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Effect of targeted coagulopathy management and 5% albumin as volume replacement therapy during lung transplantation on allograft function: a secondary analysis of a randomized clinical trial

Jaromir Vajter[1†], Jiri Vachtenheim Jr[2*†], Zuzana Prikrylova[1], Jan Berousek[1], Tomas Vymazal[1], Robert Lischke[2], Archer Kilbourne Martin[3] and Miroslav Durila[1]

Abstract

Background Primary graft dysfunction (PGD) after lung transplantation (LuTx) contributes substantially to early postoperative morbidity. Both intraoperative transfusion of a large amount of blood products during the surgery and ischemia–reperfusion injury after allograft implantation play an important role in subsequent PGD development.

Methods We have previously reported a randomized clinical trial of 67 patients where point of care (POC) targeted coagulopathy management and intraoperative administration of 5% albumin led to significant reduction of blood loss and blood product consumption during the lung transplantation surgery. A secondary analysis of the randomized clinical trial evaluating the effect of targeted coagulopathy management and intraoperative administration of 5% albumin on early lung allograft function after LuTx and 1-year survival was performed.

Results Compared to the patients in the control (non-POC) group, those in study (POC) group showed significantly superior graft function, represented by the Horowitz index (at 72 h after transplantation 402.87 vs 308.03 with $p < 0.001$, difference between means: 94.84, 95% CI: 60.18–129.51). Furthermore, the maximum doses of norepinephrine administered during first 24 h were significantly lower in the POC group (0.193 vs 0.379 with $p < 0.001$, difference between the means: 0.186, 95% CI: 0.105–0.267). After dichotomization of PGD (0–1 vs 2–3), significant difference between the non-POC and POC group occurred only at time point 72, when PGD grade 2–3 developed in 25% ($n = 9$) and 3.2% ($n = 1$), respectively ($p = 0.003$). The difference in 1-year survival was not statistically significant (10 patients died in non-POC group vs. 4 patients died in POC group; $p = 0.17$).

[†]Jaromir Vajter and Jiri Vachtenheim Jr contributed equally to this work.

*Correspondence:
Jiri Vachtenheim Jr
jiri.vachtenheim@fnmotol.cz
Full list of author information is available at the end of the article

Conclusions Utilization of a POC targeted coagulopathy management combined with Albumin 5% as primary resuscitative fluid may improve early lung allograft function, provide better circulatory stability during the early post-operative period, and have potential to decrease the incidence of PGD without negative effect on 1-year survival.

Trial registration This clinical trial was registered at ClinicalTrials.gov (NCT03598907).

Keywords Lung transplantation, Anesthetic management, Rotational thromboelastometry, Volume replacement therapy, 5% albumin

Background

Lung transplantation (LuTx) remains the ultimate treatment for end-stage lung disease refractory to optimized medical therapy. Post-implantation, long-term outcomes are impaired by ongoing medical factors including chronic lung allograft dysfunction (CLAD). CLAD (and its phenotypes) represents a major complication that limits the 5-year survival to approximately 55% [1–3]. CLAD develops as a result of various alloimmune-dependent and alloimmune-independent graft injuries and dysregulated repair processes. Primary graft dysfunction (PGD) has been identified as an important risk factor for CLAD development [4, 5].

PGD is defined by the presence of diffuse pulmonary opacities on thoracic imaging and various levels of hypoxemia without other identifiable causes developing in the first 72 h after lung allograft reperfusion [6]. Its clinical course in the most severe form resembles acute respiratory distress syndrome (ARDS) and is considered to be one of the most important causes of early death after transplantation, with an incidence of PGD reported between 10 and 25% [7]. Furthermore, patients who develop PGD also show significantly worse long-term outcomes [8, 9]. Although the pathophysiology of PGD is not completely understood and multifactorial, several intraoperative anesthetic risk factors have been described within the literature [10]. For instance, intraoperative administration of blood products is associated with a strong negative influence on PGD development and outcome in lung transplant recipients [11]. Moreover, a large volume of intraoperative fluids and red blood cells (RBCs) significantly correlates with the development of PGD grade 3. Therefore, the limitation of intraoperative fluid and blood product administration may reduce the risk for the development of PGD grade 3 and thus improve early postoperative morbidity and mortality after LuTx [12].

A reduction in blood loss during surgery and corresponding decrease in intraoperative transfusion of blood products can be achieved by utilizing intraoperative point of care (POC) targeted bleeding/coagulopathy management strategies such as rotational thromboelastometry (ROTEM), platelet function analyzer (PFA) or multiple electrode platelet aggregometry [13, 14]. The use of these approaches has been reported in studies on cardiac surgery and liver transplantation [15–17]. Previously, we reported that POC-targeted coagulopathy management decreases perioperative blood loss and consumption of RBCs and fresh frozen plasma (FFP) during LuTx [18].

Despite the abovementioned reduction in blood product transfusion, ongoing fluid resuscitation is necessary to maintain normovolemia during LuTx surgery. A few studies have described the potential benefits of 5% albumin solution administration for the treatment of patients with ARDS and during cardiac surgery [19, 20]. However, data on the role of perioperative 5% albumin administration and its effect on lung allograft function are lacking, and further investigation is highly needed.

We present a secondary analysis of our randomized clinical trial evaluating the effect of POC coagulopathy management and intraoperative administration of 5% albumin as primary resuscitative fluid during LuTx surgery on early lung allograft function, incidence of PGD, and 1-year survival.

Methods

Study design overview, surgical strategy and outcomes

A secondary analysis of the Point of Care Management of Coagulopathy in Lung Transplantation trial (NCT03598907) was performed. This study was a single-site, prospective randomized controlled trial that examined the utilization of perioperative POC-targeted coagulopathy management in conjunction with 5% albumin solution and their effect on perioperative blood loss and consumption of blood products during LuTx. This study was approved by the institutional ethics committee (reference number EK-1402/17) and was registered in the clinical trial database at ClinicalTrials.gov (identifier number NCT03598907) prior to patient enrollment. All patients provided written informed consent for participation in the study before the LuTx procedure.

As this was a pilot study, the projected number of patients to be recruited was estimated at 120 (planned for 4 years), and an a priori power analysis was not performed in this case. An interim analysis was planned after evaluation of approximately 60 patients (after 2 years). Patients were primarily randomized to two study groups – POC group and non-POC group. The

perioperative anesthesia management strategy used for both the non-POC group and POC group has been described previously [18]. Importantly, in the non-POC group, perioperative bleeding, coagulopathy management and volume replacement therapy was managed according to the clinical experience of the anesthesiologist consisting of blood loss monitoring and subjective optical inspection of the surgical field hemostasis without using POC targeted coagulopathy management or laboratory analysis.

Intravascular volume in this group was replaced with balanced crystalloid, non-albumin colloidal solutions such as 6% hydroxyethyl starch or 4% succinylated gelatin, and FFP. Median volume of balanced crystalloid solution and non-albumin colloidal solutions was 1000 ml (IQR 512.5; 987.5 – 1500) and 775 ml (IQR 500; 500 – 1000), respectively. Triggers to volume replacement in both POC and non-POC groups included circulatory stability expressed by dose of norepinephrine (μg/kg/min) and transesophageal echocardiography (TEE) assessment of decreased cardiac preload by left ventricular fractional area change in transgastric mid-papillary short axis view at 50% calculated veno-arterial extracorporeal membrane oxygenation (VA ECMO) flow. However, due to the limitations described of TEE as a sole intraoperative monitor of systemic volume during VA ECMO, monitors aiding in the assessment of ongoing resuscitation also included urine output and maintenance of pulsatility within systemic and pulmonary arterial waveforms [21].

In the POC group, perioperative bleeding and coagulopathy were managed according to the POC methods performed at the beginning of the surgery, after reperfusion of the first implanted lung and at the end of the surgical procedure (Fig. 1). In this group, a 5% albumin solution was exclusively used for intravascular volume replacement therapy to maintain normovolemia. Median volume of 5% albumin administered was 1750 ml (IQR 500; 1500—2000). The laboratory trigger for RBCs administration in both patient groups was haemoglobin level of 100 g/l. The surgical strategy, lung procurement and ECMO support handling adhered to the methods previously described by the Vienna Lung Transplant Group [22]. At our institution, intraoperative ECMO support is routinely used pre-emptively in the majority of cases during LuTx and only a smaller number of cases LuTx are performed without any extracorporeal life support, as this is purely at the discretion of the transplanting surgeon. In the POC group, the intraoperative ECMO circuit was primed with albumin. The surgical procedural aspects remained consistent throughout the study period and did not differ in either group.

Primary outcome for this secondary analysis was PGD development and grading during the first 72 h after lung transplantation. Measures of Horowitz index (P/F ratio;

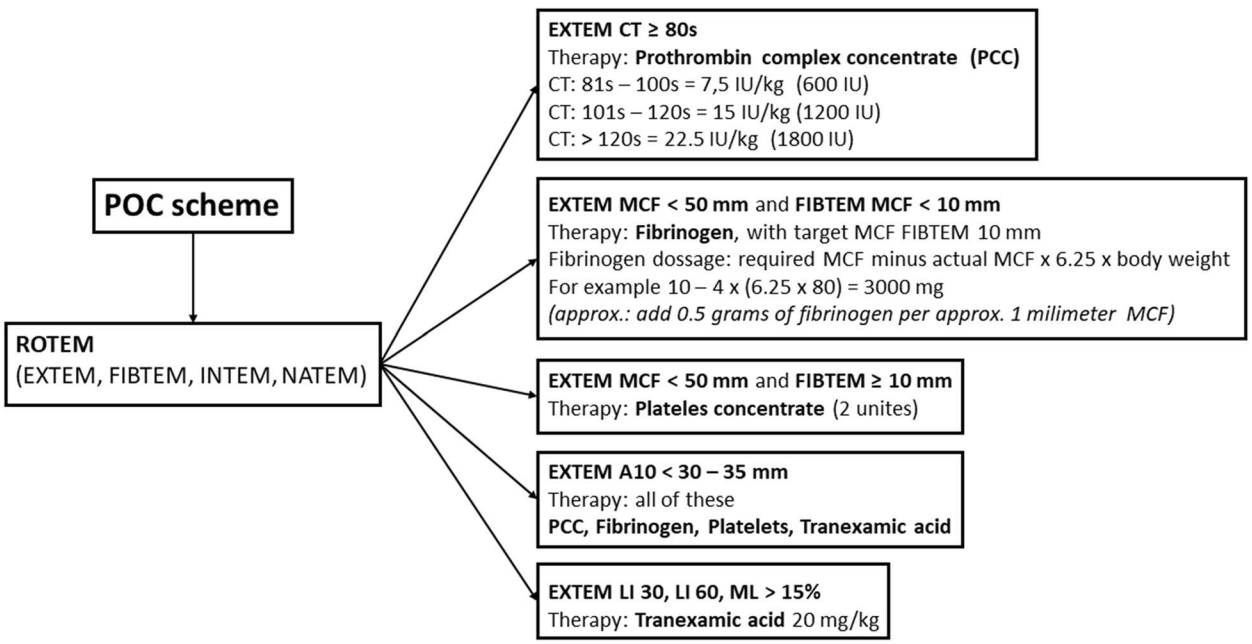

Fig. 1 ROTEM protocol for the diagnosis of coagulopathy and goal-directed therapy using EXTEM, FIBTEM, and APTEM. Abbreviations: A10: Amplitude at 10 min; CT: clotting time; IU: international unit; LI30, LI60: lysis index at 30 and 60 min, MCF: maximum clot firmness; ML: maximum lysis. Previously published in Durila M, Vajter J, Garaj M, Pollert L, Berousek J, Vachtenheim J, Jr., et al. Rotational thromboelastometry reduces blood loss and blood product usage after lung transplantation. J Heart Lung Transplant. 2021;40(7):631–41.[18]

defined as arterial oxygen pressure (P_aO_2) in mmHg divided by fraction of inspired oxygen (F_iO_2) in %) and serum albumin levels in both groups before and after lung transplantation were analyzed. Circulatory stability status characterized by the maximum level of norepinephrine administered during the first 24 h after LuTx was analyzed, with norepinephrine administration based on mean arterial pressure. Postoperative duration of mechanical ventilation and length of intensive care unit (ICU) stay were recorded. Secondary outcome for this analysis was 1-year survival in both groups.

Patient selection and enrollment

Patient selection and eligibility criteria for the current secondary analysis mirrored that of the Point of Care Management of Coagulopathy in Lung Transplantation trial and included patients who underwent LuTx at the University Hospital Motol between January 2018 and June 2020 [18]. The exclusion criteria were electively prolonged postoperative ECMO (patients with idiopathic pulmonary hypertension or preoperatively known severe secondary pulmonary hypertension on basis of underlying disease that were preoperatively identified to require intended ECMO prolongation leading automatically to classification as PGD grade 3, as this would result in negative impact on interpretation of the study), pediatric recipients, single-lung transplantations, retransplantations, heart–lung transplantations, and transplantations requiring cardiopulmonary bypass for technical reasons (concomitant cardiac surgery).

Randomization and detailed description of two randomized groups were described previously [18]. In the first group (POC group), 31 patients were analyzed, and in the second group (non-POC group), 36 patients were analyzed. A flow diagram based on the Consolidated Standards of Reporting Trials (CONSORT) is displayed in Fig. 2.

PGD definition

The definition of PGD was based on the latest International Society for Heart and Lung Transplantation (ISHLT) recommendation and was recorded 2 h after ICU admission (time 0) and then 24 h (time 24), 48 h (time 48) and 72 h (time 72) after LuTx [6]. Chest radiographs assessment was consistent with the methods previously described by the Vienna Lung Transplant Group [22].

Statistical analysis

Statistical analyses were performed with R statistical software, version 3.4.4 (available online at http://www.r-project.org/). A p-value of 0.05 was considered statistically significant. PGD grade 1 is questionably relevant clinically, therefore PGD grades were dichotomized into two groups and analyzed as follows: PGD 0—1 vs PGD 2—3. The Fischer exact test was performed with the data from each time point (0, 24, 48, 72 h) to analyze the association of dichotomized PGD in both groups. Serum albumin levels in both groups were measured before and after LuTx. Due to technical reasons, the preoperative serum albumin levels in 15 patients were not measured (9 patients in the non-POC group and 6 patients in the POC group). Postoperative serum albumin levels were completed for all patients in the study cohort.

The Horowitz index was calculated at each tracked time point (0, 24, 48, 72 h), and the measured values were evaluated with Welch's two-sample t-test. The maximum level of norepinephrine (μg/kg/min) during the first 24 h after LuTx was compared in both groups using Welch's two-sample t-test. Postoperative ICU stay and mechanical ventilation duration was recorded and analyzed by Wilcoxon tests. Moreover, 1-year survival in both study groups was followed and survival rates were compared using log-rank tests.

Results

Study patients and study flow

Patients were recruited during the period from January 2018 to June 2020, and based on the exclusion criteria, a total of 33/100 patients were excluded from the study. The non-POC group and POC group ultimately consisted of 36 and 31 patients, respectively. At this point, interim statistical analysis was performed, and the study was preliminarily terminated by the institutional review board because the results were significantly in favor of the POC approach, as significant decrease in perioperative blood loss and related decrease in blood products consumption was observed among the POC study group [18]. In the POC group and non-POC group, the mean blood loss in the operating room was 682 ml ± 399 and 1043 ml ± 547, respectively ($p = 0.003$). Mean value of RBCs units administered in the operating room was 0.83 ± 1.15 in the POC group and 1.05 ± 1.45 in the non-POC group ($p = 0.506$). Mean value of FFP units administered in the operating room was 0.00 in the POC group and 4.08 ± 2.89 in the non-POC group ($p < 0.001$) [18].

