Extracorporeal Circulation During Lung Transplantation Procedures: A Meta-Analysis

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Extracorporeal circulation (ECC) is an invaluable tool in lung transplantation (lutx). More than the past years, an increasing number of centers changed their standard for intraoperative ECC from cardiopulmonary bypass (CPB) to extracorporeal membrane oxygenation (ECMO) – with differing results. This meta-analysis reviews the existing evidence. An online literature research on Medline, Embase, and PubMed has been performed. Two persons independently judged the papers using the ACROBAT-NRSI tool of the Cochrane collaboration. Meta-analyses and meta-regressions were used to determine whether veno-arterial ECMO (VA-ECMO) resulted in better outcomes compared with CPB. Six papers – all observational studies without randomization – were included in the analysis. All were considered to have serious bias caused by heparinization as co-intervention. Forest plots showed a beneficial trend of ECMO regarding blood transfusions (packed red blood cells (RBCs) with an average mean difference of −0.46 units [95% CI = −3.72, 2.80], fresh-frozen plasma with an average mean difference of −0.65 units [95% CI = −1.56, 0.25], platelets with an average mean difference of −1.72 units [95% CI = −3.67, 0.23]). Duration of ventilator support with an average mean difference of −2.86 days [95% CI = −11.43, 5.71] and intensive care unit (ICU) length of stay with an average mean difference of −4.79 days [95% CI = −8.17, −1.41] were shorter in ECMO patients. Extracorporeal membrane oxygenation treatment tended to be superior regarding 3 month mortality (odds ratio = 0.46, 95% CI = 0.21–1.02) and 1 year mortality (odds ratio = 0.65, 95% CI = 0.37–1.13). However, only the ICU length of stay reached statistical significance. Meta-regression analyses showed that heterogeneity across studies (sex, year of ECMO implementation, and underlying disease) influenced differences. These data indicate a benefit of the intraoperative use of ECMO as compared with CPB during lung transplant procedures regarding short-term outcome (ICU stay). There was no statistically significant effect regarding blood transfusion needs or long-term outcome. The superiority of ECMO in lutx patients remains to be determined in larger multi-center randomized trials. *ASAIO Journal* 2017; 63:551–561.

Key Words: extracorporeal circulation, extracorporeal membrane oxygenation, ECMO, cardiopulmonary bypass, lung transplantation

Extracorporeal circulation (ECC) plays a pivotal role throughout the care of lung transplantation (lutx) patients: pre- and postoperatively, extracorporeal membrane oxygenation (ECMO) is used as a bridge to transplant or as a rescue therapy for primary graft failure.[1,2] Intraoperatively, ECC helps to overcome excessive pulmonary hypertension and associated right heart failure after clamping of the pulmonary hilum or global hypoxia and hypercarbia during one lung ventilation.[3–5] Whereas in the past, there has been controversy about the benefit and risks of routine ECC use during lutx procedures, there is growing evidence that patients undergoing lutx on ECC support receive more blood products, have longer mechanical ventilation time, and prolonged intensive care unit (ICU) and hospital length of stay.[6] There is a higher risk of bleeding and an elevated need for re-thoracotomies in these patients. However, overall mortality does not seem to be affected.[6] Therefore, routine ECC use in lutx is overcome in most centers and intraoperative ECC use is restricted to cases necessitating it only. Centers report an intraoperative ECC use in 20–40% of patients.[5–11] Open-circuit cardiopulmonary bypass (CPB) is the standard and most familiar modality used for intraoperative cardiorespiratory support and in some centers lutxs are routinely performed on full bypass.[6,7,10,12] However, passage of blood through the circuit activates inflammatory reactions and the mandatory full heparinization may induce coagulation disorders, bleeding complications, and an increased need of blood transfusions.[11,13–15] Further, Diamond *et al*. identified the use of CPB as an independent risk factor of severe primary graft failure which in turn is one of the major causes of death within the first year after lutx.[16,17]

Along with advances in ECMO technology and a growing experience in ECMO therapy, an increasing number of lutx centers switched their practice regarding the intraoperative extracorporeal support from CPB to ECMO.[5,8,10,11,18,19] Because of the increase in the number of patients supported by ECMO pre- or postoperatively, intraoperative ECMO use is of high

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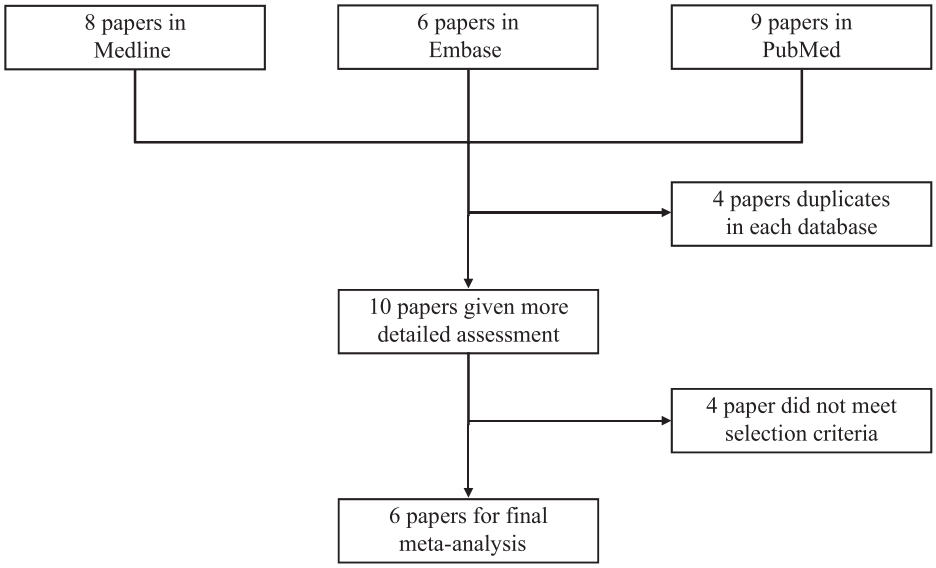

Figure 1. Flow diagram of study selection.

versatility and allows integrated perioperative patient management.[6] Whereas first reports of intraoperative ECMO replacing CPB date back to 2001,[19] the majority of centers switched to the routine use of ECMO intraoperatively from 2008 on. The data published so far vary considerably. Although some studies concluded CPB still being the method of choice,[20] other found advantageous outcomes with ECMO.[10,11,18] Given the lack of definitive data on the efficacy of ECMO in lutx, we conducted meta-analyses to summarize the current evidence on the use of ECMO versus CPB in patients undergoing lutx.

