/l)	41 (3–138)	13.5 (1–106)	0.3
CMV status (R/D)			
neg/neg	15	30	
neg/pos	4	21	
pos/neg	5	9	
pos/pos	3	13	
Donor PaO_2/FiO_2 ratio (kPa)	42.9 ± 19.9	42.5 ± 16.6	0.8
Donor age (years)	31.3 ± 12.1	37.7 ± 15.1	0.05
Donor height (cm)	172.6 ± 10.5	172.1 ± 9.9	0.6
Donor weight (kg)	68.7 ± 13.1	69.2 ± 12.5	0.8
Ischemia time; right (min)	225.8 ± 79.1	237.7 ± 78.5	0.4
Ischemia time; left (min)	312.7 ± 76.5	300.2 ± 84.3	0.5
Total operation time (min)	394.2 ± 122.1	411.6 ± 104.9	0.1
Lobar Tx (*N*)	0	10	
CPB or ECMO (*N*)	3	30	
Intubation time (days) median (range)	1 (1–9)	1 (1–163)	0.7
ICU stay (days) median (range)	6 (1–43)	3 (1–163)	0.001
Pre-Tx FEV_1 (l)	0.81 ± 0.3	0.84 ± 0.3	0.3
Pre-Tx FEV_1 (%)	25.5 ± 5.9	26.1 ± 8.2	0.9
Best FEV_1 (l)	3.3 ± 0.8	3.1 ± 0.8	0.1

All values are given as mean ± standard deviation. Tx: transplantation; BMI: body mass index; FEV_1: forced expiratory volume in 1 s; ICU: intensive care unit; PaO_2/FiO_2: ratio of arterial oxygen partial pressure to fraction of inspired oxygen; CRP: C-reactive protein (mg/l); CMV: Cytomegalovirus; ECMO: extracorporeal membrane oxygenator; CPB: cardiopulmonary bypass; R/D: recipient/donor; neg: negative; and pos: positive.

Table 2: Postoperative complications for cystic fibrosis recipients stratified by era

	Early era	Late era	*p* value
N (%)	10 (37)	20 (27)	0.3
PGD	4	5	0.2
Pleural compl.	7	17	0.7
Lymphocoele	0	2	0.7
Phrenic nerve injury	0	2	0.4
Abdominal compl.	5	12	0.1
Tracheotomy	2	10	6

PGD: primary graft dysfunction; compl.: complication

Surgical complications occurred in 30% of the recipients (Table 2). Postoperative tracheotomy was performed in two in the early and in 10 recipients in the late era (p = 0.6). There were no bronchial complications in the whole series of 100 cases.

The 30-day mortality for the overall group was 5%. We lost four patients in the early (14.8%) and one case (1.4%) in the late era (p = 0.006). The causes of death were multiple organ failure/sepsis (n = 3) and PGD/multi-organ failure (MOF) (n = 2).

The 90-day mortality was 8%. We lost only three patients between day-31 and day-90 postoperative, all of which occurred in the late era (Table 3).

Overall 28 recipients died, 13 in the early and 15 in the late era. Causes of death included bronchiolitis obliterans syndrome (BOS) (n = 11), multiple organ failure/sepsis (n = 12), PGD/MOF/sepsis (n = 2), post-transplant lymphoproliferative disease (n = 1), pancreatic cancer (n = 1), and an unknown cause (n = 1).

For the whole group, 1-year and 5-year survival was 88 ± 3 and 72 ± 5, respectively. In the early era, 3-month, 1-year, 3-year, and 5-year survival were 85 ± 6%, 77 ± 8%, 63 ± 9%, and 60 ± 9%, respectively. In the late era, 3-month, 1-year, 3-year, and 5-year survival improved to 96 ± 2%, 92 ± 3%, 83 ± 5%, and 78 ± 5%, respectively (p = 0.03) (Fig. 2).

DISCUSSION

Lung transplantation is an accepted option for selected pediatric and adult patients with severe lung disease that have failed to respond to standard medical and other surgical treatment [12]. Among more than 27 000 lung transplantations reported to the ISHLT Registry, CF constitutes the third main indication for this type of treatment [1]. However, at our center, CF is the most common indication, constituting more than one-third of lung transplantations performed. In our center, we have traditionally transplanted more CF recipients than the international average. This might have been related to our selection choice (local allocation) as well as low number of emphysema patients. Since 1 July 2007 in our country, the allocation system has changed as a central allocation. Since then, our 35% CF recipients reduced to

Table 3: Detailed data for recipients who died within 90 days of transplantation

Case	Age	Cause of death	Preop. MRSA MRPA	CPB	BCC	DM	Liver disease	Period	Survival (days)
1	36	MOF/sepsis	No	No	No	No	No	1	1
2	24	MOF/sepsis	No	No	No	No	No	1	3
3	15	MOF/sepsis	No	No	No	No	No	1	1
4	31	PGD3/MOF	No	No	No	No	No	1	8
5	20	PGD3/MOF hyperammonemia	MRPA B. gladioli	Yes	No	Yes	Portal HT	2	3
6	22	PGD3/MO	MRSA	Yes	No	Yes		2	33
7	24	PGD3/MOF/sepsis	MRPA	No	No	No	Portal HT	2	53
8*	36	PGD3		Yes	No	Yes	No	2	34

MOF: multi-organ failure, Preop.: preoperative; MRSA: methicillin resistant *Staphylococcus aureus*; MRPA: methicillin resistant *Pseudomonas aeruginosa*; CPB: cardiopulmonary bypass; BCC: Burkholderia Cepacia Complex; DM: diabetes mellitus; PGD: primary graft dysfunction; *: re-transplantation; HT: hypertension; 1: early era; and 2: late era.