Patients in the non-POC group were significantly older than patients in POC group (56.22 ± 9.05 vs 45.69 ± 16.54 years, $p = 0.002$), as the proportion of younger patients with cystic fibrosis was significantly higher in the POC group (32.3%, $n = 10$ vs 5,6%, $n = 2$; $p = 0.005$). The use of intraoperative ECMO support compared to off pump approach was higher in non-POC group, although the difference was not statistically significant (86%, $n = 31$ vs 67.7%, $n = 21$; $p = 0.07$). However, mean pulmonary arterial pressure, that would signalize

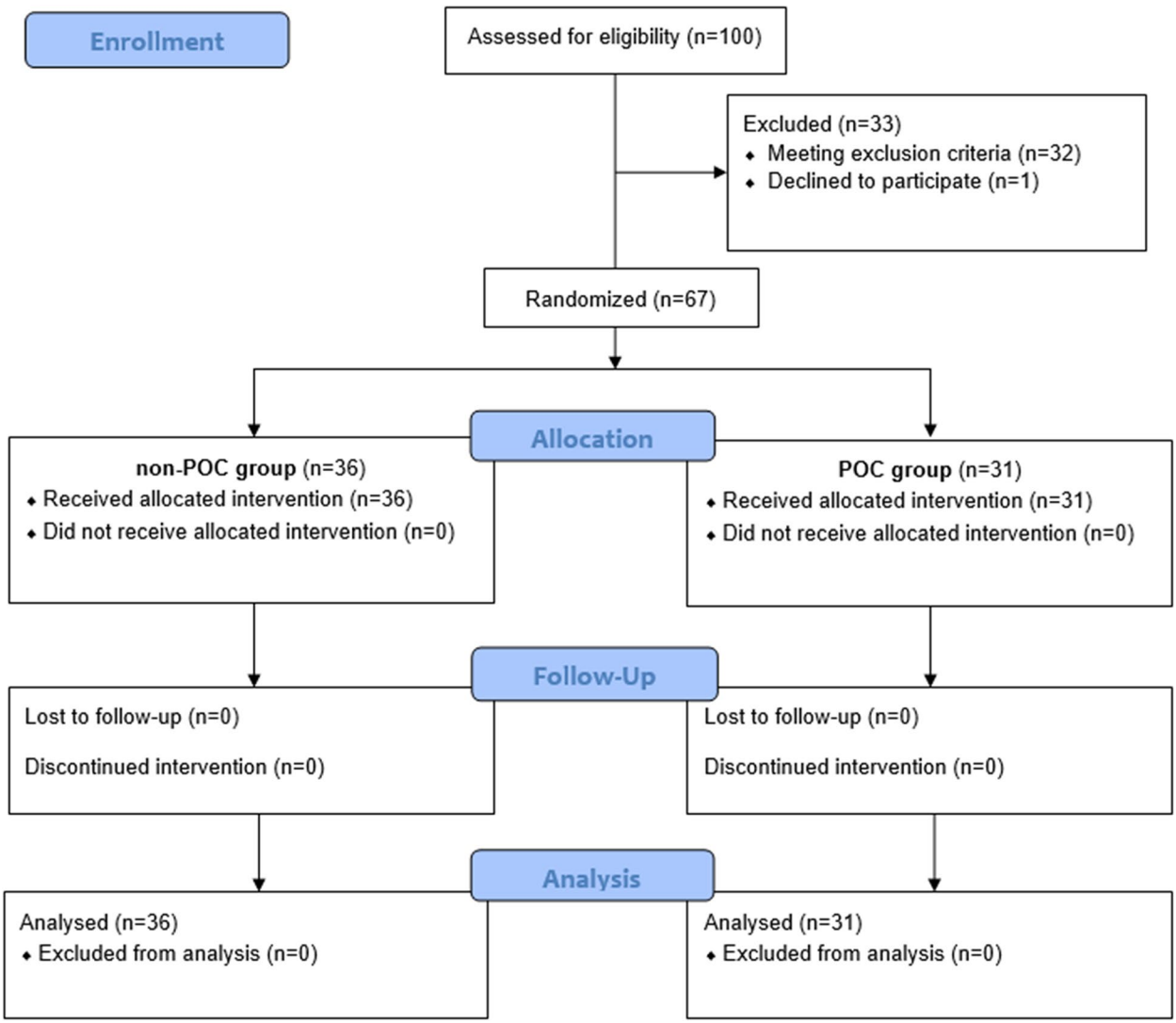

Fig. 2 Flow chart of the study population

higher degree of disease severity and complexity did not differ significantly between recipients in non-POC and POC group. Detailed preoperative and intraoperative characteristics of the recipients have been reported previously and are presented with permission in Table 1 together with donor characteristics [18]. There were no statistically significant differences in the donor variables between the non-POC and POC group. In POC group, only 1 out of 31 patients received organ from donation after circulatory death (DCD) donor and no organ from DCD donor was utilized in non-POC group. No organ from expanded criteria donor was utilized (not shown in Table 1). Importantly, no case of graft dysfunction at the end of the surgery that would require ECMO prolongation occurred in either study group.

Primary graft dysfunction evaluation

The incidence of PGD development based on ISHLT criteria at each time point in the non-POC and POC groups is displayed in Table 2 and Fig. 3 [6]. No PGD (grade 0) was found significantly more frequently in the POC group at every tracked time point, although the overall difference in PGD (regardless of grade) was statistically significant only at time point 72. However, PGD grade 0 and even 1 are questionably relevant clinically, therefore PGD grades were further dichotomized and analyzed into two categories according to clinical relevance (PGD grade 0 – 1 vs PGD grade 2 – 3) and results are shown in Table 3. Significant difference between the non-POC and POC group occurred only at time point 72, when PGD grade 0 – 1 was observed in 75% ($n=27$) and 96.8% ($n=30$), respectively. At the same time point 72, PGD

Table 1 Recipient and donor characteristics

Recipient characteristics variable	**non-POC group (*n* = 36)**	**POC group (*n* = 31)**	***p*-value**
Male sex	25 (69%)	20 (64.5%)	0.67
Age (years; mean ± SD)	56.22 ± 9.05	45.69 ± 16.54	0.002
Weight (kg; mean ± SD)	76.64 ± 18.21	67.48 ± 16.51	0.036
Height (cm; mean ± SD)	173.81 ± 9.72	169.55 ± 9.57	0.08
Body mass index (mean ± SD)	25.03 ± 4.04	23.25 ± 4.33	0.09
MPAP (mmHg; mean ± SD)	23.97 ± 6.05	25.58 ± 9.63	0.43
Transplant indication			
COPD	15 (41.6%)	12 (38.7%)	0.81
Pulmonary fibrosis	18 (50%)	9 (29%)	0.08
Cystic fibrosis	2 (5.6%)	10 (32.3%)	0.005
Sarcoidosis	1 (2.8%)	0	0.35
Intra-Operative recipient characteristics			
Thoracotomy			
Sternum sparing	5 (14%)	8 (25.8%)	0.22
Clamshell	31 (86%)	23 (74.2%)	0.22
Intraoperative ECMO	31 (86%)	21 (67.7%)	0.07
Ischemic time (min; mean ± SD)			
First lung	242.83 ± 40.23	243.52 ± 40.96	0.91
Second lung	353.69 ± 47.21	354.06 ± 58.02	0.24
Donor characteristics variable	**non-POC group (*n* = 36)**	**POC group (*n* = 31)**	***p*-value**
Male sex	23 (63.9%)	17 (54.8%)	0.45
Age (years; mean ± SD)	43.56 ± 18.84	43.81 ± 15.14	0.95
Weight (kg; mean ± SD)	71.67 ± 16.32	73.77 ± 18.12	0.62
Height (cm; mean ± SD)	170.92 ± 12.98	173.81 ± 9.95	0.32
Body mass index (mean ± SD)	25.13 ± 6.71	24.28 ± 5.26	0.57
Horowitz index (mmHg; mean ± SD)	468.56 ± 64.58	475.32 ± 63.83	0.67
Smoking history, *n* (%)	8 (22.2%)	5 (16.1%)	0.53
Cause of death, *n* (%)			
subarachnoid hemorrhage	5 (13.9%)	7 (22.6%)	0.35
intracerebral bleeding	9 (25%)	9 (29%)	0.71
trauma capitis	13 (36.1%)	11 (35.5%)	0.96
anoxic brain damage	7 (19.4%)	1(3.2%)	0.06
other	2 (5.6%)	3 (9.7%)	0.66

Abbreviations: *COPD* chronic obstructive pulmonary disease, *ECMO* extracorporeal membrane oxygenation, *MPAP* mean pulmonary arterial pressure, *POC* point of care, *SD* standard deviation. Previously published in Durila M, Vajter J, Garaj M, Pollert L, Berousek J, Vachtenheim J, Jr., et al. Rotational thromboelastometry reduces blood loss and blood product usage after lung transplantation. J Heart Lung Transplant. 2021;40(7):631–41.[18]

grade 2 – 3 developed in 25% ($n = 9$) and 3.2% ($n = 1$), respectively ($p = 0.016$). Of those 9 patients with PGD grade 2 – 3 in the non-POC group at time point 72, 8 patients had PGD grade 2 and 1 patient had PGD grade 3. There was no statistically significant difference in occurrence of PGD grade 3 between the non-POC and POC group at all tracked time points.

Horowitz index evaluation

Table 4 and Fig. 4 show the mean values of the Horowitz index at each time point (0, 24, 48, 72) in the non-POC group and the POC group. At all tracked time points, pulmonary graft function was significantly higher in the POC group, as indicated by the Horowitz index. It is of particular interest, that most significant difference between the groups occurred at time point 72, when the Horowitz index was 308.03 in the non-POC group vs 402.87 in the POC group ($p < 0.001$, difference between means: 94.84, 95% CI: 60.18–129.51).

Norepinephrine dosage and albumin serum levels evaluation

The maximum single dose of norepinephrine (μg/kg/min) administered to every patient in both groups during the first 24 h was recorded. In the non-POC group

Table 2 Primary graft dysfunction development in both groups in four tracked time periods. Data are presented as n (%)

	Time 0				
PGD grade	0	1	2	3	*p*-value
non-POC	16 (44.4)	6 (16.7)	6 (16.7)	8 (22.2)	0.048
POC	22 (70.9)	2 (6.5)	6 (19.4)	1 (3.2)	
	Time 24				
PGD grade	0	1	2	3	*p*-value
non-POC	13 (36.1)	15 (41.7)	4 (11.1)	4 (11.1)	0.08
POC	21 (67.7)	7 (22.6)	2 (6.5)	1 (3.2)	
	Time 48				
PGD grade	0	1	2	3	*p*-value
non-POC	13 (36.1)	14 (38.9)	9 (25)	0	0.052
POC	20 (64.5)	6 (19.4)	4 (12.9)	1 (3.2)	
	Time 72				
PGD grade	0	1	2	3	*p*-value
non-POC	16 (44.4)	11 (30.6)	8 (22.2)	1 (2.8)	0.003
POC	25 (80.7)	5 (16.1)	0	1 (3.2)	

Abbreviations: *PGD* primary graft dysfunction, *POC* point of care

and POC group, the maximum doses of norepinephrine were 0.379 and 0.193, respectively ($p < 0.001$, difference between the means: 0.186, 95% CI: 0.105–0.267). Serum albumin levels (g/l) in both groups were measured before and after LuTx. There was no significant difference in preoperative mean serum albumin levels between POC group and non-POC group (44.43 vs 44.19; $p = 0.84$, difference between means: 0.24, 95% CI: (-2.11)-2.58). The mean serum albumin levels after LuTx surgery were significantly higher in the POC group than in the non-POC group (41.55 vs 29.37), with $p < 0.001$, difference between means 12.18 and 95% CI: 9.81–14.55.

Postoperative mechanical ventilation duration and length of ICU stay and 1-year survival

Duration of mechanical ventilation and length of ICU stay after LuTx surgery were decreased in POC group. However, this difference did not cross the boundary for statistical significance as shown in Table 5. During the 1-year follow-up study period after LuTx, more patients died in the non-POC group than in the POC group, although the difference in 1-year survival was not

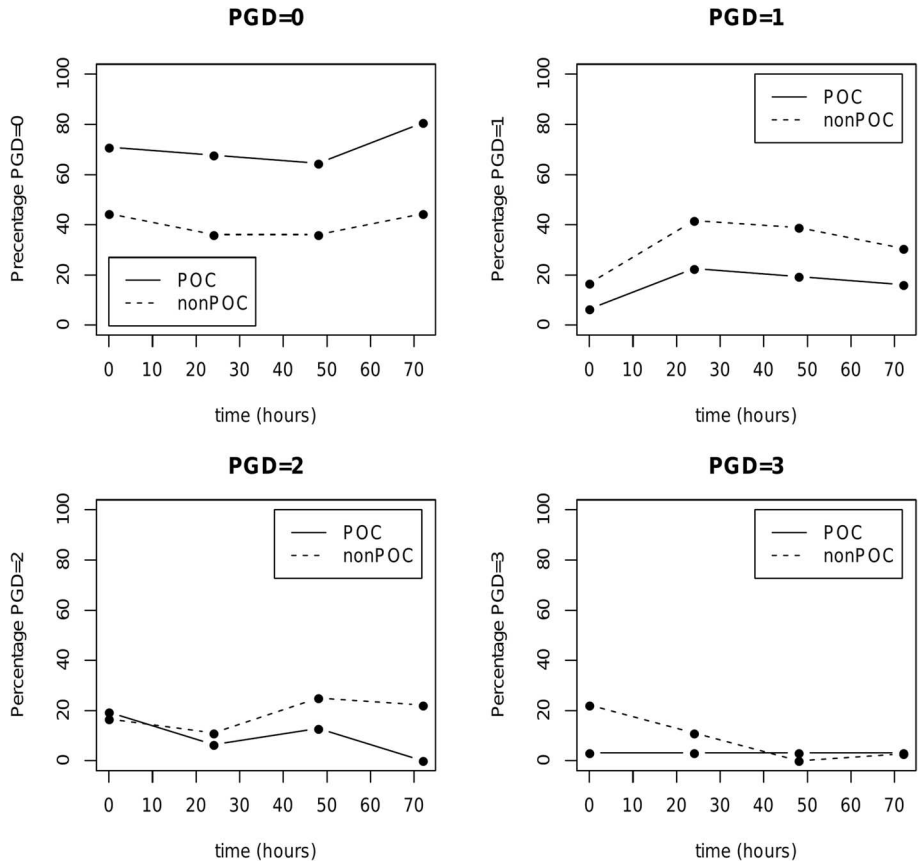

Fig. 3 Incidence of primary graft dysfunction after lung transplantation at 0, 24, 48 and 72 h after surgery. Abbreviations: PGD: primary graft dysfunction; POC: point of care

Table 3 In both patient groups, PGD grades were dichotomized and analyzed into two categories according to their clinical relevance (PGD grade 0 – 1 vs PGD grade 2 – 3). Data are presented as n (%)

	Time 0		
PGD grade	non-POC	POC	*p*-value
0—1	22 (61.1)	24 (77.4)	0.19
2—3	14 (38.9)	7 (22.6)	
	Time 24		
PGD grade	non-POC	POC	*p*-value
0—1	28 (77.8)	28 (90.3)	0.2
2—3	8 (22.2)	3 (9.7)	
	Time 48		
PGD grade	non-POC	POC	*p*-value
0—1	27 (75)	26 (83.9)	0.55
2—3	9 (25)	5 (16.1)	
	Time 72		
PGD grade	non-POC	POC	*p*-value
0—1	27 (75)	30 (96.8)	0.016
2—3	9 (25)	1 (3.2)	

Abbreviations: *PGD* primary graft dysfunction, *POC* point of care

Table 4 Horowitz index and its differences between the non-POC and POC group at each tracked time. The Horowitz index is defined as arterial oxygen pressure (P_aO_2) in mmHg divided by the fraction of inspired oxygen (F_iO_2) in %. Values are displayed together with the difference estimate and confidence intervals (CI) to illustrate the difference in mean Horowitz index values between the groups

time	non-POC group	POC group	t test		
			difference	95% CI	*p*-value
0	292.83	346.19	53.36	(5.91, 100.82)	0.028
24	350	395.61	45.61	(8.29, 82.93)	0.017
48	326.72	385.26	58.54	(16.06, 101.01)	0.008
72	308.03	402.87	94.84	(60.18, 129.51)	< 0.001

Abbreviations: *POC* point of care, *CI* confidence interval

statistically significant (10 patients in non-POC group vs. 4 patients in POC group; $p = 0.17$). In both groups, 30-day mortality was 0%. In POC group, 90-day mortality was 3.2% ($n = 1$, patient with cystic fibrosis that died at day 64 because of fulminant Burkholderia cenocepacea infection). In non-POC group 90-day mortality was 2,8% ($n = 1$, patient with pulmonary fibrosis died at day 53 because of bronchopneumonia due to Pseudomonas aeruginosa). After 90-postoperative day, other causes of death during first year were infection (8 patients) and cardio-renal failure (1 patient) in non-POC group and infection (1 patient), pancreatic cancer (1 patient) and brain stroke (1 patient) in POC group. A Kaplan–Meier 1-year survival curve is shown in Fig. 5.