Methods

Search Strategy and Selection Criteria

We systematically searched PubMed, Medline, and Embase, with no language restriction, for studies comparing intraoperative ECMO to CPB for lutx on cardiopulmonary support regarding transfusion needs, mechanical ventilation duration, and outcome and survival parameters. The search was performed from database commencement to December 2016. Our core search consisted of terms related to ECMO and CPB, combined with lutx (see Appendix 1, Supplemental Digital Content, http://links.lww.com/ASAIO/A139).

Inclusion criteria relating to participants are limited to patients undergoing either single or sequential double lutx, of any age, of any indication, of any waiting list time, requiring intraoperative extracorporeal support (ECMO or CPB), without bridge to transplant extracorporeal support, without combined transplants such as heart-lung transplantation or lung-liver transplantation, but including minor concomitant cardiac surgery. We included studies if they reported either intraoperative RBC transfusion, intraoperative fresh frozen plasma transfusion, intraoperative platelet transfusion, duration of postoperative ventilation support, length of ICU stay, or mortality rate.

Two investigators (DH, YMS) assessed the eligibility of each study independently. The studies that were not published as full reports, such as conference abstracts, were excluded. We scrutinized the reference lists of the identified reports and other relevant publications to find additional pertinent studies. No additional studies were found.

Data Extraction and Quality Assessment

For all eligible studies, data extraction was undertaken independently by two investigators (DH is an anesthesiologist in training and YMS is a trained researcher in clinical research methodology) using a modified version of the Cochrane Collaboration data extraction form.[21] The extracted information included population, setting, study design, baseline demographics and operation procedures for each group, study outcomes, and statistical methods. Subsequently, methodological quality was assessed by using a Cochrane risk of bias assessment tool for nonrandomized studies of intervention.[22] The tool covers seven domains: bias caused by confounding, bias in selection of participants into the study, bias in measurement of interventions, bias caused by departures from intended intervention, bias caused by missing data, bias in measurement of outcomes, and bias in selection of the reported results. The overall risk of bias was derived from the judgment across domains. Both investigators have double checked the extracted data and risk of bias assessment. Disagreements were resolved by discussion between the two review investigators.

Statistical Analysis

We used the raw mean difference when meta-analyzing a set of studies comparing ECMO versus CPB with respect to continuous outcomes, such as intraoperative RBC transfusion (units), intraoperative fresh frozen plasma transfusion (units), intraoperative platelet transfusion (units), duration of postoperative ventilation support (days), and length of ICU stay (days). When comparing mortality rate between ECMO and CPB across studies, the odds ratios were used. We estimated the pooled mean differences and pooled odds ratios by use of inverse-variance weight in fixed-effect or random-effect (DerSimonian and Laird) meta-analysis according to heterogeneity between studies. Sensitivity analyses were also performed to

Table 1. Study Characteristics: Showing the Main Characteristics of the Studies Included and the Bias Assessment According to a Cochrane Risk of Bias Assessment Tool for Nonrandomized Studies of Intervention

Study	Study Design	Recruitment Period	Number of CPB/ ECMO	Heparinization	Imbalance Baseline Characteristics	Confounding Adjustment	Potential Factors of Heterogeneity Across Studies	Bias Assessment and Issues
Höchter 2016	Retrospective cohort study	2011–2013 (ECMO was first used in 2012 and became the most common mode within the subsequent year.)	22/27	CPB: high dose ECMO: 23 cases with low dose and 4 cases with high dose	aPTT	No	Age: 49.6 years Male: 41% BMI: 22.7 IPF: 51% CF: 14% COPD: 14% LAS: 51.8 aU PAP: 35.5 mm Hg	Confounding: moderate risk of bias Selection of participants: low risk of bias Measurement: low risk of bias Intended intervention: serious risk of bias Missing value: low risk of bias Outcome: low risk of bias Reporting: low risk of bias Overall: serious risk of bias
Machuca 2015	Retrospective cohort study (ECMO cases were matched with CPB cases)	January 2007–December 2013 (ECMO was first used in 2012 and became the most common mode within the subsequent year.)	66/33	CPB: high dose ECMO: low dose	No	No	Age: 43.7 years Male: 49% BMI: 23.7 IPF: 55% CF: 15% COPD: no information LAS: no information PAP: no information	Confounding: low risk of bias Selection of participants: low risk of bias Measurement: low risk of bias Intended intervention: serious risk of bias Missing value: low risk of bias Outcome: low risk of bias Reporting: low risk of bias Overall: serious risk of bias
Bermudez 2014	Retrospective cohort study	July 2007–April 2013 (Since March 2012, ECMO has been their preferred method.)	222/49	CPB: high dose ECMO: low dose	Number of preoperative ECMO and LAS at transplant	No	Age: 53.7 years Male: 58% BMI: no information IPF: 39% CF: 15% COPD: 18% LAS: 56.6 aU PAP: no information	Confounding: moderate risk of bias Selection of participants: low risk of bias Measurement: low risk of bias Intended intervention: serious risk of bias Missing value: low risk of bias Outcome: low risk of bias Reporting: low risk of bias Overall: serious risk of bias
Biscotti 2014	Retrospective cohort study	January 1, 2008–July 13, 2013 (Two ECMO patient before March 4, 2011; 10 CPB patients after that day.)	55/47	CPB: high dose ECMO: low dose	Number of preoperative ECMO	No	Age: 48.7 years Male: 51% BMI: 23.7 IPF: 39% CF: 23% COPD: 10% LAS: 62.0 aU PAP: 51.3 mm Hg	Confounding: moderate risk of bias Selection of participants: low risk of bias Measurement: low risk of bias Intended intervention: serious risk of bias Missing value: low risk of bias Outcome: low risk of bias Reporting: low risk of bias Overall: serious risk of bias
Ius 2012	Retrospective cohort study	August 2008–September 2011 (Six ECMO patients before February 2010 were excluded. Only ECMO patients after February 2010 were selected.)	46/46	CPB: high dose ECMO: low dose	Pulmonary hypertension, FEV_1, preoperative ICU stay, and preoperative ECMO use	Propensity matching and multivariate analyses	Age: 42.7 years Male: 52% BMI: no information IPF: 36% CF: 14% COPD: 8% LAS: no information PAP: 64.5 mm Hg	Confounding: low risk of bias Selection of participants: low risk of bias Measurement: low risk of bias Intended intervention: serious risk of bias Missing value: low risk of bias Outcome: low risk of bias Reporting: low risk of bias Overall: serious risk of bias

