Meta-Analysis of Peripheral or Central Extracorporeal Membrane Oxygenation in Postcardiotomy and Non-Postcardiotomy Shock

Giuseppe Maria Raffa, MD,* Mariusz Kowalewski, MD,* Daniel Brodie, MD, Mark Ogino, MD, Glenn Whitman, MD, Paolo Meani, MD, Michele Pilato, MD, Antonio Arcadipane, MD, Thijs Delnoij, MD, Eshan Natour, MD, Sandro Gelsomino, MD, PhD, Jos Maessen, MD, PhD, and Roberto Lorusso, MD, PhD

Department of Cardiothoracic Surgery, Heart and Vascular Center, Maastricht University Medical Centre, Maastricht, The Netherlands; Department for the Treatment and Study of Cardiothoracic Diseases and Cardiothoracic Transplantation, IRCCS-ISMETT (Istituto Mediterraneo per i Trapianti e Terapie ad alta specializzazione), Palermo, Italy; Clinical Department of Cardiac Surgery, Central Clinical Hospital of the Ministry of Interior in Warsaw, Warsaw, Poland; Cardiothoracic Research Center, Collegium Medicum, Nicolaus Copernicus University, Bydgoszcz, Poland; Division of Pulmonary and Critical Care Medicine, Columbia University College of Physicians and Surgeons/New York-Presbyterian Hospital, New York, New York; Division of Neonatology, Alfred I. DuPont Hospital for Children, Wilmington, Delaware; Cardiovascular Surgery Intensive Care Unit, Johns Hopkins Hospital, Baltimore, Maryland; Heart Transplant, Johns Hopkins Hospital, Baltimore, Maryland; Intensive Care Unit, Heart and Vascular Center, Maastricht University Medical Center, Maastricht, The Netherlands; Department of Cardiology, Heart and Vascular Center, Maastricht University Medical Center, Maastricht, The Netherlands; and Department of Anesthesia and Intensive Care, IRCCS-ISMETT (Istituto Mediterraneo per i Trapianti e Terapie ad alta specializzazione), Palermo, Italy

Background. **Venoarterial (VA) extracorporeal membrane oxygenation (ECMO) application in postcardiotomy shock (PCS) and non-PCS is increasing. VA-ECMO plays a critical role in the management of these patients, yet may be associated with serious complications.**

Methods. **A systematic review of all available reports in the literature of patients receiving VA-ECMO, either directly or indirectly, comparing central cannulation (right atrial to ascending aorta) versus peripheral cannulation (femoral vein to femoral artery or axillary artery) were analyzed. The primary endpoint was survival. Cerebrovascular events, limb complications, bleeding requiring reoperation, sepsis, continuous venovenous hemofiltration, and transfusions were also assessed in both groups.**

Results. **Seventeen retrospective case series clearly describing the VA-ECMO access and including 1,691 patients with PCS and non-PCS were found. The peripheral approach was more commonly used (980 patients, 57.9%) than the central one. There was no difference in the analysis between the two techniques regarding all-cause mortality risk ratio (1.00, 95% confidence interval: 0.94 to 1.08, $I^2 = 0\%$, $p = 0.92$). No statistical differences were found between peripheral and central VA-ECMO with regard to cerebrovascular events, limb complications, or sepsis rates. Peripheral cannulation was associated with a significant reduction in the risk of bleeding ($p = 0.02$), continuous venovenous hemofiltration ($p = 0.03$), transfusion of red blood cells units ($p < 0.00001$), fresh frozen plasma units ($p = 0.0002$), and platelets units ($p < 0.00001$).**

Conclusions. **Peripheral and central VA-ECMO configurations showed comparable inhospital survival for PCS and non-PCS. The risk of bleeding, continuous venovenous hemofiltration, and blood product transfusion was significantly lower with the peripheral cannulation strategy.**

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*Drs Raffa and Kowalewski contributed equally to this work.

Address correspondence to Dr Raffa, Cardiac Surgery and Heart Transplantation Unit, Department for the Treatment and Study of Cardiothoracic Diseases and Cardiothoracic Transplantation, Mediterranean Institute for Transplantation and Advanced Specialized Therapies (ISMETT), Via Tricomi 5, Palermo 90127, Italy; email: giuseppe.raffa78@gmail.com.

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The application of venoarterial (VA) extracorporeal membrane oxygenation (ECMO) in patients with refractory isolated cardiac or cardiopulmonary failure is increasing [1]. In adult patients, "central" access, with the direct cannulation of the right atrium and ascending aorta, and "peripheral" access, most commonly using the femoral vein and artery, have been the predominant modalities for the initiation of VA-ECMO. Alternative approaches have included the use of a vascular prostheses for the thoracic aorta as central access, or the axillary, subclavian, or innominate arteries, either through a direct cannulation or with the interposition of a vascular graft. Undoubtedly, the application of VA-ECMO during cardiac arrest or in non-postcardiotomy shock (PCS) represent the typical scenarios in which peripheral cannulation is commonly adopted because it is a faster and easier strategy, whereas central access plays a larger role in PCS [2].

The optimal cannulation strategy for VA-ECMO, in terms of survival as well as myocardial recovery, management, and complication rate, remains controversial [3]. Despite the considerable numbers of publication regarding VA-ECMO, only a few have addressed access-related issues [4–18], particularly as the primary focus of the studies [7, 8, 10].

In the largest single center series, Rastan and colleagues [4] reported no advantage in survival with the use of different cannulation sites in 517 patients who required VA-ECMO after cardiac surgery. Although there has been a general consensus favoring a peripheral approach in PCS and non-PCS [4–9], a recent study demonstrated that a central approach should be considered a viable alternative in terms of complications rate [10]. Based on the above controversies, we performed a systematic review and meta-analysis of studies reporting the inhospital outcomes of central versus peripheral VA-ECMO in PCS and non-PCS settings.

