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Anaesthesiologic management and intraoperative risk factors in lung transplantation – first 19 years of a single centre experience

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Abstract : *Background*. There is little information about the anesthesiologic management of lung transplantation. Therefore, we characterized intraoperative variables and their impact on survival in dependence to preoperative characteristics of recipients and donors.

Methods. We analyzed 808 lung transplantations performed at our institution between 1987 and 2006, described patients in relation to the use of cardiopulmonary bypass (CPB), and used both recursive-partitioning and multivariate analyses to examine patients, donors, anesthesiologic management (e.g. gas exchange, hemodynamics, transfusions), extracorporeal life support (e.g. unplanned/planned CPB), and other variables.

Results. Compared with off-pump transplantations (n = 389), unplanned CPB (n = 216) resulted in more transfusions and both doubled duration of postoperative ventilation (7.2±16.5 vs. 16.5±23.7 days, $p<0.001$) and hospital mortality (10 vs. 19%, $p = 0.006$) ; after planned CPB (n = 88), mortality doubled again (42%, $p<0.001$). Pulmonary diseases, their severity and comorbidities differed between groups, but pulmonary diseases were similar between patients with unplanned and planned CPB. According to recursive-partitioning analyses postoperative ventilation of < 4 days 10h discriminated best between survivors and non-survivors, and the duration of postoperative ventilation was also predictive for survival (odds ratio (OR), 1.02 ; 1-day increments). Intraoperative independent risk factors were transfusions of packed red blood cells (OR, 1.10 ; 10-unit increments), planned CPB (OR 2.4) and donors at least 20 cm taller than the recipient (OR 6.0).

Conclusions. Apart from avoiding CPB, further efforts towards shorter postoperative ventilation and avoiding the intraoperative need for excessive transfusions may have the potential to improve outcomes as these were identified as important risk factors and were associated with CPB use.

Introduction

Anaesthesiologic management has to maintain hemodynamic stability and gas exchange during lung transplantation even under challenging conditions (1-6). If unsuccessful, however, unplanned cardiopulmonary bypass (CPB) may become necessary. Planned CPB is assumed when a high risk of failure is anticipated owing to progressed disease severity, expected surgical problems, or when additional cardiac surgery is planned (7-10).

The use of CPB for lung transplantation was controversial for many years (11-22). Controlled conditions and lower risks of lung injury have been mentioned as advantages of CPB use, and it has been suggested that it has no negative effects on survival (14,17,21,22). In contrast, others have reported increased mortality (7,8,11,18) that has been tied to complications related to full heparinisation – as increased bleeding risk and more blood transfusions, inflammatory reactions, primary organ failure and longer postoperative ventilation (5,7,11).

Intraoperative factors that may result in unplanned CPB include hemodynamic instability

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due, for example, to severe pulmonary artery hypertension, right ventricular failure or bleedings, or owing to failure to achieve sufficient gas exchange (1-8,23). However, little is known about how mortality and, especially, intraoperative factors relating to the anaesthesiologic management differ between patients in whom lung transplantation succeeds off-pump and those in whom unplanned or planned CPB becomes necessary (7-10). In our lung transplantation program we switched from using CPB during lung transplantation to using peripherally cannulated venoarterial extracorporeal membrane oxygenation (ECMO) in 2010 (11). Less than 30% of all lung transplantations have been performed on extracorporeal circulation (i.e. ECMO) in recent years at our centre and these results, including a flowchart recommendation on decision making upon using ECMO during lung transplantation, have been published by our group recently (12). The long standing expertise in managing lung transplantations ultimately leading to developing our current ECMO strategy is described here, retrospectively analysing data accumulated before ECMO was routinely used during lung transplantation.

At our institution we have, since the beginning of our lung transplantation program in the 1980s, aimed to perform lung transplantations off-pump. In a high proportion of patients, however, planned and (especially) unplanned CPB became necessary in the era until 2006 studied here, and we speculated that this had an unfavourable effect on outcomes.

We hypothesized that patients` characteristics, physiologic variables during transplantation and other intraoperative factors relating to the anaesthesiologic management differ between these groups and, that these differences are related to prognostic factors. Therefore, we assessed the differences between these groups and also identified independent perioperative risk factors in relation to both patient and donor factors for increased hospital mortality.

Methods

Following approval by our Ethics Committee, we retrospectively analysed characteristics of recipients and donors of all lung transplantations that were performed at our institution between December 1987 and December 2006. The analysed perioperative parameters and variables of the donors are given in detail in the online data supplement.

Corresponding to substantially different surgical and anaesthesiologic management, we characterized patients undergoing double- or single-lung transplantation without simultaneous transplantation of other organs after dividing these individuals into three groups : Lung transplantation without CPB, with unplanned CPB and with planned CPB. In the historic cohort described here, all patients intubated using a double-lumen tube were all originally planned without CPB, whereas those intubated using a single-lumen tube were transplanted with planned CPB. After 2006, we used also double-lumen tubes in planned CPB so that we included only data until 2006 as we were not able to clearly distinguish retrospectively planned from unplanned CPB.