(*Continued*)

Table 1. (*Continued*)

Study	Study Design	Recruitment Period	Number of CPB/ ECMO	Heparinization	Imbalance Baseline Characteristics	Confounding Adjustment	Potential Factors of Heterogeneity Across Studies	Bias Assessment and Issues
Bittner 2007	Retrospective cohort study	2003–2005 (No information about the time when the ECMO was used.)	7/8	CPB: high dose ECMO: heparin infusion was titrated to maintain an activated clotting time 160–220 s	No (Insufficient information in the report)	Multivariate analyses (Inappropriate categorization for outcome)	Age: 50.5 years Male: 87% BMI: no information IPF: 73% CF: no information COPD: 13% LAS: no information PAP: no information	Confounding: moderate risk of bias Selection of participants: low risk of bias Measurement: low risk of bias Intended intervention: serious risk of bias Missing value: low risk of bias Outcome: low risk of bias Reporting: moderate risk of bias Overall: serious risk of bias

ECMO, extracorporeal membrane oxygenation; CPB, cardiopulmonary bypass; aPTT, activated prothrombin time; LAS, lung allocation scores; FEV_1, forced expiratory volume in 1 s; ICU, intensive care unit; BMI, body mass index; IPF, idiopathic pulmonary fibrosis; CF, cystic fibrosis; COPD, chronic obstructive pulmonary disease; PAP, pulmonary artery pressure.

identify the robustness of our findings after excluding an outlier study. The I^2 statistics and Q statistic were used to identify heterogeneity between studies. Because we were concerned about the variation in results across studies, meta-regression analyses for each outcome of interest were used to explore study-level factors that contribute to heterogeneity between studies. Several potential factors were selected, including mean age, proportion of male, body mass index, proportion of underlying diagnosis (e.g. idiopathic pulmonary fibrosis, cystic fibrosis, and chronic obstructive pulmonary disease), mean of lung allocation scores (LAS), mean pulmonary artery pressure, and the year that the ECMO was implemented (because there is no information in Bittner *et al*. study, we took the median year during the recruitment period). Only studies reporting the number or mean of CPB and ECMO for each baseline category were included in meta-regression analyses. To assess publication bias, funnel plots were constructed for each outcome, and applied regression methods to determine funnel plot asymmetry.[23] Statistical analyses were performed using the software package R language version 3.1.2.

Results

Of seven articles found in three databases (Medline, Embase, and PubMed), we identified six articles which met the inclusion criteria. **Figure 1** shows our search, selection process, and the reasons for exclusion. The studies by Akarsu *et al*., Ius *et al*., and, Ko *et al*. were excluded because they did not compare ECMO and CPB use but reported experience using ECMO in lutx.[6,19,24] Yu *et al*. used CPB as a primary choice in all patients who were undergoing lutx but used ECMO if patients were bridged to the transplant on extracorporeal support. This does not fairly compare the two systems, implements a huge bias, and did not meet the inclusion criteria.[25] Two investigators (DH and YMS) agreed on all included papers.[5,8,10,11,18,20]

The six studies were published in English and from 2007 onwards (**Table 1**): all were retrospective cohort studies. In Machuca *et al*. study, they used a 1:2 matched design for the sake of reducing confounding. Three studies stated that ECMO has been implemented since 2012, two other studies indicated the time point of interest at 2011 and 2010, respectively. One group did not provide the year of change to ECMO but must have done so from 2003 to 2005. Heparin use was considered to being a co-intervention for ECMO and CPB: all studies stated that high dose heparinization was used in CPB patients. With regard to ECMO patients, low dose heparinization was used in four studies; in the study by Hoechter *et al*. all but four ECMO patients received low dose heparinization, four received a full dose. Bittner *et al*. state aiming for an activating clotting time (ACT) of >450 s for CPB patients and an ACT of 160–220 s for ECMO patients but do not provide the heparin doses used. There was no imbalance baseline characteristic shown in the study by Machuca *et al*. and Bittner *et al*. because of matching approach and limited reporting, respectively. The studies of Ius *et al*. and Bittner *et al*. were adjusted for the potential confounding factors. The possible factors of heterogeneity varied greatly across studies. All studies were judged to have serious risk of bias caused by heparin co-intervention.