Discussion

PGD negatively contributes to increased short-term and long-term morbidity and mortality after LuTx [8, 9]. While the exact pathogenesis is not completely understood, multiple risk factors are associated with the development of PGD including donor-specific and recipient-specific variables [23]. Additionally, postoperative risk or complicating factors such as hypotension, fluid overload, vascular anastomotic complications, inadequate mechanical ventilation, and pneumonia have been reported to contribute to PGD [6]. Finally, intraoperative anesthetic management has been reported to have a potentially significant influence on the development of PGD [10].

Ischemia–reperfusion injury after lung allograft implantation has been shown to lead to PGD development [24]. Interestingly, the pulmonary endothelial glycocalyx is particularly prone to ischemia–reperfusion injury and shedding of the glycocalyx has been linked to respiratory failure and the development of ARDS in mice [25]. The control of this reperfusion has been theorized as a method of attenuating the development of PGD in lung transplantation, and the utilization of VA ECMO for intraoperative support has been described as a method to accomplish this control. Hoetzenecker et al. demonstrated that intraoperative VA ECMO support provides optimal reperfusion conditions that translate into superior graft function [22]. Although routine use of intraoperative ECMO is generally advocated, there is still a non-negligible risk of undesirable bleeding associated with this method. Thomas et al. noted that achieving the optimal anticoagulation balance to prevent bleeding and thrombosis in ECMO patients is extremely complex, and experts in hemostasis should be a part of an institutional ECMO team and continuously available for immediate management [26].

Transfusion of a large amount of blood products, especially FFP, to manage intraoperative blood loss during LuTx is an independent risk factor for PGD through transfusion-related acute lung injury (TRALI) [27–29]. Diamond et al. reported that the prevalence of greater than 1 L RBC intraoperative transfusion was 34%, and in the adjusted analysis, this was associated with a nearly twofold increased risk for the development of PGD grade 3 [30]. In addition, apart from the abovementioned TRALI, blood product transfusion alone is associated with transfusion-associated circulatory overload (TACO), pulmonary infections and prolonged ICU stays [31]. The incidence of TACO is reported to be highest

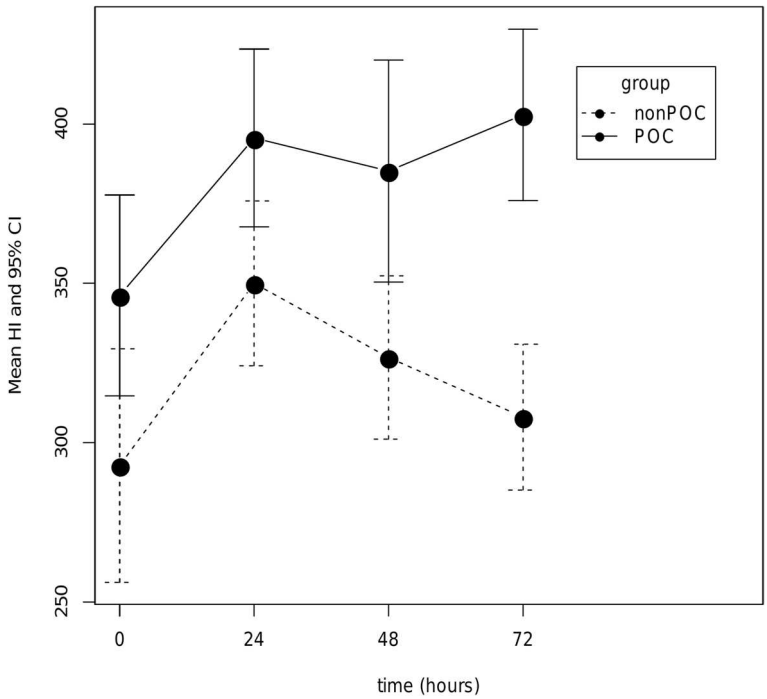

Fig. 4 Horowitz index at each time point (0, 24, 48, 72 h) after lung transplant surgery. Values are presented as the mean and 95% CI. Abbreviations: HI: Horowitz index; CI: confidence interval; POC: point of care

Table 5 Duration of mechanical ventilation and length of intensive care unit stay after LuTx surgery in non-POC vs POC group

	non-POC group			POC group			Wilcoxon test
	mean	median	IQR	mean	median	IQR	*p*-value
MV (hours)	147.8	35.5	50.5	90.3	25	36	0.17
ICU stay (days)	13	6	3.3	9.5	5	4	0.27

Abbreviations: ICU intensive care unit, *IQR* interquartile range, *LuTx* lung transplantation, *MV* mechanical ventilation, *POC* point of care

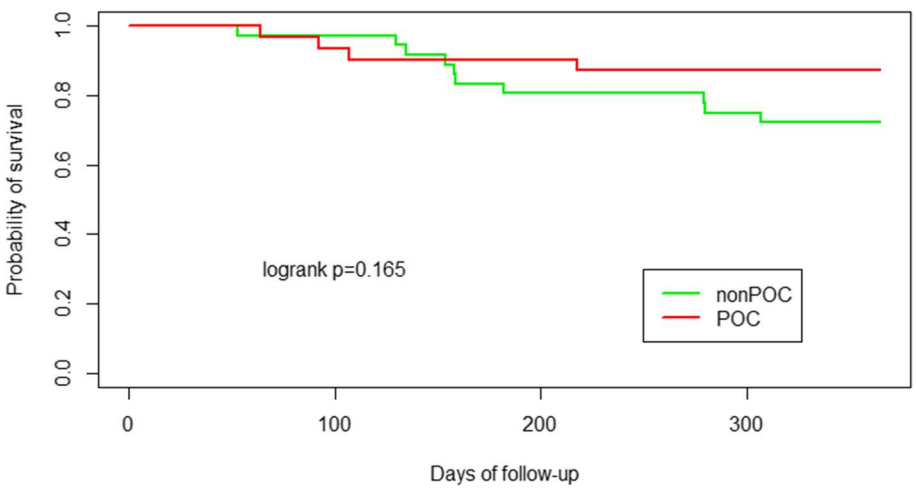

Fig. 5 Kaplan Meier survival curve for patients in non-POC group (green line) vs POC group (red line). Abbreviations: POC: point of care

after the transfusion of FFP, followed by RBCs and platelets [32]. Perioperative POC-targeted coagulopathy management reduces the amount of blood transfusion products needed [33]. We have previously demonstrated that this perioperative approach practically eliminated the need for FFP transfusion in the POC study group during LuTx surgery [18]. This is of particular interest regarding avoidance of the FFP-associated volume expansion effect, which may negatively contribute to PGD development. Despite the abovementioned reduction in blood product transfusion, a certain amount of fluid is necessary to maintain normovolemia during surgery. However, excessive perioperative crystalloid and colloid administration might be associated with fluid overload and therefore increase the risk of PGD development.

In our study, 5% albumin solution was used solely as volume replacement therapy in the POC group. Albumin is a medium-sized molecule with a molecular weight of 66–69 kDa and is the most abundant protein in human plasma (40 g/l out of a total of 70 g/l). Albumin is synthesized exclusively in the liver and plays an important role in numerous processes. For example, it serves as a major extracellular antioxidant and a major transporter in plasma, responsible for 75% of oncotic plasma pressure. Therefore, albumin solution is considered to be the standard colloidal resuscitation fluid [34]. Another crucial role of albumin appears to be its positive effect on the physiological part of the endothelial glycocalyx where it maintains a functioning vascular barrier, especially in patients where increased capillary leakage is present [35, 36]. This typically occurs during LuTx as a part of ischemia–reperfusion-induced lung graft injury or as a part of systemic inflammatory response syndrome (SIRS) aggravated by the ECMO circuit.

Fluid management during all types of surgical procedures affects postoperative outcomes [37]. Inadequate fluid management may be associated with mitochondrial dysfunction and the promotion of inflammation, which can lead to decreased lung allograft function [12, 25]. However, the use of colloids in volume replacement therapy remains a subject of debate. Uhlig et al. reviewed and performed a meta-analysis of 3 randomized controlled trials comparing albumin versus crystalloid solutions for intravascular volume expansion in critically ill patients with ARDS and based on the findings of their review, colloid therapy with albumin improved oxygenation but did not affect mortality [19]. Torres et al. studied the effect of different kinds of fluid administration on the vascular endothelium and microcirculation and found that the administration of protein-rich solutions such as albumin helped to rebuild the endothelial glycocalyx [38]. Mendes et al. conducted similar investigations in a rat model of acute lung injury (ALI), and their results revealed that both iso-oncotic and hyper-oncotic albumin solutions were associated with decreased lung injury as compared to Ringer's lactate [39]. Moreover, Moreno Garijo et al. described the importance of albumin as a primary fluid at Toronto Lung Transplant Program [40]. However, the data supporting the intraoperative albumin utilization in their review were lacking.

In our study, targeted coagulopathy management and 5% albumin solution administered exclusively as volume replacement therapy during LuTx surgery resulted in significant improvement in lung allograft function in the first postoperative 72 h in the POC study group compared to the non-POC study group measured by Horowitz index. This intervention also resulted in significant decrease of PGD grade 2–3 at time point 72 in POC group. This is of particular interest, as most studies examine the incidence of PGD grade 3 at 72 h. However, in our study there was no statistically significant difference in occurrence of PGD grade 3 between the non-POC and POC group at all tracked time points. Additionally, the mean value of the maximum norepinephrine level during the first 24 h after LuTx was found to be significantly decreased in the POC group. This finding supports the theory that albumin as volume replacement therapy during LuTx surgery may provide greater hemodynamic circulatory stability in the POC group during the first 24 h after surgery through both volume replacement and its hypothesized anti-inflammatory effect on the reduction in SIRS [34]. Our data from secondary analysis suggest that administration of 5% albumin during LuTx surgery may have a more protective effect on shedding of the glycocalyx and therefore reduce vasoplegia and SIRS. Moreover, significantly higher postoperative levels of serum albumin in the POC group may further contribute to postoperative better graft function and circulatory stability through the abovementioned mechanisms.

Our study has several limitations that require rigorous and transparent discussion. First, a major limitation is that our study design contained two interventions in one study protocol (targeted coagulopathy management and 5% albumin in POC study group). As targeted coagulopathy management led to decrease of blood loss and blood products transfusion, the study was preliminarily terminated by the institutional review board due to positive results in favor of the POC approach. This preliminary termination resulted in a relatively small cohort size in each group, precluding further evaluation of effect of the second intervention in the study (5% albumin administration). Moreover, two interventions in one study protocol limits our ability to identify the precise extent of how either the first or second intervention contributed to the study results.

Heterogeneity in the patient age distribution between the non-POC group, where patients were older, versus the POC group that contained a greater proportion of younger

patients with cystic fibrosis was another limitation. This population difference is important to highlight, as a variety of etiology-based comorbidities can impact intraoperative management and outcomes [41]. In particular, it is generally accepted that LuTx outcomes are better in younger patients with cystic fibrosis. However, a recently reported study by Fessler et al. demonstrated a higher perioperative utilization of RBCs and FFP in patients with cystic fibrosis compared to those with chronic obstructive pulmonary disease or pulmonary fibrosis [42]. Therefore, despite an imbalance between population age and etiology of end-stage lung disease, intraoperative targeted coagulopathy management together with 5% albumin administration significantly reduced blood loss and blood product transfusion in the POC group [18]. A final limitation is focused on the completeness of our preoperative laboratory evaluation. Preoperative serum albumin levels in 15 patients (9 patients in the non-POC group and 6 patients in the POC group) were not measured for technical reasons; however, the postoperative serum albumin levels records were complete for all patients in the study cohort.

To the best of our knowledge, despite abovementioned limitations, the research presented herein represents the first clinical trial attempting to investigate the effect of the perioperative use of targeted bleeding and coagulopathy management combined with 5% albumin administration on lung allograft function after LuTx. Furthermore, our data provide a level of evidence suggesting albumin as an optimal choice for intraoperative resuscitation in lung transplantation that to date has been based on expert opinion in the literature. However, further investigation in this area is highly needed to provide deeper insight into potential beneficial effect of perioperative use of 5% albumin solely as volume replacement therapy during LuTx on PGD incidence. The authors suggest design future trial with 5% albumin solution administrated intraoperatively as the only intervention in study group.

Conclusions

The results of this study indicate that targeted coagulopathy management and 5% albumin solution solely used as volume replacement therapy during LuTx surgery may improve early lung allograft function, provide better circulatory stability during the early post-operative period, and have potential to decrease the incidence of PGD without negative effect on 1-year survival. However, further investigation is highly needed to provide deeper insight into mechanisms of potential beneficial effect of perioperative use of 5% albumin solely as volume replacement therapy during LuTx on PGD incidence, CLAD development, and long-term outcomes.