Statistical Analysis

Continuous data are expressed as mean with standard deviation. Depending on the distribution of the data, the Student's t test or the Mann-Whitney test was used to compare continuous data, and the chi-square test or Fisher's exact test was employed to compare proportions. The analyses were performed using SPSS version 16.0 (SPSS Inc., Chicago, Illinois).

The same variables that qualified for the multivariate model were also analysed by means of recursive-partitioning analyses, identifying the threshold value for each variable that provided the best separation between survivors and non-survivors.

The building of the multivariable model is described in detail in the online data supplement. Briefly, we firstly selected potential prognostic factors, both by means of univariable analyses and by entering predefined variables of potential clinical importance. As entering too many predictors into a model and collinearity between predictors can lead to unstable coefficient estimation, we then grouped these selected variables into eight variable categories : a) Patient demographics and patient/donor relations (e.g. opposite sex, height difference) ; b) Donor-related factors (e.g. cause of death, ischemia time, PaO_2/FiO_2) ; c) Patient-related preoperative factors (e.g. underlying disease, comorbidities, invasive/non-invasive ventilation, preoperative medications, pulmonary artery pressure (PAP)) ; d) Anaesthesia induction (e.g. duration, anaesthetics) ; e) During mechanical ventilation before first single-lung ventilation (e.g. PaO_2/FiO_2, blood gas values, PAP, haemodynamics, ventilatory parameters) ; f) Extracorporeal circulation (e.g. unplanned/planned use of cardiopulmonary bypass (CPB)) ; g) After transplantation (e.g. total transfusion of blood products, crystalloids and

colloids, PaO_2/FiO_2, blood gas values, PAP, haemodynamics, ventilatory parameters) ; h) Time periods (e.g. duration of postoperative ventilation). Within each of these eight variable categories we separately performed a stepwise forward selection procedure to rank the factors multivariably, only considering those variables for further analysis in the final multivariable model that contributed with a p-value < 0.10. In the final model, we then used a stepwise backward elimination procedure to determine the factors independently associated with hospital mortality.

Results

Patient groups and outcomes

From all analysed 812 patients, a total of 727 lung transplantations were performed without transplantation of other organs ; due to missing data, 34 of these patients transplanted with CPB could not be firmly assigned to the group of unplanned or planned CPB, so that only 693 individuals were included for inter-group comparisons : 605 of these lung transplantations were originally planned without CPB ; in 215 patients (36%), however, unexpected complications rendered CPB necessary (Table 1). This was associated with more transfusions and doubled duration of postoperative ventilation, ICU stay and mortality and, in 88 patients with originally planned CPB, hospital mortality actually doubled again (Fig. 1, Table 1).

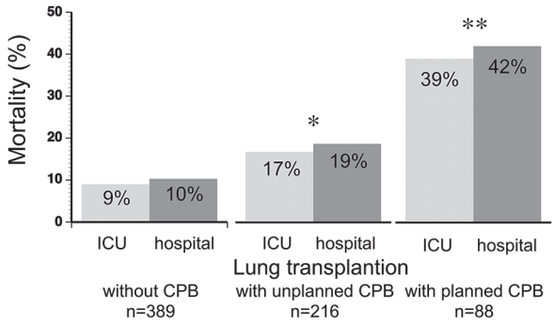

Fig. 1. — Mortality after lung transplantation during intensive-care unit (ICU) and hospital stay. These 693 patients underwent double- or single-lung transplantation without transplantation of other organs. CPB denotes cardiopulmonary bypass. * p = 0.006 in comparison to patients with lung transplantation without CPB, ** p<0.001 in comparison to the other groups.

Characteristics of patient groups

In nearly half of the patients, unplanned CPB became necessary as anaesthesiologic management failed to control respiratory and hemodynamic