Figure 2 shows the results of meta-analyses of mean difference (ECMO versus CPB) with respect to intraoperative blood transfusion requirement. Overall, the results of intraoperative

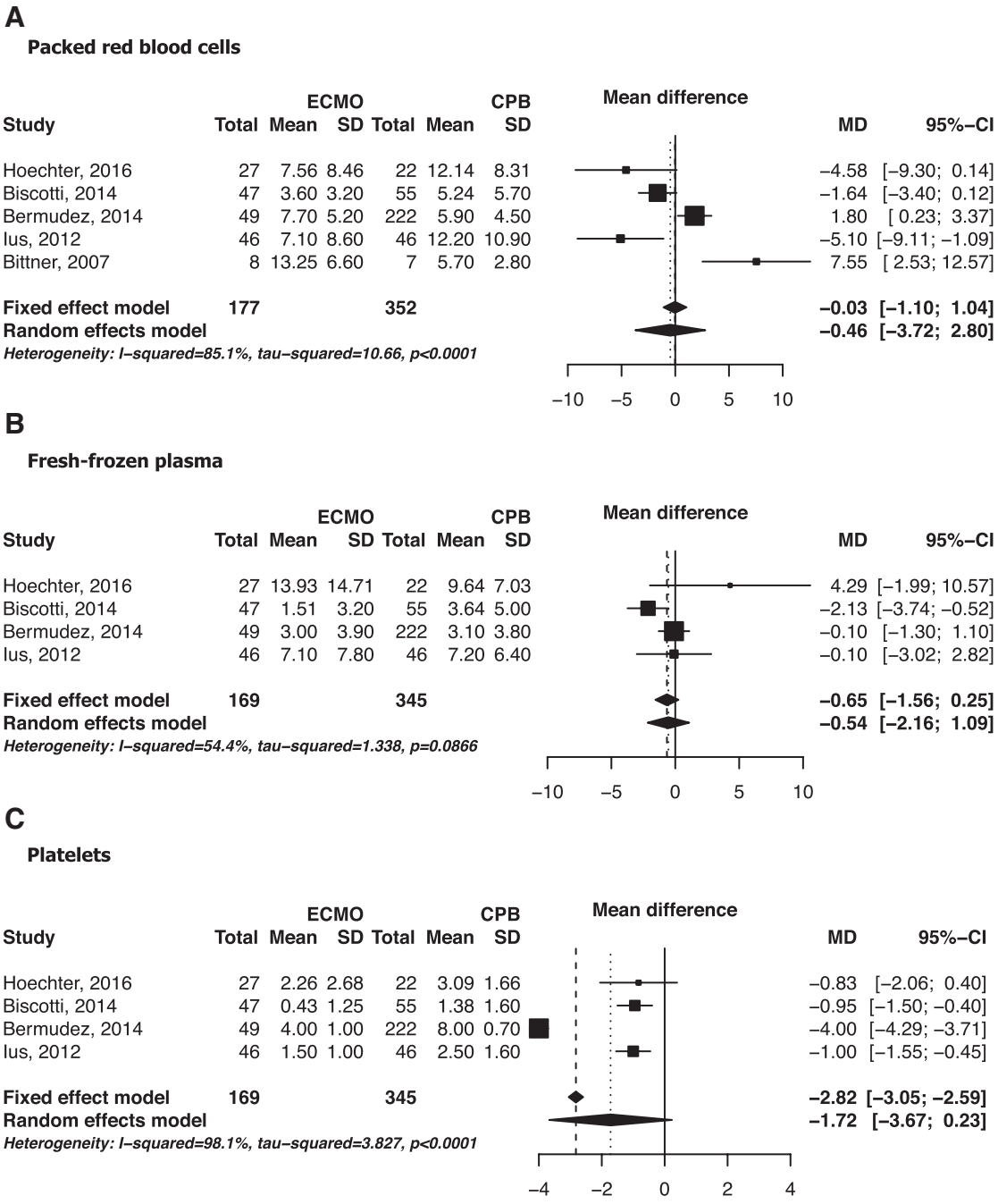

Figure 2. Forest plot showing the mean differences in intraoperative blood transfusion requirement (units). **A**: Packed RBCs; **B**: fresh-frozen plasma; **C**: platelets. (Mean difference below 0 favor ECMO whereas mean difference above 0 favor CPB.) RBC, red blood cell; ECMO, extracorporeal membrane oxygenation; CPB, cardiopulmonary bypass.

blood transfusion requirement seemed to show a tendency toward a benefit of ECMO, but the differences did not reach significance. The meta-analysis demonstrated a 0.46 reduction in the unit of RBCs requirement with ECMO intervention (mean difference −0.46; 95 CI% = −3.72, 2.80), a 0.65 reduction in the unit of fresh-frozen plasma requirement with ECMO intervention (mean difference −0.65; 95 CI% = −1.56, 0.25), and a 1.72 reduction in the unit of platelets requirement with ECMO intervention (mean difference −1.72; 95 CI% = −3.67, 0.23), respectively. There was heterogeneity of the benefit of ECMO between studies shown in the analyses of RBCs and platelets requirement. Determining heterogeneity between studies is commonly based on Q statistic. A p value of <0.05 means that the benefit of ECMO varies from one study to the next. In such case, the summary mean difference under the random-effect model is considered, otherwise the one under the fixed-effect model.

Figure 3 shows the results of the meta-analyses of mean difference (ECMO versus CPB) in the duration of ventilator support and ICU stay. The meta-analyses demonstrated a shorter duration of ventilator support (mean difference −2.86; 95 CI% = −11.43, 5.71) and ICU stay (mean difference −4.79; 95 CI%

= −8.17, −1.41) for patients with ECMO intervention compared with patients with CPB intervention. There was a statistically significant difference in the mean duration of the ICU stay. There was heterogeneity of the benefit of ECMO between studies shown in the analyses of the duration of ventilator support.

With regard to mortality, the benefit of ECMO intervention was reflected in a 54% lower mortality rate at 3 month (OR = 0.46, 95% CI: 0.21, 1.02) compared with that observed in the CPB group, but did not reach statistical significance. Analyzing the 6 month mortality rate, our results show a 12% increase in the risk of mortality after ECMO intervention compared with CPB intervention (OR = 1.12, 95% CI: 0.55, 2.28), although there was no significant difference. When the observation period was extended to one year, ECMO decreased the risk of mortality by 35% compared with the CPB group (OR 0.65; 95% CI: 0.37, 1.13) (**Figure 4**), but again this result lacks the statistical significance. There is no heterogeneity of the benefit of ECMO between studies because Q statistic shows nonsignificant difference. The summary mean difference under fixed-effect model was considered.