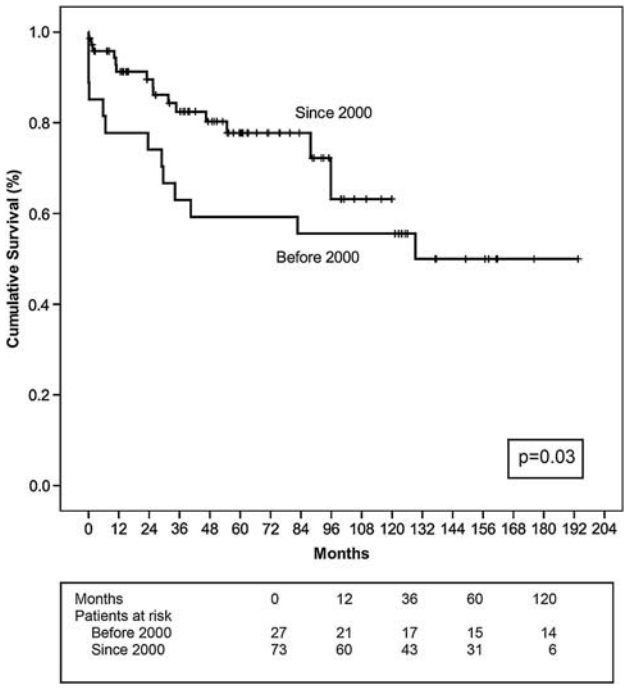

Figure 2: Cumulative survival (Kaplan–Meier) after lung transplantation in cystic fibrosis patients stratified by two eras. Before 2000: early era; and since 2000: late era.

about 30%. Our percentage of idiopathic pulmonary fibrosis (IPF) recipients underwent lung transplantation increased from 12% to 30% and, in emphysema recipients, decreased from 28% to 22%. We have chosen year 2000 as a cut-off because since then we have changed our preservation solution, surgical approach (bilateral separate thoracotomies instead of clamshell incision), as well as routine induction therapy with basiliximab.

Most of the early (within the 30 days) deaths following lung transplantation for CF were caused by sepsis [2]. Our overall 5% 30-day mortality rate is similar or even lower than that of previously reported CF series which range from 3.5% to 19.2% (Table 4) [2, 13–18]. In the late era, we only lost one of 73 recipients (1.4%) within the first 30 days post-transplant compared to four deaths in the early era (14.8%). Causes of death were sepsis/MOF and PGD3/MOF. The Newcastle Group in the United Kingdom reported that 26% of deaths were due to sepsis [2]. Moreover, when recipients had preoperative chronic BCC chronic lung infection, the mortality rate due to sepsis increased to 36% [2]. High mortality rates have also been reported from other centers in recipients with BCC following lung transplantation [19, 20]. In our series, we transplanted two recipients with BCC. One of them died of BOS after 5 years following transplantation. The other one patient is clinically stable and BOS free at 8 years post-transplant.

In other series, the rates of bronchial anastomotic complications in CF recipients were 2–15% [2, 21, 22]. A zero complication rate for bronchial anastomoses as achieved in our series has not been reported by other groups according to our knowledge. Recently, we have published our bronchial anastomoses data [9]. In a total of 391 bronchial anastomoses at risk, we only had one patient who required surgical intervention at postoperative day 5. In CF recipients, hypertrophic bronchial circulation might have played a role but we think that meticulous surgical technique and infection prevention are the most important points. Another important factor is that nearly all of the anastomoses have been performed by the chief of the division (W. Weder) or done with his attendance.

Outcomes following lung transplantation depend on many complex and interrelated factors [12], which include graft quality and preservation, the recipient's preoperative condition, surgical technique and postoperative care, the effects of long-term immunosuppression, and comorbidities. Causes of death in the early period (30-day) after lung transplantation differ from those that may occur later. PGD, infection (non-cytomegalovirus), cardiovascular failure, and acute graft rejection are the most common causes of early postoperative mortality [1].

Donor parameters (standard vs extended), explantation and preservation technique, preservation solution (extracellular vs intracellular), and the use of lung protective ventilation are important issues for the quality of the lung graft. Back-table retrograde flush has also been recommended as it might help to remove embolic material and assure better distribution of flush solution [23, 24].

In lung-transplant candidates who have experienced pneumothoraces and eventually undergone pleurodesis prior to transplantation, the operation may be technically more challenging; however, this seems not to have a significant influence on outcome [25].