Abbreviations

ACR	Acute cellular rejection
ALI	Acute lung injury
AMR	Antibody mediated rejection
ARDS	Acute respiratory distress syndrome
CI	Confidence interval
CLAD	Chronic lung allograft dysfunction
DCD	Donation after circulatory death
ECMO	Extracorporeal membrane oxygenation
FFP	Fresh frozen plasma
GERD	Gastroesophageal reflux disease
ICU	Intensive care unit
ISHLT	International Society for Heart and Lung Transplantation
LuTx	Lung transplantation
PFA	Platelet function analyzer
PGD	Primary graft dysfunction
POC	Point of care
RBCs	Red blood cells
ROTEM	Rotational thromboelastometry
SIRS	Systemic inflammatory response syndrome
TACO	Transfusion-associated circulatory overload
TEE	Transesophageal echocardiography
TRALI	Transfusion-related acute lung injury
VA ECMO	Veno-arterial extracorporeal membrane oxygenation

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Authors' contributions

JV and MD designed the study and collected the study data, JV, MD, JV Jr analyzed the data and wrote major part of the manuscript, JV, JV Jr, ZP, JB, TV, RL, AKM and MD participated in the performance of the research and/or substantially contributed to the writing of the manuscript. All authors edited the final manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

All data generated or analyzed in the current article are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study was approved by the ethical committee of University Hospital Motol with approval number EK-1402/17. Written informed consent was obtained from all included patients. The study was carried out in accordance with the declaration of Helsinki.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Author details
[1]Department of Anesthesiology and Intensive Care Medicine, Second Faculty of Medicine, Charles University and University Hospital Motol, Prague, Czech Republic. [2]Prague Lung Transplant Program, 3rd Department of Surgery, First Faculty of Medicine, Charles University and University Hospital Motol, Prague, Czech Republic. [3]Division of Cardiovascular and Thoracic Anesthesiology, Mayo Clinic College of Medicine and Science, Jacksonville, FL, USA.

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References

1. Verleden GM, Glanville AR, Lease ED, Fisher AJ, Calabrese F, Corris PA, et al. Chronic lung allograft dysfunction: Definition, diagnostic criteria, and approaches to treatment-A consensus report from the Pulmonary Council of the ISHLT. J Heart Lung Transplant. 2019;38(5):493–503.
2. Verleden GM, Raghu G, Meyer KC, Glanville AR, Corris P. A new classification system for chronic lung allograft dysfunction. J Heart Lung Transplant. 2014;33(2):127–33.
3. Tikkanen JM, Singer LG, Kim SJ, Li Y, Binnie M, Chaparro C, et al. De Novo DQ Donor-Specific Antibodies Are Associated with Chronic Lung Allograft Dysfunction after Lung Transplantation. Am J Respir Crit Care Med. 2016;194(5):596–606.
4. DerHovanessian A, Wallace WD, Lynch JP 3rd, Belperio JA, Weigt SS. Chronic lung allograft dysfunction: evolving concepts and therapies. Semin Respir Crit Care Med. 2018;39(2):155–71.
5. Verleden SE, Vos R, Vanaudenaerde BM, Verleden GM. Chronic lung allograft dysfunction phenotypes and treatment. J Thorac Dis. 2017;9(8):2650–9.
6. Snell GI, Yusen RD, Weill D, Strueber M, Garrity E, Reed A, et al. Report of the ISHLT Working Group on Primary Lung Graft Dysfunction, part I: Definition and grading-A 2016 Consensus Group statement of the International Society for Heart and Lung Transplantation. J Heart Lung Transplant. 2017;36(10):1097–103.
7. Christie JD, Kotloff RM, Ahya VN, Tino G, Pochettino A, Gaughan C, et al. The effect of primary graft dysfunction on survival after lung transplantation. Am J Respir Crit Care Med. 2005;171(11):1312–6.
8. Cantu E, Diamond JM, Suzuki Y, Lasky J, Schaufler C, Lim B, et al. Quantitative evidence for revising the definition of primary graft dysfunction after lung transplant. Am J Respir Crit Care Med. 2018;197(2):235–43.
9. Whitson BA, Prekker ME, Herrington CS, Whelan TP, Radosevich DM, Hertz MI, et al. Primary graft dysfunction and long-term pulmonary function after lung transplantation. J Heart Lung Transplant. 2007;26(10):1004–11.
10. Martin AK, Yalamuri SM, Wilkey BJ, Kolarczyk L, Fritz AV, Jayaraman A, et al. The Impact of anesthetic management on perioperative outcomes in lung transplantation. J Cardiothorac Vasc Anesth. 2020;34(6):1669–80.
11. Weber D, Cottini SR, Locher P, Wenger U, Stehberger PA, Fasshauer M, et al. Association of intraoperative transfusion of blood products with mortality in lung transplant recipients. Perioper Med (Lond). 2013;2(1):20.
12. Geube MA, Perez-Protto SE, McGrath TL, Yang D, Sessler DI, Budev MM, et al. Increased intraoperative fluid administration is associated with severe primary graft dysfunction after lung transplantation. Anesth Analg. 2016;122(4):1081.
13. Smith I, Pearse BL, Faulke DJ, Naidoo R, Nicotra L, Hopkins P, et al. Targeted Bleeding Management Reduces the Requirements for Blood Component Therapy in Lung Transplant Recipients. J Cardiothorac Vasc Anesth. 2017;31(2):426–33.
14. Jonas J, Durila M, Malosek M, Maresova D, Stulik J, Barna M, et al. Usefulness of perioperative rotational thrombelastometry during scoliosis surgery in children. J Neurosurg Spine. 2020;32(6):865–70.
15. Karkouti K, Callum J, Wijeysundera DN, Rao V, Crowther M, Grocott HP, et al. Point-of-Care Hemostatic Testing in Cardiac Surgery: A Stepped-Wedge Clustered Randomized Controlled Trial. Circulation. 2016;134(16):1152–62.
16. Abeysundara L, Mallett SV, Clevenger B. Point-of-Care Testing in Liver Disease and Liver Surgery. Semin Thromb Hemost. 2017;43(4):407–15.
17. Donohue CI, Mallett SV. Reducing transfusion requirements in liver transplantation. World J Transplant. 2015;5(4):165–82.
18. Durila M, Vajter J, Garaj M, Pollert L, Berousek J, Vachtenheim J Jr, et al. Rotational thromboelastometry reduces blood loss and blood product usage after lung transplantation. J Heart Lung Transplant. 2021;40(7):631–41.
19. Uhlig C, Silva PL, Deckert S, Schmitt J, de Abreu MG. Albumin versus crystalloid solutions in patients with the acute respiratory distress syndrome: a systematic review and meta-analysis. Crit Care. 2014;18(1):R10.
20. Kingeter AJ, Raghunathan K, Munson SH, Hayashida DK, Zhang X, Iyengar S, et al. Association between albumin administration and survival in cardiac surgery: a retrospective cohort study. Can J Anesth/Journal canadien d'anesthésie. 2018;65(11):1218–27.
21. Martin AK, Harrison BA, Fritz AV, Landolfo KP, Makey IA, Sareyyupoglu B, et al. Intraoperative management of a hybrid extracorporeal membrane oxygenation circuit for lung transplantation. J Card Surg. 2020;35(12):3560–3.
22 Hoetzenecker K, Benazzo A, Stork T, Sinn K, Schwarz S, Schweiger T, et al. Bilateral lung transplantation on intraoperative extracorporeal membrane oxygenator: An observational study. J Thorac Cardiovasc Surg. 2020;160(1):320-7 e1.
23. de Perrot M, Liu M, Waddell TK, Keshavjee S. Ischemia-reperfusion-induced lung injury. Am J Respir Crit Care Med. 2003;167(4):490–511.
24. Gelman AE, Fisher AJ, Huang HJ, Baz MA, Shaver CM, Egan TM, et al. Report of the ISHLT Working Group on Primary Lung Graft Dysfunction Part III: Mechanisms: A 2016 Consensus Group Statement of the International Society for Heart and Lung Transplantation. J Heart Lung Transplant. 2017;36(10):1114–20.
25. Sladden TM, Yerkovich S, Grant M, Zhang F, Liu X, Trotter M, et al. Endothelial glycocalyx shedding predicts donor organ acceptability and is associated with primary graft dysfunction in lung transplant recipients. Transplantation. 2019;103(6):1277–85.
26. Thomas J, Kostousov V, Teruya J. Bleeding and thrombotic complications in the use of extracorporeal membrane oxygenation. Semin Thromb Hemost. 2018;44(1):20–9.
27. Diamond JM, Arcasoy S, Kennedy CC, Eberlein M, Singer JP, Patterson GM, et al. Report of the International Society for Heart and Lung Transplantation Working Group on Primary Lung Graft Dysfunction, part II: Epidemiology, risk factors, and outcomes-A 2016 Consensus Group statement of the International Society for Heart and Lung Transplantation. J Heart Lung Transplant. 2017;36(10):1104–13.
28. Christie JD, Shah CV, Kawut SM, Mangalmurti N, Lederer DJ, Sonett JR, et al. Plasma levels of receptor for advanced glycation end products, blood transfusion, and risk of primary graft dysfunction. Am J Respir Crit Care Med. 2009;180(10):1010–5.
29. Goodwin J, Tinckam K, denHollander N, Haroon A, Keshavjee S, Cserti-Gazdewich CM. Transfusion-related acute lung injury (TRALI) in graft by blood donor antibodies against host leukocytes. J Heart Lung Transplant. 2010;29(9):1067–70.
30. Diamond JM, Lee JC, Kawut SM, Shah RJ, Localio AR, Bellamy SL, et al. Clinical risk factors for primary graft dysfunction after lung transplantation. Am J Respir Crit Care Med. 2013;187(5):527–34.
31. Ong LP, Thompson E, Sachdeva A, Ramesh BC, Muse H, Wallace K, et al. Allogeneic blood transfusion in bilateral lung transplantation: impact on early function and mortality. Eur J Cardiothorac Surg. 2016;49(2):668–74 discussion 74.
32. Klanderman RB, Bosboom JJ, Korsten H, Zeiler T, Musson REA, Veelo DP, et al. Colloid osmotic pressure of contemporary and novel transfusion products. Vox Sang. 2020;115(8):664–75.
33. Pena JJ, Bottiger BA, Miltiades AN. Perioperative Management of Bleeding and Transfusion for Lung Transplantation. Semin Cardiothorac Vasc Anesth. 2020;24(1):74–83.
34. Artigas A, Wernerman J, Arroyo V, Vincent JL, Levy M. Role of albumin in diseases associated with severe systemic inflammation: Pathophysiologic and clinical evidence in sepsis and in decompensated cirrhosis. J Crit Care. 2016;33:62–70.
35. Vincent J-L, Russell JA, Jacob M, Martin G, Guidet B, Wernerman J, et al. Albumin administration in the acutely ill: what is new and where next? Crit Care. 2014;18(4):1–10.
36. Alphonsus CS, Rodseth RN. The endothelial glycocalyx: a review of the vascular barrier. Anaesthesia. 2014;69(7):777–84.

37. Shin CH, Long DR, McLean D, Grabitz SD, Ladha K, Timm FP, et al. Effects of Intraoperative Fluid Management on Postoperative Outcomes: A Hospital Registry Study. Ann Surg. 2018;267(6):1084–92.
38. Torres LN, Chung KK, Salgado CL, Dubick MA, Torres Filho IP. Low-volume resuscitation with normal saline is associated with microvascular endothelial dysfunction after hemorrhage in rats, compared to colloids and balanced crystalloids. Crit Care. 2017;21(1):1–10.
39. Mendes RS, Oliveira MV, Padilha GA, Rocha NN, Santos CL, Maia LA, et al. Effects of crystalloid, hyper-oncotic albumin, and iso-oncotic albumin on lung and kidney damage in experimental acute lung injury. Respir Res. 2019;20(1):155.
40. Moreno Garijo J, Cypel M, McRae K, Machuca T, Cunningham V, Slinger P. The Evolving Role of Extracorporeal Membrane Oxygenation in Lung Transplantation: Implications for Anesthetic Management. J Cardiothorac Vasc Anesth. 2019;33(7):1995–2006.
41. Martin AK, Fritz AV, Wilkey BJ. Anesthetic management of lung transplantation: impact of presenting disease. Curr Opin Anaesthesiol. 2020;33(1):43–9.
42. Fessler J, Davignon M, Sage E, Roux A, Cerf C, Feliot E, et al. Intraoperative implications of the recipients' disease for double-lung transplantation. J Cardiothorac Vasc Anesth. 2021;35(2):530–8.

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Point of Care Management of Perioperative Bleeding or Coagulopathy and Volume Replacement Strategy with Albumin 5% Seems to Reduce Primary Graft Dysfunction after Lung Transplantation (Preliminary Results)

J. Vajter[1], M. Durila[1], J. Berousek[1], Z. Prikrylova[1], R. Lischke[2], J. Havlin[2], T. Vymazal[1]

[1]Department of Anesthesiology and Intensive Care Medicine, 2nd Faculty of Medicine, Motol University Hospital, Charles University, Prague, Czech Republic, [2]Department of Surgery, 1st Faculty of Medicine, Charles University, Motol University Hospital, Charles University, Prague, Czech Republic

Introduction

Primary Graft Dysfunction (PGD) is the most common complication within the first 72 hours after lung transplantation. Volume of perioperative blood loss and blood product administration may be some of the causes. Intravascular volume during surgery and in ICU is usually maintained by the administration of crystalline and colloids solutions and by administration of fresh frozen plasma (FFP) due to coagulopathy. In the field of the allogenic ischemic organ FFP essentially becomes another allogenic material and can cause undesired immunomodulation and contribute to the development of PGD. Nowadays Point Of Care (POC) management of coagulopathy and bleeding is available using methods such as thromboelastometry (ROTEM), platelet function analyzer (PFA 200) and agregometer (Multiplate) which contribute to the optimalization of blood products and coagulation factors administration. The purpose of this study is to find out if POC management of perioperative bleeding or coagulopathy can reduce postoperative PGD development and length of artificial ventilation.

Methods

18 patients undergoing bilateral lung transplantation were randomized into 2 groups. In the first „standard“ group (9 subj.) the management of perioperative bleeding or coagulopathy and volume replacement strategy were based on clinical experience of the anesthesiologist. In the second „POC“ group (9 subj.) the management of perioperative bleeding or coagulopathy and volume replacement strategy were based on the results of POC methods. Albumin 5% solution was preferably used for volume replacement therapy.

Results

In the POC management group the PGD development, length of artificial ventilation and lenght of stay at the ICU were significantly reduced.

Postoperative PGD development „POC“ versus „Standard“ group

	After admission	24 hours	48 hours	72 hours
POC group, PGD grade 3 development	0%	0%	0%	0%
Standard group, PGD grade 3 development	22,2%	11,1%	0%	0%
POC group, PGD grade 2 development	22,2%	11,1%	2,2%	0%
Standard group, PGD grade 2 development	22,2%	33,3%	55,5%	33,3%

Lenght of stay at the ICU „POC“ versus „Standard“ group

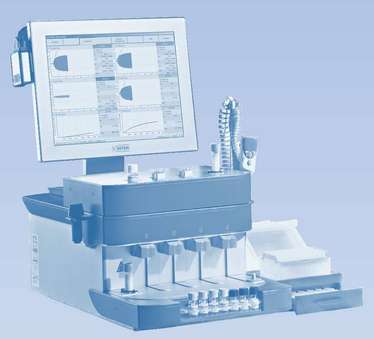
	Mean (days)	Median (days)	Minimal (days)	Maximal (days)
Lenght of stay at the ICU – POC group	4,5	4	2	8
Lenght of stay at the ICU – Standard group	25	6	3	128

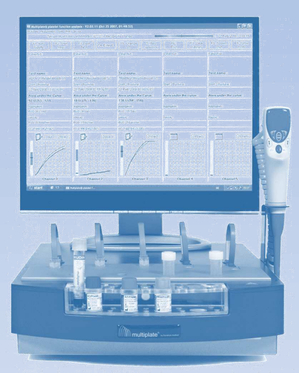
Lenght of artifical ventilation „POC“ versus „Standard“ group

	Mean (hours)	Median (hours)	Minimal (hours)	Maximal (hours)
Artifical ventilation – POC group	29,5	22	9	71
Artifical ventilation – Standard group	433,6	48	10	3072

Conclusion

The POC management of perioperative bleeding or coagulopathy and volume replacement strategy with Albumin 5% significantly reduces the PGD development and decreases length of artificial ventilation and lenght of stay at the ICU . The current preliminary results seem to be promising in this area and subsequent research should further develop and confirm these findings.