There was little evidence of funnel plot symmetry for each outcome because of the small number of studies included.

In meta-regression analyses, the advantage of ECMO was substantially influenced by the heterogeneity across the studies (**Table 2**). The advantage of ECMO in intraoperative RBCs requirement may depend on the proportion of male patients, as CPB seemed to be superior, the higher the proportion of male was (**Table 2**, **Figure 5A**). The results indicate that 1% increase in proportion of male corresponds to a change of 0.28 units, in terms of the mean difference of intraoperative RBC requirement (ECMO versus CPB). Here we displayed the bubble plots that are an informative tool to interpret the regression of coefficients in meta-regression. In a bubble plot, each study is represented by a corresponding circle. The size of each circle is proportional to that study's weight in the analysis. The solid line shows the predicted difference in intraoperative RBC requirements. Three studies under the equator (such as the study performed in Hoechter *et al*., Biscotti *et al*., and Ius *et al*., whose proportion of male are 41%, 51%, and 52%, respectively) would have a benefit from ECMO (corresponding to mean difference of intraoperative RBCs requirement near −4.58, −1.64, and −5.10, respectively).

Similarly, the year that the ECMO was implemented had substantial effect on mean difference of intraoperative RBCs requirement (**Figure 5B**). The year that the ECMO was implemented in Hoechter *et al*., Biscotti *et al*., and Ius *et al*. were 2012, 2012, and 2010, respectively. Three studies under the equator would have a benefit from ECMO. The use of ECMO would reduce intraoperative RBCs requirement near 4.58, 1.64, and 5.10 units, respectively.

We repeated analyses with potential factors on mean difference of intraoperative fresh-frozen plasma, intraoperative platelets requirement, postoperative duration of ventilator support, and mortality rate. The heterogeneity of the effect of

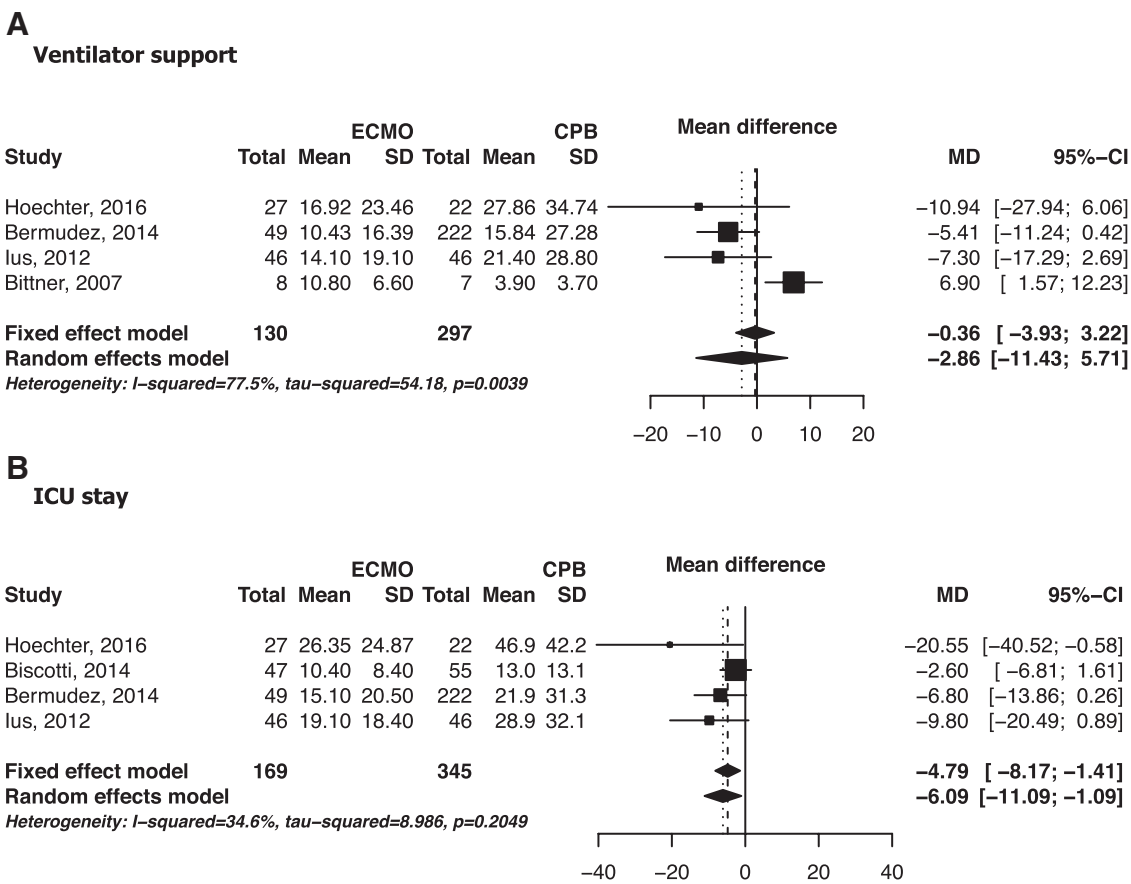

Figure 3. Forest plot showing the mean differences in duration of ventilator support and ICU stay (days). **A**: Ventilator support; **B**: ICU stay. (Mean difference below 0 favor ECMO whereas mean difference above 0 favor CPB.) CPB, cardiopulmonary bypass; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit.