The use of CPB during lung transplantation can be necessary due to preexisting pulmonary hypertension or on an emergency basis for refractory hypercapnia, pulmonary hypertension,

Table 4: Comparison of published survival and 30-day mortality in cystic fibrosis recipients

	Current series	Meachery et al. [2]	Bech et al. [13]	Algar et al. [14]	Quattrucci et al. [15]	Wiebe et al. [16]	Spahr et al. [17]	Egan et al. [18]
N	100	176	29	78	55	35	57	123
1 year	88	82	89	75	79	91	95	81
5 years	72	62	80	58	58	76	67	59
30-day mortality (%)	5	NR	3.5	19.2	17.8	NR	3.5	8.1[a]

NR: not recorded.
[a]30 days or in-hospital mortality.

technical complications, and graft dysfunction. As CPB may lead to an increased inflammatory status, it should be evaluated carefully if there is a clear indication to use CPB. The Newcastle Group uses CPB routinely during lung transplantation, as it is believed that this technique allows one to perfuse the both lungs simultaneously and to control pressure and to avoid circulatory overload of one lung [2]. At our center, we do not use CPB routinely; however, we achieve excellent results. The decision to perform the operation with or without the use of CPB or ECMO was made according to the hemodynamic and gas-exchange status including one-lung ventilation, temporary clamping of the ipsilateral pulmonary artery, and/or after transplantation of one side.

PGD is the most important complication in the early postoperative period. It generally occurs within 24 h following transplantation and is characterized by severe impairment of oxygenation, low pulmonary compliance, and diffuse parenchymal infiltrates. It likely results from a combination of events resulting from brain death of the donor, cold ischemic storage, preservation, and reperfusion of the graft.

Our series of lung transplantation for CF is one of the largest reported series in the world with similar 1-year survival rate as previously reported (Table 4). The best 1-year survival rate so far has been reported by Spahr et al. (95%) [17]. Their series included 57 adult recipients, of whom 17.5% were transplanted while receiving mechanical ventilation. Patients with BCC chronic lung infection were not included. In our previous publication, we calculated the overall survival without lung transplantation in our CF recipients [3]. Calculated 5-year survival without transplantation was 33% and 72% after transplantation which showed a true survival benefit for transplanted patients. In the current series, we analyzed our data for survival of CF recipients versus other recipients with end-stage lung disease who underwent lung transplantation in our center. We found no difference between CF and other diagnosis (p = 0.3). This was also valid for two eras (before 2000 and after 2000).

In conclusion, despite the potential complications of lung transplantation, CF recipients undergoing lung transplantation in our center have good quality of life. Further improvements of post-transplant survival in the recent era at our center are most likely multifactorial. Better surgical techniques, organ preservation, and intensive-care management likely play a role. In addition, careful post-transplant management, including rigorous treatment of airway infections, sinus surgery, and routine nasal care, long-term therapy with macrolide antibiotics for BOS, and extracorporeal photopheresis in selected recipients with BOS and recurrent acute allograft rejection might have contributed to improved outcomes at our center as well [3].

Conflict of interest: none declared.

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EDITORIAL COMMENT

Lung transplantation for cystic fibrosis: satisfactory results in specialized centres

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Keywords: Lung transplantation • Cystic fibrosis • Organ procurement

Cystic fibrosis (CF) is a formidable genetic disease. Respiratory physiotherapy, care and management in specialized centres have considerably lengthened life expectancy.

The advances made in lung transplantation for CF can clearly be seen in the International Registry. It is particularly true for highly specialized teams like that of Zurich. CF is their primary indication for transplantation with excellent results at 1 and 5 years presented in this issue of *EJCTS* [1]. Improved results have also been noted for our team [2], which has carried out 185 transplants for CF to date.

Management by teams of specialized paediatricians and pulmonologists makes it possible to carry out transplantation as late as possible, but not too late.

Modifications to the graft allocation systems in the United States and several European countries allow transplantation of the most seriously ill patients [3]. Use of grafts with extended donor criteria, and evaluation of very marginal grafts with an *ex vivo* reperfusion machine, should limit preoperative deaths by increasing the pool of grafts available.

Some problems are specific to transplantation for CF [4].

The patients are usually underweight which increases the risk of postoperative mortality [5]. Therefore, a programme of hyper-nutrition and physiotherapy should be set up during the waiting time.

Some patients have a Burkholderia cepacia complex (BCC) chronic lung infection. A high mortality rate after transplantation is associated with Burkholderia ceno-cepacia infection (and these patients are excluded from transplantation in many teams) but not with non-ceno-cepacia BCC species [6]. Infection with *Burkholderia gladioli* increases morbidity.

In case of infection with *Mycobacterium abscessus*, a multi-resistant mycobacteria, pre-transplant eradication therapy should be attempted [7]. Long-term treatment with multiple drugs may be complicated in the CF patient with severe disease.

In some severe patients listed for transplantation, mechanical ventilation and extra corporal membrane oxygenation must be instituted. In these cases, a rise in postoperative mortality has been reported in the International Registry [8]. However, if transplantation is carried out in the case of pulmonary failure alone,