Contact

Jaromir Vajter, MD
Department of Anaesthesiology and ICM
Motol University Hospital
Prague, Czech Republic
Tel: 00420 603 512 475
E-mail: jaromir.vajter@fnmotol.cz

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Volume replacement therapy with Albumin 5% and bedside coagulopathy management during lung transplantation improves cardiopulmonary stability and P/F Ratio in patients undergoing lung transplantation

J. Vajter[1], M. Durila[1], J. Vachtenheim Jr[2], R. Lischke[2],T. Vymazal[1]

[1]Department of Anesthesiology and Intensive Care Medicine, Second Faculty of Medicine, Motol University Hospital, Charles University, Prague, Czech Republic,
[2]Third Department of Surgery, First Faculty of Medicine, Charles University, Motol University Hospital, Charles University, Prague, Czech Republic

Introduction

Lung transplantation is a very demanding procedure often accompanied by circulatory instability, bleeding, and postoperative development of primary graft dysfunction. Circulatory instability is mostly treated with a combination of fluid and vasopressor support. 5% Albumin solution appears to be a very promising alternative for volume replacement therapy. In addition, intraoperative use of bedside methods such as thromboelastometry (ROTEM) and platelet function analyzer (PFA 200) seems very promising to correct coagulopathy and reduce bleeding symptoms during lung transplantation.

Methods

In the prospective randomized trial, patients undergoing lung transplantation between 2018 and 2020 at the Motol Lung Transplant Center were divided into two groups. Group 1 **POC** (Point Of Care) - 5% albumin was used almost exclusively as a volume replacement and bedside methods (ROTEM, PFA) were used to correct coagulopathy. Group 2 **nonPOC** - volume replacement and correction of coagulopathy were solved according to the clinical experience of the anesthesiologist.

Results

The total number of analyzed patients is 67 (36 non-POC, 31 POC). In the POC group, there was a significant decrease in vasopressor support of norepinephrine ($p < 0.05$) and a significant improvement in the P/F ratio ($p < 0.05$) in the first 24 hours after lung transplant. The results are shown in Figures I. and II.

Conclusion

The perioperative approach using 5% albumin volume replacement in combination with bedside methods for diagnosis and correction of coagulopathy contributes to improved circulatory stability (the lower dose of norepinephrine) and also helps to improve lung graft function (better P/F ratio) during and after lung transplantation.

Fig. I

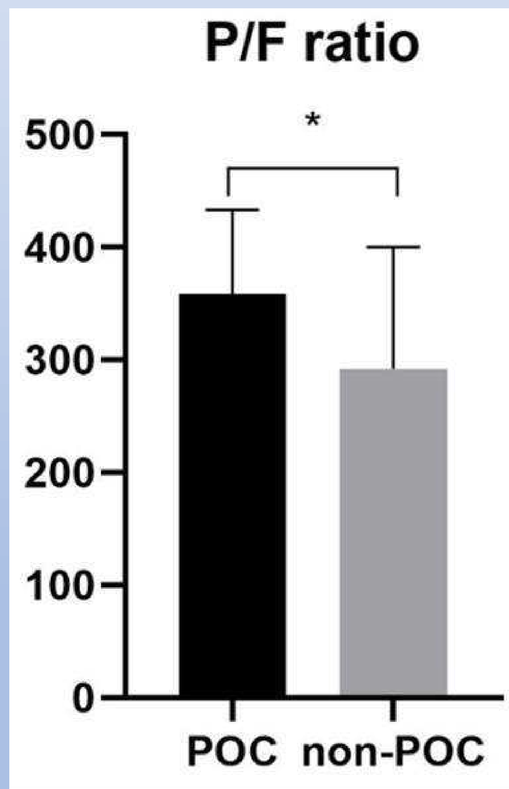
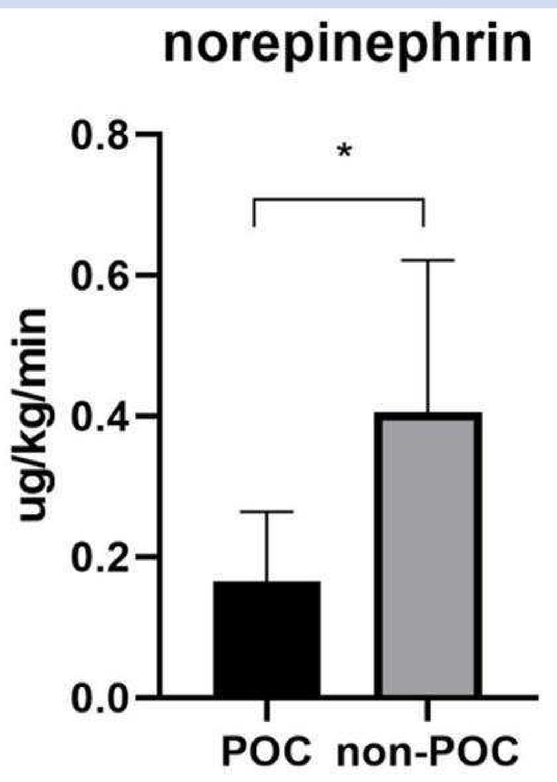


Fig. II



24 hours after lung transplant

Contact

Jaromir Vajter, MD
Department of Anaesthesiology and ICM
Motol University Hospital
Prague, Czech Republic
Tel: 00420 603 512 475
E-mail: jaromir.vajter@fnmotol.cz

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Rotational thromboelastometry reduces blood loss and blood product usage after lung transplantation

Miroslav Durila, MD, PhD,[a] Jaromir Vajter, MD,[a] Michal Garaj, MD,[a] Lukas Pollert, MD,[a] Jan Berousek, MD,[a] Jiri Vachtenheim, Jr, MD,[b] Tomas Vymazal, MD, PhD,[a] and Robert Lischke, MD, PhD[b]

From the [a]Department of Anesthesiology and Intensive Care Medicine, Second Faculty of Medicine, Charles University and Motol University Hospital, Prague, Czech Republic; and the [b]Third Department of Surgery, First Faculty of Medicine, Charles University and Motol University Hospital, Prague, Czech Republic.

KEYWORDS:
bleeding;
blood transfusion products;
point of care;
ROTEM;
transplantation

BACKGROUND: The shortage of blood products has become a worldwide problem, especially during the COVID-19 Pandemic. Here, we investigated whether a point of care (POC) approach to perioperative bleeding and coagulopathy based on rotational thromboelastometry (ROTEM) results could decrease perioperative blood loss and the perioperative consumption of blood products during lung transplantation.

METHODS: Patients undergoing bilateral lung transplantation were randomized into two groups: In the first group, designated the "non POC" group, the management of perioperative bleeding and coagulopathy was based on the clinical experience of the anesthesiologist; in the second group, designated the "POC" group, the management of perioperative bleeding, and coagulopathy was based on the ROTEM results.

RESULTS: After performing an interim statistical analysis, the project was prematurely terminated as the results were significantly in favor of the POC approach. Data were analyzed for the period January 2018 until June 2020 when 67 patients were recruited into the study. There was significantly decreased perioperative blood loss in the POC group ($n = 31$ patients) with $p = 0.013$, decreased perioperative consumption of RBC with $p = 0.009$, and decreased perioperative consumption of fresh frozen plasma with $p < 0.0001$ (practically no fresh frozen plasma was used in the POC group) without deteriorating clot formation in secondary and primary hemostasis as compared to the non POC group ($n = 36$).

CONCLUSION: POC management of perioperative bleeding and coagulopathy based on ROTEM results is a promising strategy to decrease perioperative blood loss and the consumption of blood products in lung transplantation.

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Abbreviations: CT, clotting time; CFT, clot formation time; ECMO, extracorporeal membrane oxygenation; EXTEM, extrinsic pathway of coagulation; FFP, fresh frozen plasma; FIBTEM, functional level of fibrinogen; MCF, maximum clot firmness; ML, maximum lysis; MODS, multiorgan dysfunction syndrome; PGD, primary graft dysfunction; PCC, prothrombin complex concentrate; PFA, platelet function analyzer; PLT, platelet count; POC, point of care; RBC, red blood cells; ROTEM, rotational thromboelastometry; vWF, von Willebrand factor

Reprint requests: Miroslav Durila, MD, PhD, Department of Anesthesiology and Intensive Care Medicine, Second Faculty of Medicine, Charles University and Motol University Hospital, V Uvalu 84, 150 06 Prague 5, Czech Republic. Telephone: +00420224435401. Fax: 00420224435420.

E-mail address: miroslav.durila@fnmotol.cz

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Introduction

The COVID-19 pandemic has amplified the shortage of blood supplies, and blood donors have become a worldwide problem.[1-6] Surgical procedures such as lung transplantation are inevitably accompanied by significant perioperative blood loss and the consumption of blood products: Red blood cells (RBC), fresh frozen plasma (FFP), and platelets (PLT). The worldwide shortage of blood products might limit the ongoing uncomplicated "lung transplant programs" in many countries. Therefore, it is extremely important to find ways to decrease perioperative blood loss and the consumption blood products. Contrarily, the amount of perioperative blood loss and blood product transfusions belong among the factors which may cause primary graft dysfunction (PGD) and multiorgan dysfunction syndrome (MODS) in patients after lung transplantation surgery and increase the morbidity and mortality of those patients.[7-9] An association also exists between blood product consumption and the development of infection, dialysis requirement, worse early outcomes, longer hospital stays, and higher mortality in patients after liver transplantations.[10,11] Similar results are reported in patients after cardiac surgery in both adults and children.[12,13] On the other hand, people who did not receive any blood products after cardiac surgery, such as Jehovah's Witnesses, had a reduced incidence of acute kidney injuries, shorter hospital stays, and reduced postoperative blood loss, although mortality was not influenced.[14]

All of these studies encourage researchers to improve the perioperative management of bleeding and coagulopathy with the aim of minimizing perioperative blood loss and the consumption of blood products. One possible way to achieve this goal could be to use the point of care test (POC) rotational thrombelastometry (ROTEM) to diagnose perioperative coagulopathy early and begin subsequent goal directed therapy. According to a relatively new paradigm of hemostasis termed the "cell-based model" of hemostasis, whole blood seems to be more suitable for assessing coagulation in vivo as cells, including platelets, RBC, white blood cells, among others, that play a role in coagulation.[15] This approach using POC ROTEM testing perioperatively was successfully used during scoliosis surgery, which we have recently published. Perioperative management of bleeding and coagulopathy based on ROTEM results significantly reduced perioperative blood loss, the consumption of RBC units, and prevented the administration of FFP in those patients.[16]We performed a study in which this approach to the perioperative management of bleeding and coagulopathy was assessed during the perioperative period of lung transplantation. The aim of the study was to evaluate whether this approach is efficient in decreasing perioperative blood loss and the consumption of RBC, FFP, and PLT without impairing the clot formation of secondary hemostasis as assessed by ROTEM (ROTEM delta machine, Tem International GmbH) or the clot formation of primary hemostasis as assessed by a PFA 200 (platelet function analyzer, Siemens Healthcare Diagnostics Products GmbH, Germany).

Methods

This study was approved by the Local Ethics Committee with the reference number EK-1402/17 and was registered in the clinical trial database at ClinicalTrials.gov with the identifier number NCT03598907 before the enrollment of patients. Informed consent was obtained from all the patients undergoing lung transplantation surgery, all of whom were older than 18 years of age. This study was a pilot, single site, prospective, and a randomized controlled trial designed to investigate the role of POC ROTEM testing in decreasing primary graft dysfunction (PGD), perioperative blood loss, and the consumption of blood products during lung transplantation surgery. The indication for lung transplantation was the end stage of chronic obstructive disease (COPD), pulmonary fibrosis, and cystic fibrosis. Patients who were put on extracorporeal membrane oxygenation (ECMO) before surgery (as a "bridge" to transplantation) were not included in the study. The only patients who were recruited into the study were those in whom ECMO was implanted at the beginning of surgery and explanted at the end of surgery or those cases where ECMO was not used at all. Patients who stayed on ECMO postoperatively were excluded from the study. Other exclusion criteria were pediatric recipients, single-lung transplantations, retransplantations, heart-lung transplantations, and transplantations requiring cardiopulmonary bypass for technical reasons (concomitant cardiac surgery). As this was a pilot study, the projected number of patients to be recruited was estimated at 120 (planned for 4 years'). The a priori power analysis was not performed in this case. An interim analysis was planned to be performed after approximately 60 patients (after 2years'). Due to this study being relatively small and short and the fact that planned intervention in both groups was very safe (the main aim of the study was to compare two routinely used approaches to bleeding management), a local safety monitor board consisting of an experienced surgeon, an intensivist, and a statistician was set up instead of a data safety and monitoring board (DSMB). Randomization was performed before the first patient was recruited into the trial. A computerized random number generator was used as the method of sequence generation during the randomization. Patients undergoing lung transplantations were randomized into two groups: A. In the first group, the "non POC" group, the management of perioperative bleeding and coagulopathy and the administration of RBC, FFP, and PLT was based on the clinical experience of the anesthesiologist. If transfusion products were not sufficient to maintain normovolemia, crystalloids (plasmalyte), and colloids (Gelatin) were used. B. In the second group, the "POC" group, the management of perioperative bleeding and coagulopathy was based on ROTEM results. Coagulation factors were administered according to the ROTEM results using the protocol shown in Figure 1, and 5% albumin solution was used to maintain normovolemia. In both groups, the ROTEM, and PFA 200 tests were performed before and after surgery to evaluate the impact of both approaches on clot formation in secondary and primary hemostasis. In the POC group, ROTEM was also performed after every 20% blood loss during surgery (calculated from the estimated blood volume).