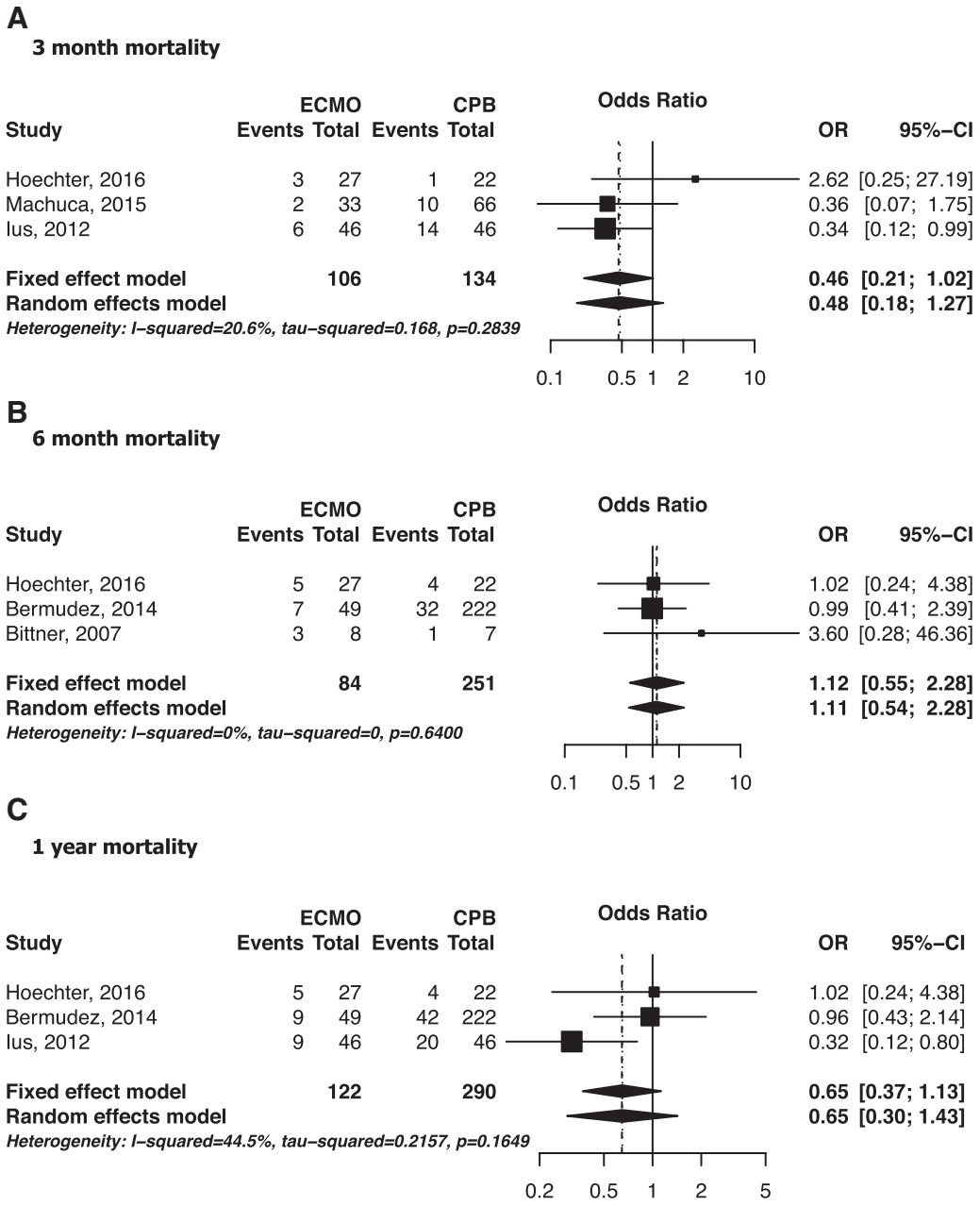

Figure 4. Forest plot showing the odds ratios for mortality. **A**: 3 month mortality; **B**: 6 month mortality; **C**: 1 year mortality. (Odds ratio below 1 favor ECMO whereas odds ratio above 1 favor CPB.) ECMO, extracorporeal membrane oxygenation; CPB, cardiopulmonary bypass.

ECMO was caused by proportion of male patients and the diagnoses of cystic fibrosis, chronic obstructive pulmonary disease, and idiopathic pulmonary fibrosis; furthermore the mean LAS, and the year that the ECMO program has been implemented influenced the association between outcome measurement and advantage of ECMO (**Table 2** and bubble plots shown in Appendix 2, Supplemental Digital Content, http://links.lww.com/ASAIO/A140).

Discussion

Our meta-analysis systemically examined the effects of veno-arterial ECMO (VA-ECMO) versus CPB during lutx surgery. The results show comparable outcomes for patients on ECMO and CPB regarding to blood transfusion requirements, duration of mechanical ventilation, or survival. A significant improvement for the ECMO group was observed in the length of ICU stay. Our findings show a trend toward favorable survival rates at 3 month among ECMO patients although results lacked statistical significance. However, the outcome differences between ECMO and CPB were affected by heterogeneity across study characteristics.

Meta-analyses of observational studies are prone to biases, caused, for example, by confounding and deviating from intended interventions. Three studies were trying to adjust confounding factors by using matching approach in study design stage,[10] multivariate analyses with propensity matching,[5] and multivariate analysis only,[20] respectively. Because Bittner *et al*.

Table 2. Univariate Meta-Regression Analysis of Potential Factors of Heterogeneity Across the Published Studies; Showing Significant Results Only

	No. of Study	Mean Difference [95% CI]	*p* Value
Intraoperative blood transfusion			
RBCs requirement (units)			
Intercept		−16.28 [−25.19 to −7.37]	0.0034
Proportion of male	5	0.28 [0.13 to 0.44]	0.0004
Intercept		2,354.2 [243.5 to 4,464.8]	0.0288
The year that the ECMO was implemented	5	−1.17 [−2.22 to −0.12]	0.0288
Fresh-frozen plasma requirement (units)			
Intercept		4.02 [−0.21 to 8.25]	0.0624
Proportion of cystic fibrosis	4	−0.27 [−0.51 to −0.03]	0.0266
Intercept		24.4 [4.09 to 44.7]	0.0185
Mean LAS at transplant	3	−0.43 [−0.78 to −0.08]	0.0153
Platelets requirement (units)			
Intercept		1.85 [−0.83 to 4.53]	0.1753
Proportion of COPD	4	−0.29 [−0.50 to −0.09]	0.0047
Postoperative outcomes			
Duration of ventilator support (days)			
Intercept		−28.92 [−44.67 to −13.17]	0.0003
Proportion of male	4	0.41 [0.19 to 0.63]	0.0003
Intercept		−20.71 [−32.72 to −8.71]	0.0007
Proportion of IPF	4	0.37 [0.16 to 0.58]	0.0005
Intercept		3,829.8 [1,735.6 to 5,924.1]	0.0003
The year that the ECMO was implemented	4	−1.91 [−2.95 to −0.86]	0.0003