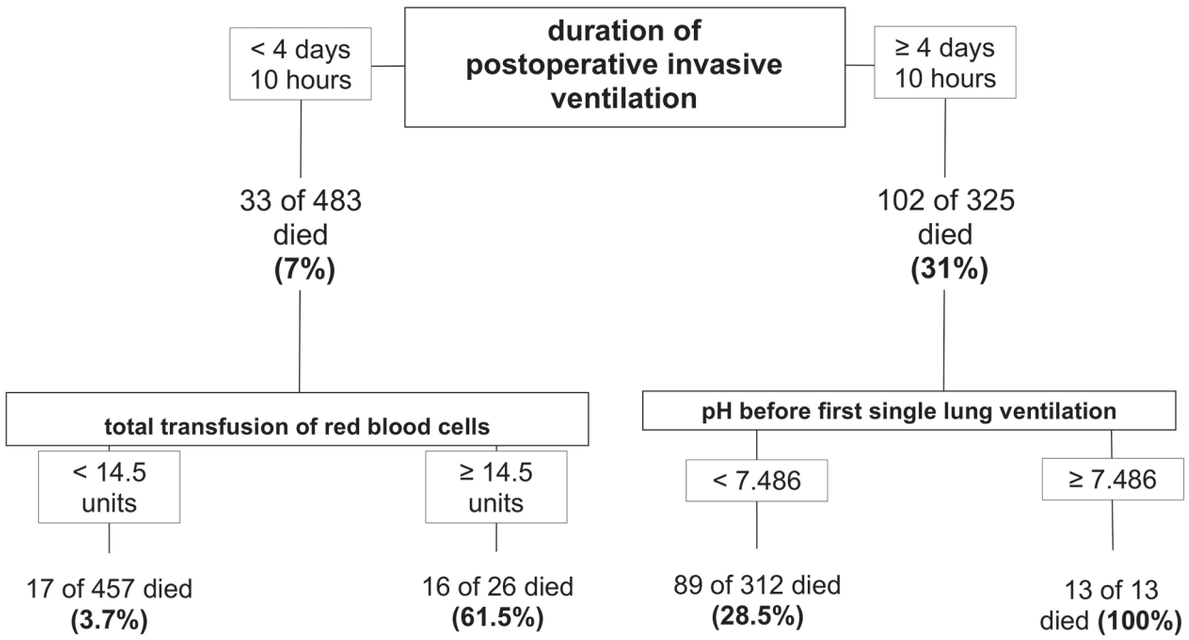

Fig. 2. — Recursive-partitioning analysis tree. The duration of postoperative ventilation of 4 days and 10 hours was selected as the best predictor of the first branch of the tree that achieved the most precise separation of deceased and living patients. The recursive-partitioning procedure was repeated for each of the two subgroups that resulted from the first split, again searching for all the cut-off points for each separation of deceased and living patient groups. For continuous variables, potential threshold values are all the values represented in the data. For dichotomous variables, the threshold value is the integer value of the two categories. For non-ordered categorical variables that have more than two categories, all factorial arrangements of the category were evaluated.

Table 1.
Surgical variables, durations and time periods

	Lung transplantation		
	without CPB (n=389)	with unplanned CPB (n=216)	with planned CPB (n=88)
Double / single lung transplantation (%)	286/103 (64/36)	179/37† (79/21)	69/19 (72/28)
Characteristics of donors (mean±SD)			
Body height (cm)	174.9±9.2	174.0±9.2	172.4±10.8
PaO_2/FiO_2 before explantation (mmHg)	439±114	461±102	412±101‡
Temperature (°C)	36.46±1.06	36.46±1.01	36.83±1.08†§
Reasons for cardiopulmonary bypass (CPB) (%)‡			
Surgical			
Surgical request		13.1	44
Severe hemorrhage		6.2	0
Surgical problem		6.2	4
Additional aortic valve replacement		0	2.7
Additional ventricular septum defect occlusion		0	1.3
Respiratory			
Hypoxia		10.8	14.7
CO_2-retention		6.8	1.3
Insufficient ventilation		4	5.3
Hemodynamic			
PAP-increase		16.5	1.3
Right ventricular decompensation		5.7	0
Acute heart insufficiency		1.7	0
Other		29	25.4
Time periods			
CPB (minutes)		147±62	174±66§
Operation (minutes)	227±75	291±76*	281±75
Postoperative ventilation (days)	7.2±16.5	16.5±23.7*	22.1±24.9*§
ICU stay (days)	10.5±19	21.7±27.7*	28.2±33*
Hospital stay (days)	34.1±30.8	48.8±42.3*	52.6±49*
Time periods - n (% of all patients in this group / % of all patients in this time period)†§			
1988–1994 (n=90)	59 (15/66)	27 (13/30)	4 (5/4)
1995–2000 (n=189)	95 (25/50)	74 (34/39)	20 (23/11)
2001–2006 (n=412)	234 (60/57)	114 (53/28)	64 (73/16)

CPB denotes cardiopulmonary bypass, SLV, single-lung ventilation, PAP, pulmonary artery pressure; mortality did not differ between time periods within groups and combining all groups. *p<0.001 and †p<0.05 as compared to patients without CPB, ‡p<0.001 and §p<0.05 compared to patients with unplanned CPB

Table 2. — Patient characteristics before operation.

More than one underlying disease was assigned to the patient if the disease was appreciably contributing to the pulmonary disease as a whole. Other underlying diseases were bronchiectasis, sarkoidosis, and Eisenmenger´s syndrome. CPB denotes cardiopulmonary bypass, ECLA extracorporeal lung assist, ECMO extracorporeal membrane oxygenation, ASA American Society of Anesthesiologists. Accompanying cardiac disease included patients with atrial or ventricular septal defects, valvular dysfunctions, cardiomyopathy, congenital cardiac defects, or previous cardiac surgery. ECLA and ECMO were used in the studied time period only in the most severe cases to enable gas exchange in the pre- or/and post-operative period. *p≤0.003 and †p≤0.05 compared to patients without CPB, ‡p<0.001 and §p<0.05 compared to patients with unplanned CPB.