Patients and surgical characteristics: Double lung transplantations were performed by three experienced transplant surgeons following a standardized strategy of extracorporeal support. The surgical technique and handling of ECMO was also consistent throughout the study period among all the transplant surgeons. At our institution, intraoperative ECMO support is routinely used preemptively in the majority of cases during lung transplantations. The surgical approach comprised clamshell thoracotomies (86%

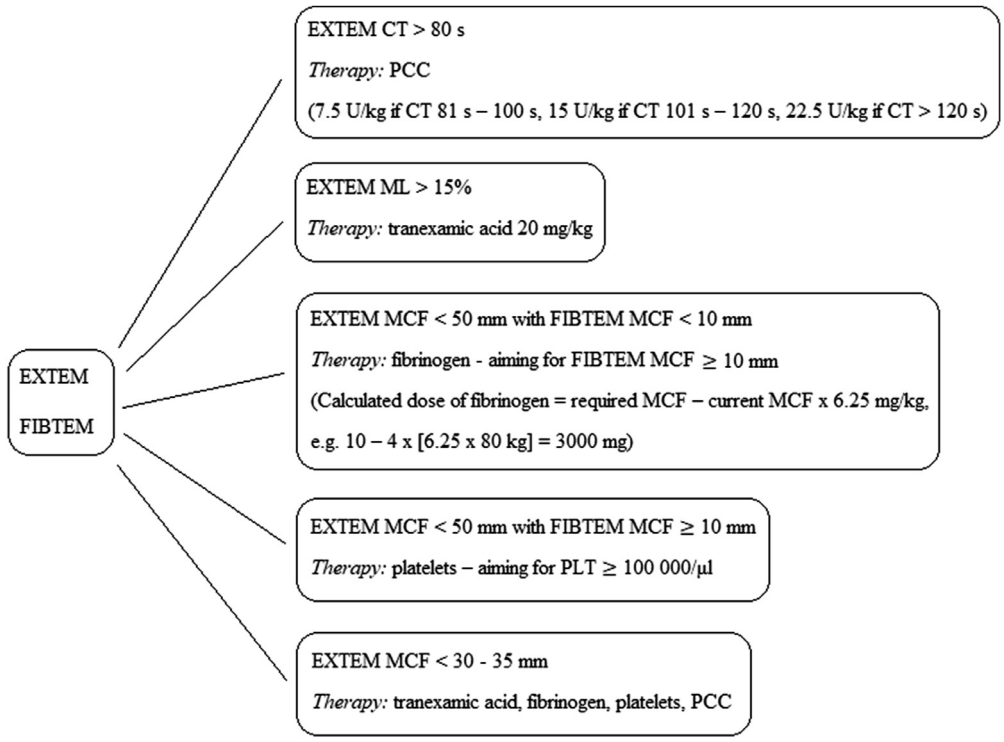

Figure 1 ROTEM protocol for the diagnosis of coagulopathy and goal directed therapy using EXTEM and FIBTEM. APTEM, a test containing aprotinin to confirm fibrinolysis; CT, clotting time; EXTEM, extrinsic pathway of coagulation; FIBTEM, a test investigating functional level of fibrinogen; MCF, maximum clot firmness; ML − maximum lysis, PCC, prothrombin complex concentrate; PLT, platelet count; ROTEM, rotational thromboelastometry.

in the non POC group; $n = 31$ vs 74.2% in the POC group; $n = 23$) and sternum sparing bilateral anterolateral thoracotomies (14% in the non POC group; $n = 5$ vs 25.8% in the POC group; $n = 8$). Intraoperative ECMO support was introduced in 86% of patients in the non POC group ($n = 31$) and in 67.7% of patients in the POC group ($n = 21$).

The preoperative and intraoperative recipient characteristics are reported in Table 1. No patient in any group had a history of coagulopathy or had received any anticoagulation drugs. The ROTEM test is a viscoelastic method which evaluates the mechanical properties of a whole blood clot. It evaluates every phase of clot formation, including the initiation phase, the propagation

Table 1 Preoperative and Intraoperative Patients Data Characteristics

Variable	Non POC group ($n = 36$)	POC group ($n = 31$)	p-value
Pre Operative recipient characteristics			
Male sex	25 (69%)	20 (64.5%)	0.67
Age (years'; mean ± SD)	56.22 ± 9.05	45.69 ± 16.54	0.002
Weight (kg; mean ± SD)	76.64 ± 18.21	67.48 ± 16.51	0.036
Height (cm; mean ± SD)	173.81 ± 9.72	169.55 ± 9.57	0.08
Transplant indication			
COPD	15 (41.6%)	12 (38.7%)	0.81
Pulmonary fibrosis	18 (50%)	9 (29%)	0.08
Cystic fibrosis	2 (5.6%)	10 (32.3%)	0.005
Sarcoidosis	1 (2.8%)	0	0.35
Intra Operative recipient characteristics			
Thoracotomy			
Sternum sparing	5 (14%)	8 (25.8%)	0.22
Clamshell	31 (86%)	23 (74.2%)	0.22
Intraoperative ECMO	31 (86%)	21 (67.7%)	0.07
Ischemic time (min; mean ± SD)			
First lung	242.83 ± 40.23	243.52 ± 40.96	0.91
Second lung	353.69 ± 47.21	354.06 ± 58.02	0.24

COPD, chronic obstructive pulmonary disease; ECMO, extracorporeal membrane oxygenation

phase, the strength of coagulum, and fibrinolysis. Compared to standard coagulation tests such as prothrombin time or activated partial thromboplastin time (which analyze fibrin formation from plasma), this test evaluates the clot formation of whole blood. In this study, the following ROTEM tests were analyzed: EXTEM (contains an activator of the extrinsic pathway of coagulation-recombinant tissue factor; gives information about the coagulation of the extrinsic pathway, which is crucial for clotting in vivo), INTEM (contains an activator of the intrinsic pathway of coagulation-recombinant tissue factor; gives information about the coagulation of the intrinsic pathway, which is crucial for thrombosis in vivo), and FIBTEM (contains platelet blocker-cytochalasin D; gives information about the fibrinogen level). The following parameters were evaluated in the EXTEM and INTEM tests: CT-clotting time, the time from the initiation of measurement until the first fibrin formation, representing the initiation phase of clotting; CFT- clot formation time, the time from CT until there is clot firmness of an amplitude of 20 mm; alfa angle, the angle between the time axis and the ROTEM curve, together with CFT it represents the propagation phase of clot formation and its kinetics; MCF-maximum clot firmness, which represents the maximal strength of clots.

Concerning the PFA 200 tests, COL/EPI, and COL/ADP were carried out and the closure time (CT) was assessed. Closure time provides information about platelet clot formation under high shear stress conditions, which is influenced by platelet adhesion, aggregation, von Willebrand factor (vWF), and hematocrit. The PFA 200 test is the gold standard test for the assessment of primary hemostasis.

Statistics

The GraphPad Prism 8 statistical program was used for the statistical analysis of the data. Most of the data passed normality tests using the D'Agostino & Pearson test. Therefore, a parametric unpaired two-tailed t-test was selected for use in this study. The data are displayed in the figures and tables as the mean ±SD (standard deviation) except Figure 3, where data are displayed as mean with 95% CI (confidence intervals). CI values for differences of mean between groups for parameters of blood loss and blood transfusion units' consumption was also calculated. The differences in data were considered statistically significant with $p < 0.05$. Because the patients in the non POC group were significantly older compared to the POC group, a linear regression was performed to evaluate the impact of age on the perioperative blood loss and consumption of blood products.

Results

After performing an interim statistical analysis of the results in approximately the middle of the study, the project was prematurely terminated as it would have been unethical to

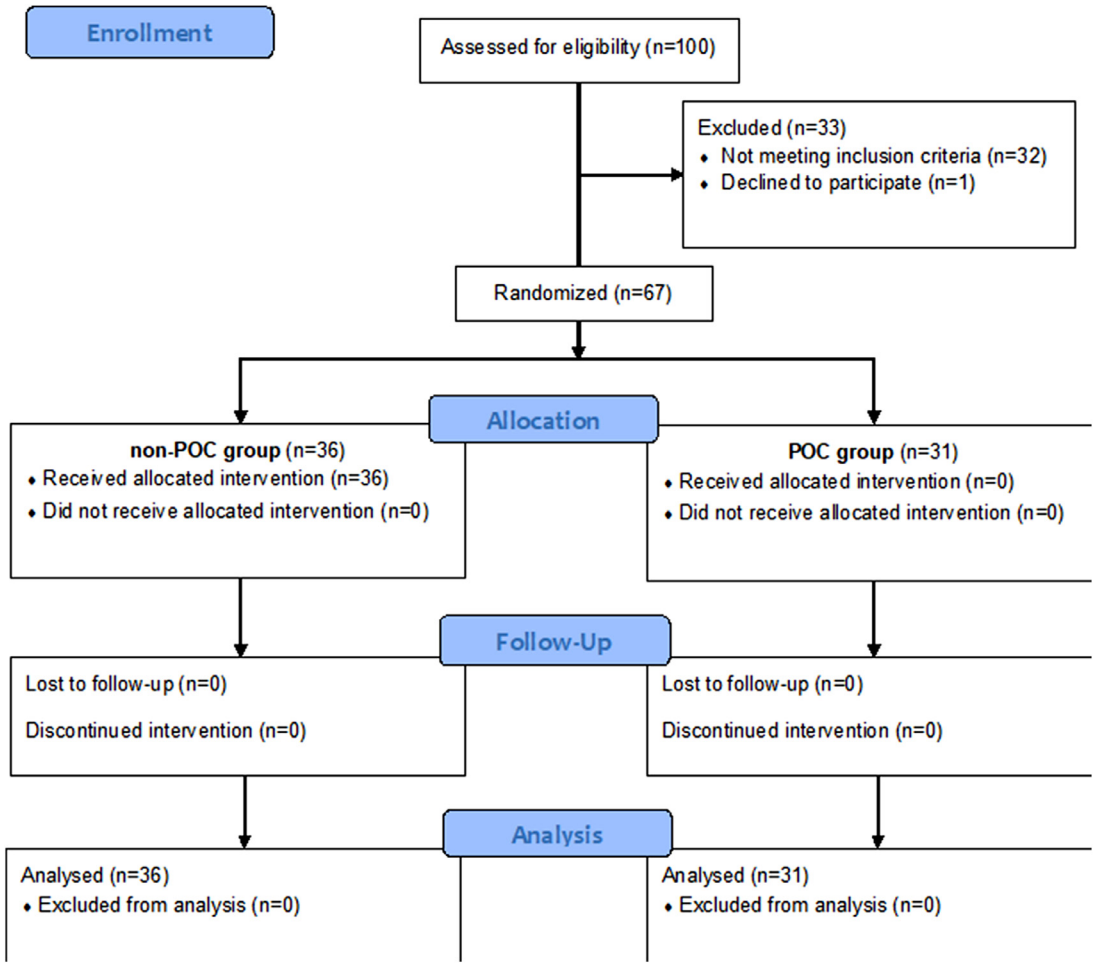

Figure 2 CONSORT flow diagram CONSORT - consolidated standards of reporting trials flow diagram; Non-POC means non point of care group; POC, point of care group.

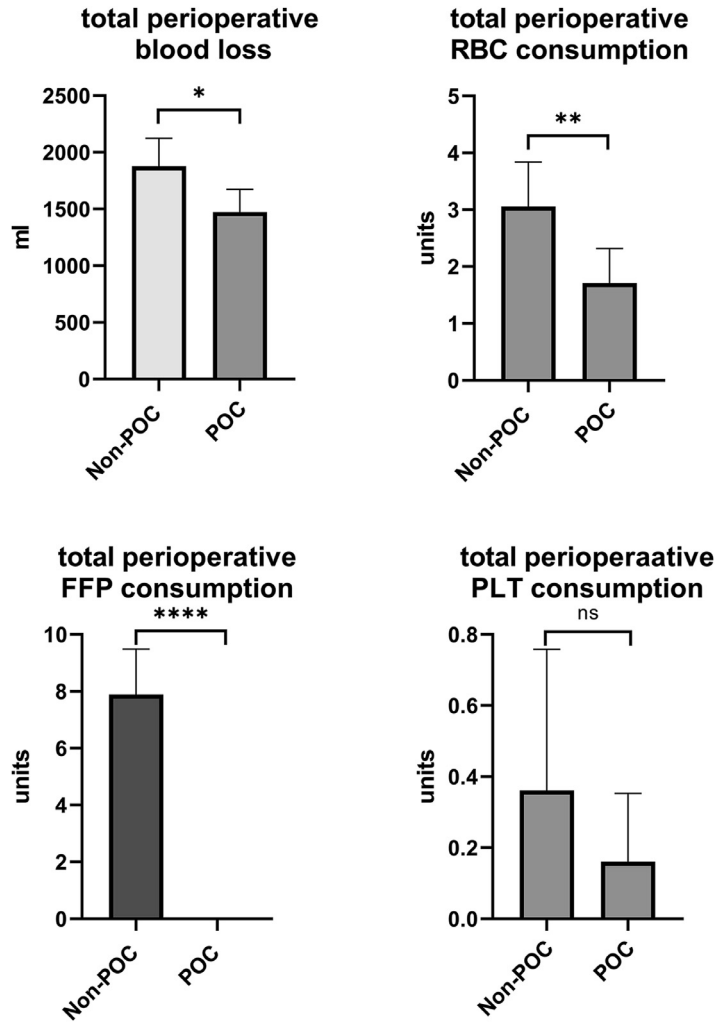

Figure 3 Total perioperative blood loss and consumption of blood transfusion products represented by mean with 95% CI (operating room plus the next 24-hour postoperative period). FFP, fresh frozen plasma; Non POC, non point of care group; ns, non significant; POC, point of care group; PLT, platelets; RBC, red blood cells; * $p < 0.05$; ** $p < 0.01$; **** $p < 0.0001$.

continue. The main objective of the study was to compare the incidence of primary graft dysfunction (PGD) between non POC and POC groups of patients. The secondary aim was to compare the blood loss and consumption of blood products in both groups. The results were significantly in favor of the POC approach to the management of bleeding and coagulopathy ($p < 0.05$). Data were analyzed for the period January 2018 to June 2020, and 67 patients took part in the study. In the first non POC group 36 patients were analyzed, and in the second POC group 31 patients were analyzed. A CONSORT (Consolidated Standards of Reporting Trials) Flow Diagram is displayed in Figure 2. There was a significant decrease in the overall perioperative blood loss (blood loss in the operating room in addition to blood loss in the next 24 hours postoperatively in the intensive care unit in ml) in the POC group with $p = 0.013$ [difference between means of 405 with 95% CI 87-724], decreased overall perioperative consumption of RBC (in units) with $p = 0.009$ [difference between means of 1.35 with 95% CI 0.3-2.3], and decreased overall perioperative consumption of FFP (in units) with $p < 0.0001$ [difference between means of 7.9 with 95% CI 6.2-9.6] (practically no FFP was used in the POC group). Overall, the perioperative consumption of PLT (in units) was not different between both groups ($p = 0.384$) [difference between means of 0.2 with 95% CI -0.3-0.7]. Data are displayed in Figure 3. The differences in blood loss and the consumption of blood products between both groups during surgery itself and during the following 24-hour postoperative period is shown in Tables 2,3,4, and 5. As patients in the non POC group were statistically older compared to the POC group (Table 1), a linear regression was performed to evaluate the impact of age on blood loss and the consumption of blood products. According to the analysis, age did not affect any of the investigated parameters such as perioperative blood loss ($p = 0.8449$), the consumption of RBC ($p = 0.2849$), the consumption of FFP ($p = 0.6800$), and the consumption of PLT ($p = 0.575$). Regarding clot formation in secondary and primary hemostasis and the differences between both groups, data are shown in Figures 4,5, and 6. There were no significant differences between both groups (comparing the differences between the tests performed before and after surgery) when analyzing the EXTEM, INTEM, and the PFA tests ($p > 0.05$). This indicates that the initiation and

Table 2 Differences in blood loss in the operating room and the next 24 hours postoperatively

BLOOD LOSS IN THE OPERATING ROOM			
Total blood loss (ml)	Non POC group 1043 ± 547	POC group 682 ± 399	$p = 0.003$
Non POC group (ml)	ECMO group 1095 ± 554	Non ECMO group 625 ± 250	$p = 0.042$
POC group (ml)	ECMO group 745 ± 439	Non ECMO group 527 ± 227	$p = 0.179$
ECMO group (ml)	Non POC group 1095 ± 554	POC group 745 ± 439	$p = 0.016$
Non ECMO group (ml)	Non POC group 625 ± 250	POC group 527 ± 227	$p = 0.390$
POSTOPERATIVE BLOOD LOSS IN THE NEXT 24 HOURS			
Total blood loss (ml)	Non POC group 835 ± 403	POC group 790 ± 339	$p = 0.626$
Non POC group (ml)	ECMO group 855 ± 404	Non ECMO group 674 ± 401	$p = 0.404$
POC group (ml)	ECMO group 777 ± 347	Non ECMO group 823 ± 336	$p = 0.737$
ECMO group (ml)	Non POC group 855 ± 404	POC group 777 ± 347	$p = 0.462$
Non ECMO group (ml)	Non POC group 674 ± 401	POC group 823 ± 336	$p = 0.414$

data represented as mean ± SD (standard deviation); ECMO group, procedure performed with the use of extracorporeal membrane oxygenation; non ECMO group, procedure performed without the use of extracorporeal membrane oxygenation; non-POC, non point of care group; POC, point of care group

propagation phases of clot formation represented by ROTEM CT, CFT, and alfa angle parameters were not negatively influenced in the POC group, and the strength of clots represented by MCF parameter was not decreased in the POC group. Despite a statistically significant drop in fibrinogen which was detected by FIBTEM MCF during the surgery period in the POC group compared to the non POC group ($p = 0.008$), the level was still within the normal range and this decrease did not negatively affect the global EXTEM or INTEM tests or blood loss in the group. No patient in either group suffered any thrombotic complications such as a myocardial infarction or a pulmonary embolism.