COPD, chronic obstructive pulmonary disease; IPF, idiopathic pulmonary fibrosis; RBC, red blood cell; ECMO, extracorporeal membrane oxygenation; LAS, lung allocation score.

performed multivariate analyses by categorizing outcome variables, we may doubt that the results came from data dredging. Therefore, we consider that the results from the prior two studies are less prone to bias.

With regards to bias caused by deviations from intended intervention, heparinization is a critical co-intervention unbalanced between ECMO group and CPB group. A low dose heparinization is currently used for ECMO patients whereas a full dose heparinization is administered necessarily for CPB patients. From what we know so far, running ECMOs with a low dose heparinization does not seem to cause a markedly increased rate of thromboembolic complications.[26] In the study of Hoechter *et al*., the results show that the patients with high dose heparinization required more blood transfusion during operation than those with low dose heparinization – irrespective of the types of ECC used.[11] Because heparinization is used to achieve the desired anticoagulation level, intraoperative blood transfusion requirement may favor the ECMO group (less intraoperative blood transfusion requirement in the ECMO group).

In this regard, another aspect is the use of cell savers versus pericardial suction: both seem to have negative influence on coagulation and inflammation, yet to different degrees and hereby can influence blood loss and transfusion needs.[27,28] Only the studies of Hoechter *et al*. and Biscotti *et al*. mention the use of a cell saver and provide cell saver retransfusion volumes in both ECMO and CPB patient groups. None of the studies provides any details regarding the use of pericardial suction.

For intraoperative RBCs requirement, however, there was no statistically significant evidence of a beneficial effect of ECMO. There are two studies showing that their ECMO group received relatively more RBCs: in the study by Bermudez *et al*., the ECMO group has higher proportion of preoperative ECMO use. The consecutive activation of coagulation and inflammation and the ongoing hemolysis may result in higher blood cells requirement.[8,29] In the study by Bittner *et al*., because there are no unbalance patient characteristics between the two groups, they speculated that liberal volume replacement and prevention of transcapillary leakage with interstitial edema formation may be the main reasons for the increased use of red blood transfusion in the ECMO group.[20] Our meta-regression analyses revealed that gender and the year that ECMO was implemented significantly influence the difference of intraoperative RBC requirements between groups: studies with predominantly male patients and performed in an earlier era tended to favor CPB use. We found that in the study by Bittner *et al*., 87% patients were male and the ECMO was implemented between 2003 and 2005; these are much higher and earlier than those of other four studies, respectively. Thus, we performed sensitivity analysis based on the other four studies. However, the result remained unchanged because the small sample size of Bittner *et al*. study gave little weight for the pooled mean difference. All studies showed a trend toward a reduction of the platelet transfusion rate in the ECMO group; however, the effect did not achieve statistical significance. Weber *et al*. showed that a higher number of intraoperative blood transfusions was associated with increased mortality in lung transplant recipients, reasonable best efforts to minimize blood transfusions should be made.[16,30]

Moreover, a large-volume blood product transfusion, has been identified as a risk factor of severe primary graft dysfunction (PGD)[16,31]; PGD typically occurs during the first 3 days after lutx. Poor oxygenation is the main characteristic of the condition. It is further characterized by a low pulmonary compliance, interstitial or alveolar edema, pulmonary infiltrates on chest radiographs, increased pulmonary vascular resistance, intrapulmonary shunt, and acute alveolar injury.[32] Additional risk factors conclude elevated pulmonary artery pressures, a high fraction of inspired oxygen during allograft reperfusion, and the use of