Table 2

Patient characteristics before operation

	Lung transplantation		
	without CPB (n = 389)	with unplanned CPB (n = 216)	with planned CPB (n = 88)
Demographic variables (mean±SD)			
Body height (cm)	170.8±9.7	169.6±9.1	164.7±12.1†§
Weight (kg)	62±14.4	62.8±14.8	59.9±18.4
Body mass index	21.1±4.0	21.8±4.2	21.8±4.8
Female / male (%)	45 / 55	51 / 49	47 / 53
Age (years)	43.1±13.1	40.3±13.6†	38.4±15.2*§
Patient/donor relations (mean±SD)			
Body height exceeding recipient`s height (cm)	4.2±8	4.1±8	7.5±11.4§
Body height > 20 cm compared to recipient (%)	4.3	3.8	15#§
Opposite-sex transplantations (%)	22.5	16.6	30.7§
Ischemia of the right lung (min)	311±114	302±88	331±147
Ischemia of the left lung (min)	375±116	366±94	391±143
Ischemia of the left lung > 8 hours (%)	14.9	7†	19§
Underlying pulmonary diseases (%)			
Emphysema	41	20*	14
COPD	24	8*	10
Primary pulmonary hypertension	0.5	7*	8
Alpha-1 antitrypsin deficiency	18	7*	3.4*
Fibrosis	24	36*	33
Cystic fibrosis	28	24	30
Sarcoidosis	1.5	4	2.3
Bronchiolitis obliterans	4.6	7.4	9.1
Other	5	12	7
Circulatory comorbidity factors (%)			
Accompanying cardiac disease	6.2	11.6†	15.9†
Secondary pulmonary hypertension*			
Latent (< 20 mmHg)	18	10	5
Apparent (20-40 mmHg)	51	28	27
Severe (> 40 mmHg)	12	41	44
Unknown class	20	21	25
Cor pulmonale	22	43*	32
Cardiac insufficiency	14	27*	18
Localization of cardiac insufficiency*			
Right ventricular	9.6	21	15
Left ventricular	1.3	1	2.3
Biventricular	0.3	2.3	0
Unknown	2.3	2.3	1.1
NYHA classification* I / II / III / IV (%)	0 / 14 / 17 / 9	2 / 13 / 33 / 20	0 / 16 / 26 / 16
Other preoperative factors (%)			
Invasive ventilation	6	11.5†	37.2‡*
Non-invasive ventilation	13.4	16.5	24.7†
Pneumonia	12.1	12	21.8†§
ECLA	2.4	1.9	22.1‡*
ECMO	1.5	0.9	12.5‡*
ASA classification (%) *§			
3	53	44	25
4	44	46	55
5	2	10	19

Table 3.

Circulatory, ventilatory and blood gas variables before, during and after lung transplantation before transfer to ICU

	Lung transplantation		
	without CPB (n = 389)	with unplanned CPB (n = 216)	with planned CPB (n = 88)
% of patients before first SLV with			
Mean PAP>40 mmHg	19	44*	33
PaO_2/FiO_2<200 mmHg	10	23*	44‡
PaO_2/FiO_2 (mmHg)			
Before 1st SLV	397±127	335±154*	253±164‡*
During 1st SLV	360±167	299±175†	139±132§*
After transplantation	346±147	273±146*	259±135§*
$PaCO_2$ (mmHg)			
Before 1st SLV	59.9±17.9	68.3±24.7*	67.3±30.9
During 1st SLV	61.0±18.9	71.7±27.9*	65.0±22.1
After transplantation	51.5±13.2	51.4±11.6	52.8±14.0
pH			
Before 1st SLV	7.32±0.09	7.29±0.11*	7.34±0.12§
During 1st SLV	7.27±0.10	7.23±0.12*	7.28±0.11
After transplantation	7.34±0.10	7.31±0.09*	7.32±0.10
Further acid-base balance parameters after transplantation			
Base excess	0.9±4.5	-1.5±4.1*	0.8±6.0§
Bicarbonate	26.9±4.6	24.7±3.8*	26.6±6.1§
Lactate	2.6±1.9	4.5±2.6*	4.2±2.4*
Inspiratory peak pressure (mbar)			
Before 1st SLV	29.3±8	32.9±9.8†	32.6±7.1*
During 1st SLV	32.1±8.2	35.1±9.0†	-
After transplantation	27.4±5.8	29.3±5.8†	30.7±7.5†
Mean PAP (mmHg)			
Before 1st SLV	32±10.2	39.5±13.8*	40.1±14.3*
During 1st SLV	35.3±11.7	41.8±16.8†	31.2±12§
After transplantation	25.7±10.6	28.6±9.4†	29.6±10.2†
Heart rate (beats/min)			
Before 1st SLV	95.4±15.8	101.2±17.7*	101.5±21.8†
During 1st SLV	100.4±16.9	102.7±19.8	-
After transplantation	99.0±16.3	105.1±18.2*	105.4±17.5*
Mean arterial pressure (mmHg)			
Before 1st SLV	80.7±10.1	79.2±11.1	77.2±11.7†
During 1st SLV	75.7±8.6	72.4±11.8†	71.6±8.6†
After transplantation	77.7±8.9	75.5±9.2†	77.1±10.4
Central venous pressure (mmHg)			
Before 1st SLV	13.5±7.3	15.4±7.8†	17.1±10.3†
During 1st SLV	17.5±9.5	18.1±11.0	19.8±9.1
After transplantation	10.0±5.1	12.0±5.0*	13.0±6.3*