Discussion

The worldwide shortage of blood products is a serious problem and, according to the results of our study, a POC ROTEM testing approach to the management of perioperative bleeding and coagulopathy seems to be promising in helping solve this problem. This was a pilot study and was performed during double lung transplantation surgeries, a procedure generally accompanied by significant perioperative blood loss and consumption of blood products. Most transplantations were performed using perioperative central V-A ECMO (venoarterial extracorporeal membrane oxygenation) support to prevent lung reperfusion edema and subsequent primary graft dysfunction. A similar study was carried out by Smith et al. in patients undergoing lung transplantations, however, they used cardiopulmonary bypass instead of ECMO. Nevertheless, they also describe reduced perioperative blood loss and consumption of blood products.[17] Compared to that study, we were able to perform surgery without the administration of FFP at all. This might be explained by the character of our study, as it was prospective and randomized and due to the fact that ECMO was used perioperatively instead of cardiopulmonary bypass. Because certain procedures were done without using ECMO support, to eliminate bias we compared the results between the ECMO and non ECMO groups. Again, we found a significantly decreased total of perioperative blood loss as well as a decreased consumption of blood products in the POC groups (Tables 2,5). Interestingly, a higher occurrence of patients with CF in the POC group in our study (Table 1) did not result in increased perioperative consumption of RBC and FFP. However, a recently reported study by Fessler at al. demonstrated a higher perioperative utilization of RBC and FFP compared to those with COPD and pulmonary fibrosis, who prevailed in our non POC group.[18] Because there was no FFP used in our POC groups, one would question what happened to the coagulation profile. As Figures 4 and 5 demonstrate, the clot formation in those patients does not show any deterioration compared to the non POC groups. ROTEM tests such as EXTEM and INTEM show that there is no significant deficiency of coagulation factors of extrinsic and intrinsic pathways of coagulation. Nor was there a problem in the clot formation of primary hemostasis as measured by a PFA 200, meaning a significant deficiency of von Willebrand factor can be ruled out. Only a small decrease in fibrinogen level was observed in the POC group, but this was not clinically relevant as the basic tests such as EXTEM and

Table 3 Differences in RBC consumption in the operating room and the next 24 hours postoperatively

RBC CONSUMPTION IN THE OPERATING ROOM			
Total RBC consumption (units)	Non POC 1.05 ± 1.45	group POC group 0.83 ± 1.15	$p = 0.506$
Non POC group (units)	ECMO group 1.18 ± 1.49	Non ECMO group 0.00 ± 0.00	$p = 0.190$
POC group (units)	ECMO group 1.04 ± 1.25	Non ECMO group 0.33 ± 0.70	$p = 0.139$
ECMO group (units)	Non POC group 1.18 ± 1.49	POC group 1.04 ± 1.25	$p = 0.715$
Non ECMO group (units)	Non POC group 0.00 ± 0.00	POC group 0.33 ± 0.70	$p = 0.538$
POSTOPERATIVE RBC CONSUMPTION IN THE NEXT 24 HOURS			
Total RBC consumption (units)	Non POC group 2.00 ± 1.60	POC group 0.87 ± 0.92	$p = 0.001$
Non POC group (units)	ECMO group 2.18 ± 1.57	Non ECMO group 0.50 ± 1.00	$p = 0.045$
POC group (units)	ECMO group 1.13 ± 0.88	Non ECMO group 0.22 ± 0.66	$p = 0.009$
ECMO group (units)	Non POC group 2.18 ± 1.57	POC group 1.13 ± 0.88	$p = 0.006$
Non ECMO group (units)	Non POC group 0.50 ± 1.00	POC group 0.22 ± 0.66	$p = 0.561$

data represented as mean ± SD (standard deviation); ECMO group, procedure performed with the use of extracorporeal membrane oxygenation; non ECMO group, procedure performed without the use of extracorporeal membrane oxygenation; non-POC, non point of care group; POC, point of care group; RBC, red blood cells

Table 4 Differences in FFP (consumption in the operating room and the next 24 hours postoperatively

FFP CONSUMPTION IN THE OPERATING ROOM			
Total FFP consumption (units)	Non POC group 4.08 ± 2.89	POC group 0.00 ± 0.00	$p < 0.0001$
Non POC group (units)	ECMO group 4.28 ± 2.95	Non ECMO group 2.50 ± 1.91	$p = 0.251$
POC group (units)	ECMO group 0.00 ± 0.00	Non ECMO group 0.00 ± 0.00	$p > 0.999$
ECMO group (units)	Non POC group 4.28 ± 2.95	POC group 0.00 ± 0.00	$p < 0.0001$
Non ECMO group (units)	Non POC group 2.50 ± 1.91	POC group 0.00 ± 0.00	$p = 0.014$
POSTOPERATIVE FFP CONSUMPTION IN THE NEXT 24 HOURS			
Total FFP consumption (units)	Non POC group 3.80 ± 3.27	POC group 0.00 ± 0.00	$p < 0.0001$
Non POC group (units)	ECMO group 4.15 ± 3.25	Non ECMO group 1.00 ± 2.00	$p = 0.051$
POC group (units)	ECMO group 0.00 ± 0.00	Non ECMO group 0.00 ± 0.00	$p > 0.999$
ECMO group (units)	Non POC group 4.15 ± 0.25	POC group 0.00 ± 0.00	$p < 0.0001$
Non ECMO group (units)	Non POC group 1.00 ± 2.00	POC group 0.00 ± 0.00	$p = 0.139$

data represented as mean ± SD (standard deviation); ECMO group, procedure performed with the use of extracorporeal membrane oxygenation; FFP, fresh frozen plasma; non ECMO group, procedure performed without the use of extracorporeal membrane oxygenation; non-POC, non point of care group; POC, point of care group

Table 5 Differences in PLT consumption in the operating room and the next 24 hours postoperatively

PLT CONSUMPTION IN THE OPERATING ROOM			
Total PLT consumption (units)	Non POC group 0.30 ± 1.09	POC group 0.09 ± 0.39	$p = 0.316$
Non POC group (units)	ECMO group 0.06 ± 0.35	Non ECMO group 0.00 ± 0.00	$p > 0.999$
POC group (units)	ECMO group 0.09 ± 0.42	Non ECMO group 0.00 ± 0.00	$p > 0.531$
ECMO group (units)	Non POC group 0.06 ± 0.35	POC group 0.09 ± 0.42	$p = 0.790$
Non ECMO group (units)	Non POC group 0.00 ± 0.00	POC group 0.00 ± 0.00	$p > 0.999$
POSTOPERATIVE PLT CONSUMPTION IN THE NEXT 24 HOURS			
Total PLT consumption (units)	Non POC group 0.30 ± 1.09	POC group 0.09 ± 0.39	$p = 0.316$
Non POC group (units)	ECMO group 0.28 ± 1.14	Non ECMO group 0.50 ± 1.00	$p = 0.305$
POC group (units)	ECMO group 0.13 ± 0.46	Non ECMO group 0.00 ± 0.00	$p = 0.393$
ECMO group (units)	Non POC group 0.28 ± 1.14	POC group 0.13 ± 0.46	$p = 0.567$
Non ECMO group (units)	Non POC group 0.50 ± 1.00	POC group 0.00 ± 0.00	$p = 0.139$

data represented as mean ± SD (standard deviation); ECMO group, procedure performed with the use of extracorporeal membrane oxygenation; non ECMO group, procedure performed without the use of extracorporeal membrane oxygenation; Non POC, non point of care group; POC, point of care group; PLT, platelets

INTEM were normal and blood loss was decreased in this group. Authors working in other medical fields, such as with hepatic transplantations, have also published data supporting a POC ROTEM testing approach to perioperative bleeding management during liver transplantations. They also describe decreased perioperative blood loss and consumption of blood products as well as improved patient outcome.[19] Other authors working in the same profession proclaim that a POC ROTEM testing approach has no negative effect on the mortality of patients after liver transplantations, which is in accordance with our findings.[20] The authors Ichikawa et al. show data from cardiac surgeries that also support a POC ROTEM testing approach to the management of perioperative bleeding as a method that reduces blood loss and the consumption of blood products and decreases the duration of postoperative hospitalization.[21] Using a POC ROTEM testing approach in the management of significant bleeding, in decreasing blood loss, and lowering the consumption of blood products also proved to be helpful and justified in trauma patients and obstetrics.[22,23] The results of our study, together with the findings of the above-mentioned literature, point out that ROTEM and its use in a POC ROTEM testing approach to perioperative bleeding management seems to be a promising way to save blood products, especially during this complicated situation caused by the COVID-19 pandemic.

In conclusion, the point of care management of perioperative bleeding and coagulopathy based on ROTEM results seems to be a promising way to decrease perioperative blood loss, the consumption of RBC and PLT, and to prevent FFP consumption without deteriorating clot formation in secondary and primary hemostasis. This approach can easily be used in many different medical fields worldwide and can help clinicians save blood products.

Disclosure statement

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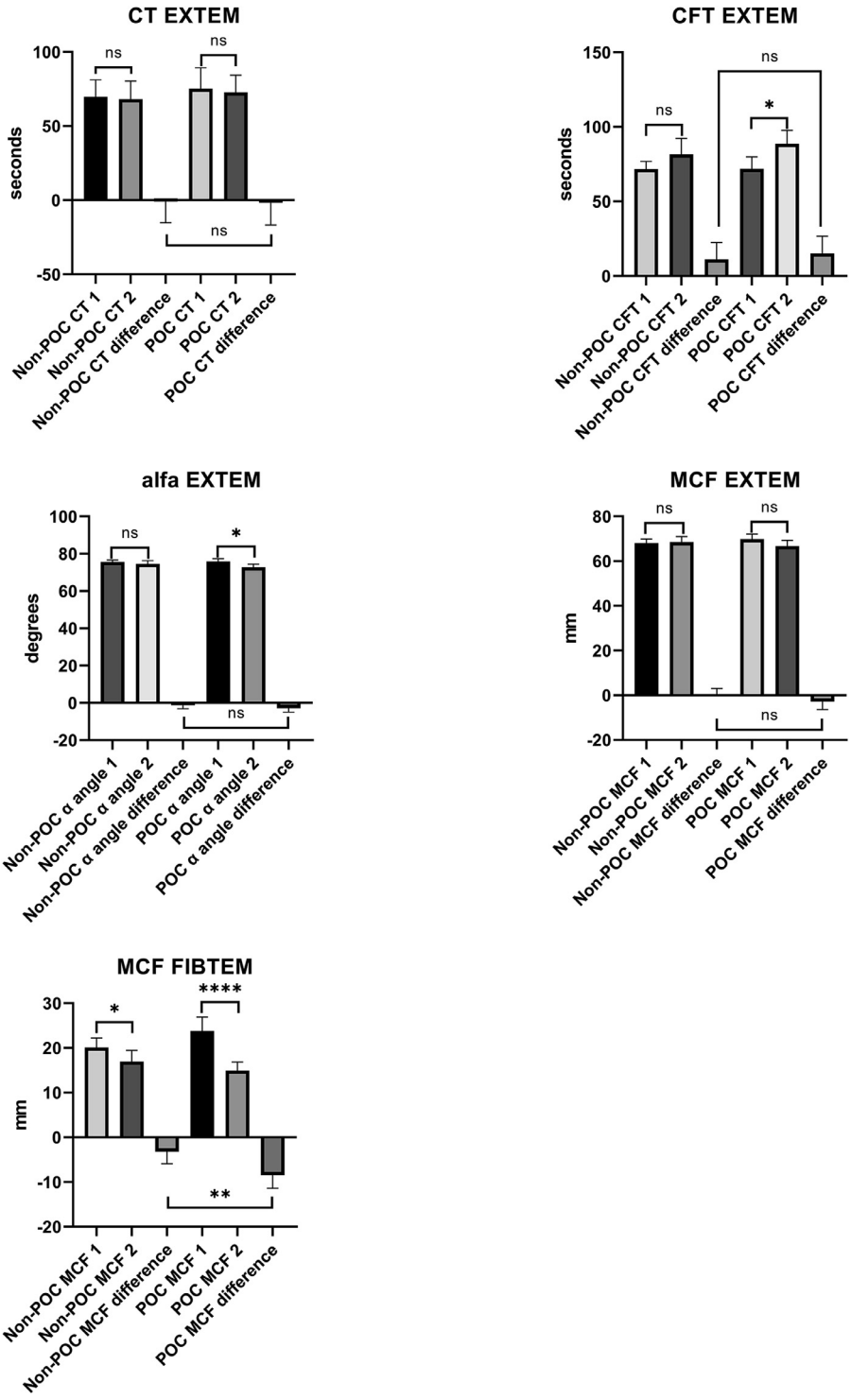


Figure 4 ROTEM- EXTEM and FIBTEM differences between both groups. CFT 1, clot formation time before surgery; CFT 2, clot formation time after surgery; CFT difference, difference between CFT 1 and CFT 2; CT 1, clotting time before surgery; CT 2, clotting time after surgery; CT difference, difference between CT 1 and CT 2; EXTEM, extrinsic pathway of coagulation; FIBTEM, a test investigating functional level of fibrinogen; MCF difference, difference between MCF 1 and MCF 2; Non POC, non point of care group; ns- non significant; MCF 1, maximum clot firmness before surgery; MCF 2, maximum clot firmness after surgery; POC, point of care group; ROTEM, rotational thromboelastometry; α-Angle 1, before surgery; α-Angle 2, after surgery; α-Angle difference, difference between α angle 1 and α angle 2; * $p < 0.05$; ** $p < 0.01$; **** $p < 0.0001$.