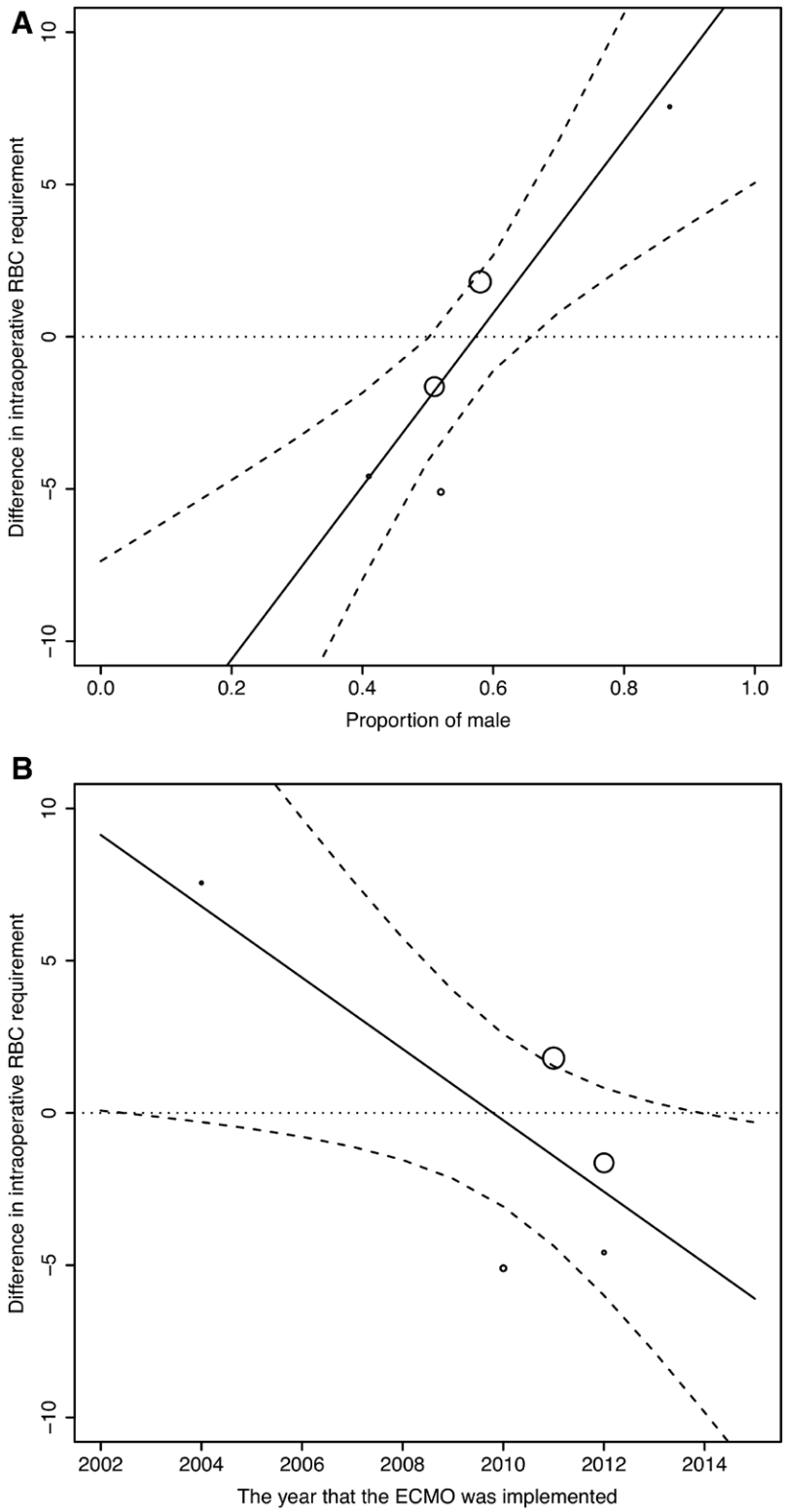

Figure 5. A: Bubble plot showing the mean difference in intraoperative RBCs requirement (units) versus proportion of male. **B**: Bubble plot showing the mean difference in intraoperative RBCs requirement (units) versus the year that ECMO was implemented in the study. ECMO, extracorporeal membrane oxygenation; RBC, red blood cell.

CPB.[16] The International Society for Heart and Lung Transplantation grades the severity according to the paO2–FiO2 ratio and the radiographic findings.[33] Only two of the studies separately assessed the incidence of PGD: in the study by Ius *et al*. the incidence of severe PGD did not differ between groups.[5] Bermudez *et al*. found that the CPB group was more likely to have any PGD at 24 and 72 h post transplantation than the ECMO group; in addition, the severity of PGD was lower in the ECMO group.[18]

All but the study by Bittner *et al*. found a trend toward a shorter ventilation time in the ECMO group. This study was performed very early on. More than the past eight years, the emphasis on lung protective ventilation gained importance in the field of lutx; the use of lower tidal volumes resulted in a reduced inflammation reaction and shorter durations of postoperative mechanical ventilation.[34] Nowadays, early extubation should be regarded as the best option in the postoperative period, as it minimizes complications such as pulmonary infections.[34] Some centers even evaluate the use of a very early extubation strategy aiming for a termination of invasive ventilation right after the transplant procedure.[35] For patients who do not quite tolerate this rapid extubation, the immediate institution of noninvasive positive pressure ventilation might be an option.[34]

To allow for lung protective ventilation even in case of reperfusion edema or primary graft failure, extracorporeal support might be extended into the postoperative care. Postoperative ECMO use ranges from 10.6% to 55% in ECMO patients and 5.5–27% in CPB patients.[8,11,18] Here, an extension of the intraoperative support is associated with a better outcome compared with secondary inserted ECMOs.[34,36]

Patients who were intraoperatively supported by ECMO had a significantly shorter ICU stay. Seiler *et al*. recently identified a long ICU stay as a risk factor for a lower health related quality of life in lutx patients.[37] Furthermore, prolonged ICU stay is associated with an increased mortality rate.[38] In this context, the shorter ICU stay in the ECMO group is not only a statistically significant difference but also a clinically relevant advantage. Therefore, it is not surprising that there was a trend seen toward a decreased mortality 3 months after the transplant procedure. However, in the mid- and long-term, there was no difference in the mortality between the groups. Whereas early deaths after lutx are attributable to perioperative complications, uncontrollable bleedings or primary graft failure, death in the long-term is because of multifactorial origin including graft rejection, lethal infections, and complications of a prolonged ICU and hospital stay. It is questionable whether effects on the long-term can still be attributed to the intraoperative extracorporeal support technique. Further research on the causality of death is needed to then improve long-term survival.

This systematic review has several limitations. First, a small number of studies were included in this review. The studies are not controlled or randomized trials but retrospective analyses of case series. Furthermore, all of the studies had a historical control group; therefore the results are unaccounted for other developments in lutx such as advances in surgical techniques and the grade of experience of the physicians' team or the change in the lutx population after introduction of the LAS.[39] Observational studies rarely provide sufficiently robust evidence to recommend changes to clinical practice or health policy decision-making. However, for reasons such as little case numbers and ethical concerns, these are the only ones available for certain topics such as extracorporeal support in lutx.

Conclusion

In conclusion, this meta-analysis summarizes the experience of intraoperative ECMO versus CPB in lutx. Still, there are no clear-cut advantages of one system over the other. Only the ICU length of stay was shorter in the ECMO group. There was no statistically significant effect regarding the remaining parameters. More studies are needed to further clarify which patient population benefits from what extracorporeal support technique. Because we have an ongoing scarcity of organs available, it must be the unanimous aim to provide best possible care to all lung transplant patients.

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