CPB denotes cardiopulmonary bypass, SLV single lung ventilation, PAP pulmonary artery pressure *p≤0.001 and †p<0.05 as compared to patients without CPB, ‡p<0.001 and §p<0.03 compared to patients with unplanned CPB.

Table 4

Catecholamines, fluid administration and blood transfusions

	Lung transplantation		
	without CPB (n = 389)	with unplanned CPB (n = 216)	with planned CPB (n = 88)
Catecholamine administration - n (%)			
Norepinephrine	273 (70)	169 (78)†	68 (77)
Epinephrine	109 (28)	90 (42)*	30 (34)
Dobutamin	38 (10)	45 (21)*	12 (14)
Administration of crystalloids and colloids (ml) / n (%)			
Ringer`s solution	1298±862/125 (32)	836±624*/67 (31)	594±198§*/32 (36)
Ringer`s lactate	1561±949/240 (62)	1265±1012*/130 (60)	743±346‡*/37 (42)§*
Sodium chloride	926±770/34 (9)	1129±1246/17 (8)	800±447/5 (6)
Gelatin	683±405/63 (16)	790±451/19 (9)†	500±0/4 (5)†
Hydroxyethyl starch	684±289/311 (80)	650±350†/155 (72)†	583±331*/49 (55)§*
Prefilling of the heart-lung machine (ml)			
Ringer`s solution	-	1000	1000
Sodium chloride	-	500	500
Bicarbonate	-	40	40
Transfusions - units / n (%)			
Packed red blood cells	5.0±3.7/304 (78)	7.8±5.4*/203 (94)*	8.9±6.4*/84 (95)*
Fresh frozen plasma	5.4±3.6/339 (87)	5.8±3.4†/208 (97)*	6.0±3.2†/85 (97)†
Platelet concentrates	1.5±1.1/75 (19)	1.5±0.8/156 (73)*	1.6±0.7†/61 (69)*
Hemoglobin after transplantation (g/dl)	10.8±1.5	9.1±2.0*	9.2±1.4*
Furosemide mg, n (%)	27.9±33/128 (33)	30.3±31.8/107 (50)*	40.4±43*/50 (57)*
Urine output	602±568	774±709*	773±694†
Mean total volume of fluid administration (ml) / n (%)			
Crystalloids	1461±974/377 (97)	2650±983*/216 (100)†	2114±391*‡/88 (100)
Colloids	657±493/321 (83)	536±500*/162 (75)†	347±405*‡/51 (68)*§
Transfusion	2394±2067/358 (92)	3816±2465*/215 (100)*	4236±2440*/88 (100)†
Cell saver auto transfusion	841±1049/111(29)	1159±1160*/72 (34)	997±536†/22 (25)
Total fluid administration (ml)	4753±2752	7388±2945*	6946±2725*
Positive fluid balance (without blood loss) (ml)	4237±2678	6696±2969*	6288±2849*

CPB denotes cardiopulmonary bypass, SLV single lung ventilation, PAP pulmonary artery pressure. The volume of transfusions was calculated with a mean volume of 280 ml for a unit of packed red blood cells, 260 ml for a unit of fresh frozen plasma and 300 ml for platelet concentrates. Blood loss was not considered due to missing values.*p≤0.001 and †p<0.05 as compared to patients without CPB, ‡p<0.001 and §p<0.03 compared to patients with unplanned CPB

parameters (Table 1). Individuals for whom CPB was planned more frequently received donor lungs with disadvantageous characteristics, as reflected by lower oxygenation before explantation and a higher proportion of cases of prolonged ischemia, sex mismatch and inadequate organ size (Tables 1 and 2). These patients were also younger and smaller ; however, the body height of the donors did not differ between groups, resulting in almost double the height difference between donor and recipient (Tables 1 and 2).

Both underlying diseases and comorbidities were similar between patients with unplanned and planned CPB but in patients with planned CPB invasive ventilation, pneumonia, ECLA and ECMO before operation were more frequent and,

ASA classifications and temperature were higher ; PaO_2/FiO_2 during ventilation before transplantation was decreased, and CPB lasted longer (Tables 1 and 2). In patients with unplanned CPB both underlying diseases and comorbidities differed compared to patients in whom lung transplantation succeeded off-pump : Primary pulmonary hypertension and fibrosis were more frequent and patients with unplanned CPB had at least two times more frequently severe secondary pulmonary hypertension, cor pulmonale, cardiac insufficiency and higher NYHA and ASA classifications (Table 2).