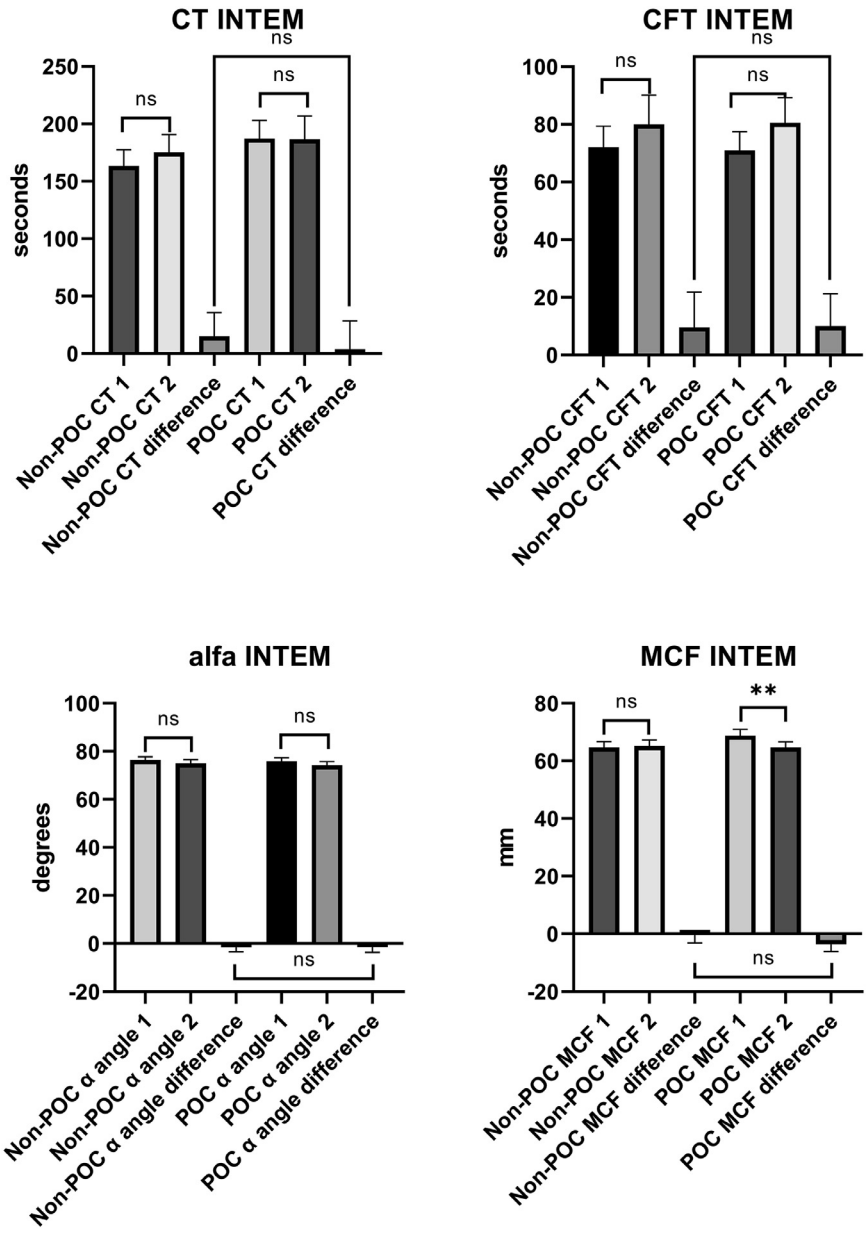


Figure 5 ROTEM- INTEM differences between both groups. Non POC, non point of care group; POC, point of care group; ROTEM, rotational thromboelastometry; INTEM, intrinsic pathway of coagulation; CT 1, Clotting time before surgery; CT 2, clotting time after surgery; CT difference, difference between CT 1 and CT 2; CFT 1, clot formation time before surgery; CFT 2, clot formation time after surgery; CFT difference, difference between CFT 1 and CFT 2; α-Angle 1, before surgery; α-Angle 2, after surgery; α-Angle difference, difference between α angle 1 and α angle 2; MCF 1, maximum clot firmness before surgery; MCF 2, maximum clot firmness after surgery; MCF difference, difference between MCF 1 and MCF 2; ns, non significant; ** $p < 0.01$.

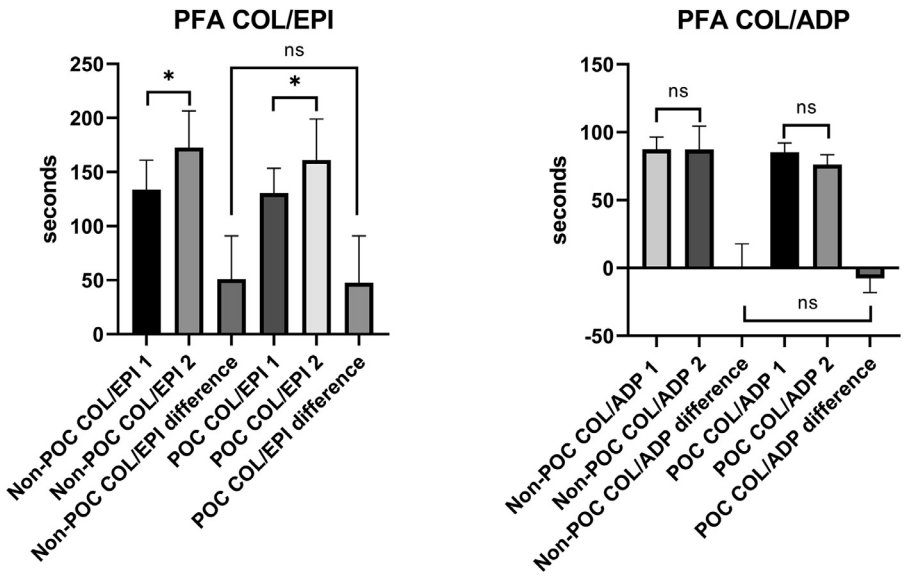


Figure 6 PFA COL/EPI and COL/ADP differences between groups. CT 1, closure time before surgery; CT 2, Closure time after surgery; CT difference, difference between CT 1 and CT 2; Non POC, non point of care group; POC, point of care group; PFA COL/EPI, platelet function analyzer test containing collagen and epinephrine; ns, non significant; PFA COL/ADP, platelet function analyzer test containing collagen and adenosine diphosphate; * $p < 0.05$.

References

1. Stanworth SJ, New HV, Apelseth TO, et al. Effects of the COVID-19 pandemic on supply and use of blood for transfusion. Lancet Haematol 2020;7:e756-64.
2. Shander A, Goobie SM, Warner MA, et al. Essential role of patient blood management in a pandemic: A call for action. Anesth Analg 2020;131:74-85.
3. Doughty H, Green L, Callum J, Murphy MF. Triage tool for the rationing of blood for massively bleeding patients during a severe national blood shortage: guidance from the national blood transfusion committee. Br J Haematol 2020;191:340-6.
4. Singh G, Nahirniak S, Arora R, et al. Transfusion thresholds for adult respiratory extracorporeal life support: an expert consensus document. J Cardiol 2020;36:1550-3.
5. Wang Y, Han W, Pan L, et al. Impact of COVID-19 on blood centres in Zhejiang province China. Vox Sang 2020;115:502-6.
6. Ibrahim Amar, Yahia Omer. Management of blood supply and demand during the COVID-19 pandemic in King Abdullah hospital, Bisha, Saudi Arabia. Transfus Apher Sci 2020;59:102836.
7. Geube MA, Perez-Protto SE, McGrath TL, et al. Increased intraoperative fluid administration is associated with severe primary graft dysfunction after lung transplantation. Anesth Analg 2016;122:1081-8.
8. Weber D, Cottini SR, Locher P, et al. Association of intraoperative transfusion of blood products with mortality in lung transplant recipients. Perioper Med (Lond) 2013;2:20.
9. Singh SSA, Banner NR, Rushton S, Simon AR, Berri C, Al-Attar N. ISHLT primary graft dysfunction incidence, risk factors, and outcome: A UK national study. Transplant 2019;103:336-43.
10. Ming Y, Liu J, Zhang F, et al. Transfusion of red blood cells, fresh frozen plasma, or platelets is associated with mortality and infection after cardiac surgery in a dose-dependent manner. Anesth Analg 2020;130:488-97.
11. Kasraian L, Nikeghbalian S, Karimi MH. Blood product transfusion in liver transplantation and its impact on short-term survival. Int J Organ Transplant Med 2018;9::105-111.
12. Goldaracena SN, Méndez P, Quiñonez E, et al. Liver transplantation without perioperative transfusions single-center experience showing better early outcome and shorter hospital stay. J Transplant 2013 2013. 649209.
13. O'Halloran CP, Alexander PMA, Andren KG, et al. RBC exposure in pediatric extracorporeal membrane oxygenation: epidemiology and factors associated with large blood transfusion volume. Pediatr Crit Care Med 2018;19:767-74.
14. Willcox TW, Newland RF, Baker RA. Cardiopulmonary bypass management and acute kidney injury in 118 Jehovah's witness patients: a retrospective propensity-matched multicentre cohort from 30,942 patients. Perfusion 2020;35:833-41.
15. Hoffman M, Monroe DM 3rd. A cell-based model of hemostasis. Thromb Haemost 2001;85:958-65.
16. Jonas J, Durila M, Malosek M, et al. Usefulness of perioperative rotational thrombelastometry during scoliosis surgery in children. J Neurosurg Spine 2020;24:1-6.
17. Smith RI, Pearse BL, Faulke DJ, et al. Targeted bleeding management reduces the requirements for blood component therapy in lung transplant. J Cardiothorac Vasc Anesth 2017;31:426-33.
18. Fessler J, Davignon M, Sage E, et al. Intraoperative implications of the recipients' disease for double-lung transplantation. J Cardiothorac Vasc Anesth 2020;35:530-8.
19. Leon-Justel A, Noval-Padillo JA, Alvarez-Rios AI, et al. Point-of-care haemostasis monitoring during liver transplantation reduces transfusion requirements and improves patient outcome. Clin Chim Acta 2015;446:277-83.
20. Hartmann M, Walde C, Dirkmann D, Saner FH. Safety of coagulation factor concentrates guided by ROTEM^{TM}-analyses in liver transplantation: results from 372 procedures. BMC Anesthesiol 2019;19:97.
21. Ichikawa J, Marubuchi T, Nishiyama K, et al. Introduction of thromboelastometry-guided administration of fresh-frozen plasma is associated with decreased allogeneic blood transfusions and post-operative blood loss in cardiopulmonary-bypass surgery. Blood Transfus 2018;16:244-52.
22. Deng Q, Hao F, Wang Y, Guo C. Rotation thromboelastometry (ROTEM) enables improved outcomes in the pediatric trauma population. J Int Med Res 2018;46:5195-204.
23. McNamara H, Kenyon C, Smith R, Mallaiah S, Barclay P. Four years' experience of a ROTEM(®) -guided algorithm for treatment of coagulopathy in obstetric haemorrhage. Anaesth 2019;74:984-91.

Náhrada objemu 5% albuminem a bedside management koagulopatie zlepšuje oběhovou stabilitu a zlepšuje hodnotu Horowitzova Indexu u pacientů podstupujících transplantaci plic

J. Vajter[1], M. Durila[1]. Klinika Anesteziologie, resuscitace a intenzivní medicíny 2. LF UK a FN Motol

Úvod

Transplantace plic je velmi náročný operační výkon, často provázený oběhovou nestabilitou, krvácením a pooperačním rozvojem primární dysfunkce štěpu. Oběhová nestabilita bývá léčena kombinací tekutinové a vazopresorické podpory. 5% albumin se jeví jako velmi slibná objemová náhrada. Použití bedside metod, jako je tromboelastometrie (ROTEM) a analyzátor funkce krevních destiček (PFA 200), se jeví jako velmi užitečný nástroj pro korekci koagulopatie a snížení krvácení během transplantace plic.

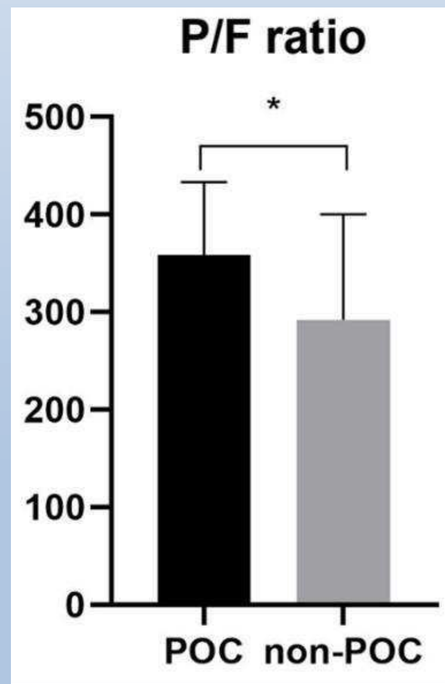
Souhrn

Perioperační přístup využívající 5% albumin jako objemovou náhradu v kombinaci s bedside metodami pro diagnostiku a korekci koagulopatie přispívá ke zlepšení oběhové stability (nižší dávka noradrenalinu) a pomáhá zlepšit funkci plicního štěpu (vyšší hodnota Horowitzova indexu) během transplantace plic a v pooperačním období.

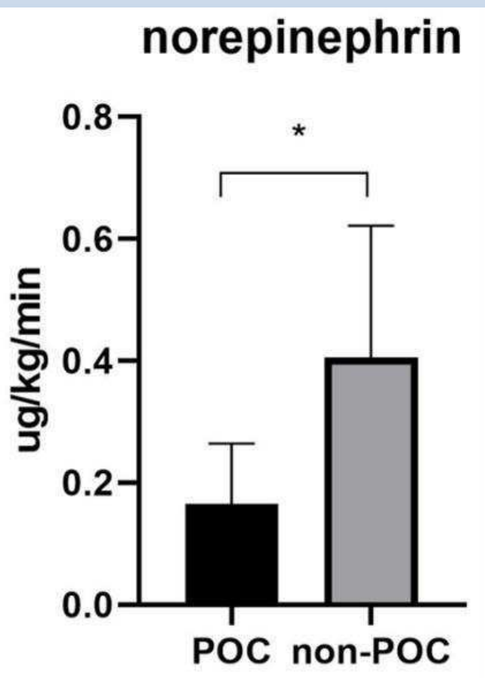
Metodika

V rámci prospektivní randomizované studie byli pacienti podstupující transplantaci plic v roce 2018 až 2020 v Centru pro transplantace plic FN Motol rozděleni do dvou skupin. 1. skupina **POC** (Point Of Care) - jako objemová náhrada byl téměř výhradně použit 5% albumin a ke korekci koagulopatie byly využity bedside metody (ROTEM, PFA). 2. skupina **nonPOC** - objemová náhrada a korekce koagulopatie byly řešeny dle klinické zkušenosti anesteziologa.

Obr. I



Obr. II



Výsledky

Celkový počet analyzovaných pacientů je 67. Ve skupině POC došlo k signifikantnímu snížení vazopresorické podpory noradrenalinem ($p < 0,05$) a významnému zlepšení hodnoty Horowitzova indexu ($p < 0,05$). Výsledky viz obr. I. a II.

Kontakt:
MUDr. Jaromir Vajter
Klinika Anesteziologie a Intenzivní medicíny
Fakultní Nemocnice Motol
Prague, Czech Republic
Tel: 00420 603 512 475
E-mail: jaromir.vajter@fnmotol.cz

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