Physiologic variables of patient groups

Physiologic variables differed significantly during the intraoperative course between groups and varied considerably between patients (Online data supplement : Fig. E1-E5). Compared to patients in whom transplantation succeeded off-pump patients transplanted with unplanned and planned CPB had lower PaO_2/FiO_2 and PaO_2, higher PAP, CVP, heart rate and peak inspiratory pressures – both before and after lung transplantation (Table 3, Online data supplement : Fig. E1-E3). In patients with unplanned CPB the $PaCO_2$ before transplantation was increased and pH was decreased both before and also after lung transplantation compared to patients transplanted off-pump (Table 3, Online data supplement : Fig. E2). Furthermore, the mean arterial pressure was lower after unplanned CPB, catecholamines were administered more often and also more crystalloids and transfusions were given ; the postoperative haemoglobin concentration was lower and these patients had decreased base excess and bicarbonate and a twice as high postoperative lactate compared to patients transplanted off-pump (Table 3 and 4, Online data supplement : Fig. E4-E5). In addition, intraoperative ventricular fibrillation occurred three times more often when off-pump transplantation failed (4.8% vs. 1.6%, p = 0.03).

Recursive-partitioning analyses and multivariable logistic regression

Including all 808 patients recursive partitioning determined postoperative ventilation with a threshold of less than 4 days and 10 hours as the variable with the best separation between survivors and non-survivors, showing a fourfold decrease in mortality (Fig. 2). According to multivariable logistic regression the mortality increased by 2% with every postoperative ventilatory day and by 10% with every 10 transfused RBC units (Table 5) ; planned CPB more than doubled the mortality risk, and the highest odds ratio was found for severe size discrepancy, with a donor's body height exceeding the recipient`s height by more than 20 cm (Table 5).

Table 5

Multivariable analysis of factors associated with increased hospital mortality after lung transplantation

Variable	**Multivariable analysis***	
	Odds Ratio (95% CI)	*p-value*
Duration of postoperative invasive ventilation (1-day increments)	1.02 (1.01-1.03)	*<0.001*
Transfusion of packed red blood cells (10-unit increments)	1.10 (1.06-1.16)	*<0.001*
Planned cardiopulmonary bypass (CPB)	2.4 (1.2-5.0)†	*<0.02*
Donor at least 20 cm taller than recipient	6.0 (2.4-14.9)	*<0.001*
Liver cirrhosis	3.8 (1.4-10.3)	*<0.01*
Accompanying cardiac disease	3.2 (1.5-6.6)	*0.002*
Preoperative systemic glucocorticoids	2.2 (1.3-3.8)	*0.005*
Preoperative nitrate medication	4.3 (1.7-10.9)	*0.002*

Including all assessed patients (n = 808) ; †in reference to transplantations without CPB, (planned CPB excluding heart-lung transplantation or liver-lung transplantation); only those variables are shown that remained significant in the final multivariable model with stepwise backward elimination using a threshold of p =0.05 according to Wald statistics.

Height difference and opposite-sex transplantation

In females, this height difference was more frequent in opposite-sex compared with same-sex transplantation, but not in males (females : 20.0 vs. 1.2%, p<0.001 ; males : 3.6 vs. 4.9%, n.s.). Sex mismatch occurred more often in females as compared to males (25.6 vs. 17.8%, p<0.01). This opposite-sex transplantation was associated with doubled mortality in females (27.8% vs. 13.2%, p<0.03) but only a trend towards increased mortality in males (24.6% vs. 15.1%, p = 0.055).

Discussion

Here we describe data collected until 2006, identifying perioperative risk factors for increased mortality after lung transplantation due to anaesthesiologic and surgical strategies addressable

for modification. We found considerable differences in hospital mortality between the three groups of patients transplanted off-pump, with unplanned or planned CPB in respect of intraoperative factors relating to anaesthesiologic management that were related to independent risk factors. We considered these factors with a view to optimizing operative conditions, to facilitating lung transplantation without CPB, and to favourably influencing those prognostic factors that are associated with increased mortality. Therefore, we deem these older data still relevant, since they reflect our experiences with the intraoperative management of lung transplantation that pave the way during the past 10 years for all protocol modifications and the improved early survival noted in the most recent era of lung transplantation (11,12,24).

As detected by recursive partitioning, short postoperative ventilation of less than 4 days and 10 hours discriminated best between survivors and non-survivors, and in these survivors a low RBC transfusion rate constituted the best cut-off. Both the duration of postoperative ventilation and RBC transfusions were also independent risk factors for mortality in the multivariable analysis. When unplanned CPB was unavoidable, more blood products were transfused and the duration of postoperative ventilation and mortality doubled. When lung transplantation was performed with planned CPB, mortality increased as much as fourfold, with planned CPB representing an important independent risk factor. By contrast, unplanned CPB was eliminated in the final multivariable analysis when the duration of postoperative ventilation was entered into the model indicating most probably that the increased mortality risk after unplanned CPB is predominantly mediated by this risk factor.

Severe size discrepancy, with a donor`s body height exceeding the recipient`s height by more than 20 cm, was also independently associated with an increased mortality risk. This size discrepancy occurred more frequently in lung transplantation with planned CPB, probably reflecting the urgency of transplantation in these patients, but it was also more frequent in females in opposite-sex transplantation. We suspect that even after downsizing, transplantation of oversized lungs may promote lung collapse and atelectasis that could further aggravate lung injury owing to repeated alveolar collapse and high shear forces between open and closed lung areas (25,26). These effects are reduced by postoperative recruitment of atelectatic lung regions and subsequent adjustment of positive end-expiratory pressure (PEEP) in order that it is sufficiently high as a precondition for achieving lung protective ventilation with low driving pressures (25,26).

Our data indicate that opposite-sex transplantation appears to be disadvantageous especially for females, as their mortality as much as doubled when they received male lungs. Sex mismatch has been reported as being an independent risk factor for increased mortality when female lungs are transplanted to males, but with the converse not applying (9,27,28). By contrast, although we observed increased mortality where there was sex mismatch, it was not an independent risk factor in our analysis ; we incorporated size discrepancies into our model that eliminated sex mismatch during multivariate regression. Furthermore, none of the following – underlying disease, body mass index (29,30), physiologic variables such as PAP, preoperative mechanical ventilation, and pneumonia (18,31-33) – were independently associated with increased hospital mortality. This was, however, the case with preoperative medications and comorbidities, including liver cirrhosis and accompanying cardiac disease (33). Among patients in whom unplanned CPB became necessary, the proportion of individuals with accompanying cardiac disease was doubled compared with those in whom transplantation succeeded off-pump. This indicates that the higher mortality risk in these patients may be associated with a greater risk of failed off-pump transplantation, and this has to be considered, especially during anaesthesiologic management in those who are at increased risk.

CPB use, high CVP and low postoperative oxygenation have been described as being associated with prolonged ventilation (34-37). We were able to demonstrate that, following CPB, the CVP was higher and PaO_2/FiO_2 ratio lower compared with off-pump transplantation, and that CPB resulted in at least doubled duration of postoperative ventilation (this also having been observed by Dalibon *et al*. in unplanned CPB (7)). Postoperative ventilation is an outcome parameter that depends on numerous factors ; however, ventilation itself determines outcome by increasing lung injury, inflammation and infections (25,26). The postoperative duration of ventilation depends on various factors, but unplanned CPB doubled both this duration and hospital mortality, suggesting that the avoidance of CPB should be an important aim in the perioperative management of lung transplantation.

As observed by others (5,7,13,21,22), we also found that transplantation with CPB leads to

more RBC transfusions, these also having been independently associated with increased hospital mortality in our analysis. CPB use and RBC transfusions of more than 1L were independent risk factors for primary graft dysfunction that was associated with increased mortality (38). Weber et al. found an association between mortality and RBC transfusion, but not with the use of CPB (39) whereas Wang et al. identified CPB as predictive for the use of blood products (40). In addition to RBCs, greater quantities of FFP and thrombocytes were administered to patients with unplanned CPB, with even larger amounts of RBCs and FFP being transfused in those with planned CPB. Despite the greater number of RBC transfusions, transplantation with CPB resulted in lower haemoglobin concentration in the present study ; this could be related to diluting effects, with more FFP and crystalloids also having been administered.

However, despite higher volumes of transfusions and crystalloids in patients with unplanned CPB, more norepinephrine and furosemide was administered than in off-pump transplantations. The mean arterial pressure was lower and the heart rate higher, presumably reflecting more severe intravascular hypovolemia and mediator-related vasodilatation in these patients. Furthermore, lactate almost doubled compared with off-pump transplantations ; this may be related to reduced tissue perfusion during CPB and more transfusions of old RBCs, but is less likely to be related to longer graft ischemia time (41) as the duration of ischemia did not differ between groups. Considerably fewer transfusions – but more colloids – were given by both Myles *et al*. (5) and McIlroy *et al*., who also added a colloid solution with albumin when prefilling the pump (6). They identified an increasing volume of intraoperative colloid (predominately gelatin) as being independently associated with a lower PaO_2/FiO_2 ratio after transplantation (6). In our hospital it was mainly hydroxyethyl starch (instead of gelatin) that was used and, although smaller quantities of crystalloids were administered intravenously than in patients transplanted off-pump, the total amount of crystalloids given was greater in those transplanted with CPB, this being due to the prefilling of the pump with 1.54 L of crystalloid. Hence, the lower PaO_2/FiO_2 ratio observed in the present study following CPB might also reflect effects of crystalloid-associated lung edema, and crystalloids might also contribute to the higher frequency of pulmonary edema after transplantation with CPB (7). Thus, avoiding CPB is associated not only with fewer RBC transfusions (this being prognostically relevant) but also with fewer crystalloid administrations (when crystalloid prefilling is used), with corresponding possible advantages.

In the present analysis, one in five patients in whom transplantation succeeded off-pump had a mean PAP > 40 mmHg after anaesthesia induction before first single lung ventilation ; in those who needed unplanned CPB, it was almost one in two. These observations suggest that the risk of unplanned CPB is higher in individuals with high PAP, but also indicate that lung transplantation can be performed successfully without CPB in these patients. At our institution, nitric oxide (NO) inhalation has been used for PAP regulation since the early 1990s, with iloprost nebulization also in use since 2005 (3,4). Hemodynamic impairments may occur as a result of pulmonary clamping, hypoxia, volume loss or surgical manipulation, as (in particular) may low cardiac output (1-6,12). Ventricular fibrillation occurred three times more frequently in patients with unplanned CPB, indicating the increased difficulty of maintaining stable conditions in these individuals. Postulating intravascular normovolemia, we administered norepinephrine to secure coronary arterial pressure and epinephrine to improve the (often compromised) right heart function (1-4). However, in one in four patients in whom transplantation failed off-pump, severe hemodynamic instability led to unplanned CPB mainly due to increased PAP and right ventricular decompensation.

Patients in whom transplantation succeeded off-pump had lower ASA and NYHA classifications, and both the underlying pulmonary diseases and physiologic variables differed compared with those who were transplanted with CPB. In individuals with fibrosis, primary and secondary pulmonary hypertension or cardiac dysfunction, there appears to be an increased risk that unplanned CPB will be necessary. In addition, patients in whom off-pump transplantation failed and unplanned CPB was necessary had more severe lung dysfunctions, as reflected by lower PaO_2/FiO_2 ratios, higher $PaCO_2$, more severe acidosis and higher peak inspiratory pressures before, during and except for $PaCO_2$ even following transplantation.

Most importantly, neither the underlying nor accompanying diseases differed between patients with planned and unplanned CPB, except for the rate of preoperative pneumonia. Those with planned CPB had lower PaO_2/FiO_2 ratios, and received preoperative mechanical ventilation and

extracorporeal circulation several times more often than those with unplanned CPB. This reflects the increased severity of lung injury and illness, suggesting that the timing of transplantation could be optimized in these individuals. Furthermore, under these high-urgency conditions patients with planned CPB received donor lungs with more unfavourable characteristics, and these individuals had the lowest PaO_2/FiO_2 ratio both before and after transplantation, the longest periods of postoperative ventilation, and the highest mortality. By contrast, others have described higher mortality in patients with unplanned than with planned CPB, this probably being due to differing disease severity and selection criteria (7-10). In our analysis, it was only planned (but not unplanned) CPB that represented an independent risk factor for increased hospital mortality. The present analysis encourages consideration of off-pump transplantation of these individuals at an earlier disease stage, using donor lungs with more favourable characteristics ; if unplanned CPB cannot, even then, be avoided, mortality might be still less than in our patient group with planned CPB.

Limitations

The major limitation of this study is its retrospective nature ; unmeasured or unrecognized confounding cannot be eliminated in a retrospective analysis, and there is also the potential of bias secondary to missing data. Furthermore, these findings are from a single centre only, and considerable caution is required when transferring these observations to other centres. In addition, data are now more than 10 years old and do not represent the current state of therapy in our institution :

In view of the better outcome of lung transplantation without CPB, our protocol was changed over the years in order to avoid both planned and unplanned CPB. In our hospital, increasing use of 'awake ECMO' has been made since the beginning of 2010 to avoid preoperative mechanical ventilation and as a bridge to lung transplantation (24). In addition, the routine intraoperative protocol has been changed to venoarterial ECMO in order to avoid CPB (11,12,16). Consequently, RBC transfusions have halved in the more recent era and we performed less size reductions in high urgency recipients, effectively addressing intraoperative risk factors identified in the present analysis, resulting in a considerable reduction of the duration of postoperative ventilation, ICU stay and hospital mortality (12).

AUTHOR CONTRIBUTIONS

Conception, design and acquisition of the data : CG, IM, SM, CL, KR ; Analysis of the data : CG, TD, JA, IM, SM, CL, HH, KR ; Interpretation of data ; CG, TD, JA, IM, SM, CL, PW, EC, BJ, MS, JZ, KHM, WL, FL, NRM, MW, MS, AS, GW, IT, AH, HH TW, SP, KR ; Drafting the manuscript : CG, IM, SM, CL, GW, KR ; Critical revision of manuscript : CG, TD, JA, IM, SM, CL, PW, EC, BJ, MS, JZ, KHM, WL, FL, NRM, MW, MS, AS, GW, IT, AH, HH TW, SP, KR ; Statistical expertise : TD, HH.

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