REVIEW

Material and Methods

Definitions

Central cannulation was defined as cannulation involving the aorta for the patients' arterial inflow and right atrium or both venae cavae for patients' outflow. Peripheral cannulation was defined as cannulation of the femoral and axillary artery for patients' arterial inflow and femoral vein for patients' inflow. Right atrium and femoral artery cannulation or aorta and femoral vein cannulation strategies were considered peripheral and central, respectively, as the access for inflow cannula dictates the actual configuration.

Bleeding was defined as any bleeding requiring reoperation. Limb complication was defined as any limb complication involving the vascular access (excluding groin and wound infection).

Distal limb perfusion strategy to avoid limb ischemia in case of peripheral cannulation included the cannulation of a Dacron (C.R. Bard, Haverhill, PA) or Hemashield (Maquet, Wayne, NJ) prosthetic graft anastomosed end to side onto the femoral artery, thereby maintaining arterial flow to the ipsilateral lower limb or the insertion of a distal perfusion cannula inserted into the femoral artery.

Data Sources and Search Strategy

This systematic review and meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and meta-analyses (PRISMA) statement [19]. The PRISMA checklist is available as Supplemental Table 1. Relevant studies to be included were searched for through October 31, 2017, through PubMed, EMBASE, CINAHL, Web of Science, Cochrane Register of Controlled Clinical Trials (CENTRAL), and Google Scholar, as well as congress proceedings from major cardiothoracic and cardiology societies meetings. The search term was "extracorporeal membrane oxygenation." The literature was limited to articles published in English. References of original articles were reviewed manually and cross-checked for other relevant reports.

Selection Criteria, Quality Assessment, and Outcomes

Studies were included if they met all of the following criteria: (1) human study; (2) studies comparing directly peripheral versus central cannulation in patients undergoing VA-ECMO for cardiogenic shock; and (3) studies reporting VA-ECMO outcomes of interest with separate (indirect comparison) results for peripheral versus central cannulation. Exclusion criteria were as follows: (1) pediatric and congenital heart surgery-related studies; (2) animal studies; and (3) studies not reporting cannulation site strategy for VA-ECMO. Reviews were not considered.

Two independent reviewers (G.M.R and M.K.) selected the studies for inclusion, extracted studies, as well as patient characteristics of interest and relevant outcomes. Two authors (G.M.R. and M.K.) independently assessed the trials' eligibility and risk of bias. Risk of bias at the individual study level was assessed using the ROBINS-I tool (Risk of Bias in Not-randomized Studies-of Interventions) [20]. Any divergences were resolved by a third reviewer (R.L.) and quantified using the approach of Cohen's kappa.

Endpoint Selection

The primary endpoint was inhospital mortality. Secondary endpoints were inhospital cerebrovascular events (CVE), limb complications, bleeding requiring reoperation, sepsis, continuous venovenous hemofiltration (CVVH), and transfusions. Long-term follow-up and out-of-hospital data were not considered.

Statistical Analysis

Data were analyzed according to the intention-to-treat principle wherever applicable. Risk ratio and 95% confidence interval (CI) served as primary index statistics for dichotomous outcomes; for continuous outcomes, mean difference and corresponding 95% CI were calculated using a random effects model. To overcome the low statistical power of the Cochran Q test, the statistical inconsistency test $I^2 = [(Q - df) / Q] \times 100\%$, where Q is

the χ^2 statistic and *df* its degrees of freedom, was used to assess heterogeneity [21]. It examines the percentage of interstudy variation, with values ranging from 0% to 100%. An I^2 value less than 40% indicates no obvious heterogeneity, values between 40% and 70% suggest moderate heterogeneity, and I^2 greater than 70% were considered high heterogeneity.

Because of the high degree of heterogeneity anticipated among the available studies (only nonrandomized trials) an inverse variance (DerSimonian-Laird) random effects model was applied as a more conservative approach for observational data accounting for between- and within-study variability. Whenever a single study reported median value and interquartile range instead of mean ± SD, the latter were approximated as described by Wan and colleagues [22]. Potential publication bias was evaluated for the primary endpoint by constructing a "funnel plot" in which the standard error of the log risk ratio was plotted against the risk ratio. The asymmetry of the plot was estimated both visually and by a linear regression approach. Prespecified sensitivity analysis for the primary endpoint was conducted and stratified by type of heart surgery where applicable: (1) after coronary artery bypass graft surgery; (2) after valvular surgery; and (3) combined or other surgery. The latter group encompassed combined coronary and valvular surgery, along with surgery on thoracic aorta, other cardiac surgery, and non-PCS indications for VA-ECMO. In addition, by means of meta-regression, the impact of percentage prevalence of non-PCS patients across single studies and its relationship to occurrence of the primary endpoint was investigated. Review Manager v.5.3 (Nordic Cochrane Centre, Copenhagen, Denmark) and Comprehensive Meta-Analysis, v.2 (Biostat, Englewood Cliffs, NJ) were used for statistical computations. All p values less than 0.05 were considered statistically significant and reported as two-sided, without adjustment for multiple comparisons.

Results

The PRISMA flow diagram describing the study selection process along with reasons for exclusion is presented in Supplemental Figure 1. After removal of reports not pertinent to the design of the current meta-analysis, 17 retrospective observational studies that met explicit inclusion criteria remained, including a total of 1,691 patients. Of those, 980 patients (57.95%) underwent peripheral, and 711 (42.05%) central, cannulation for VA-ECMO. Most commonly (85.1% of the time), VA-ECMO was instituted for PCS; remaining indications included acute myocardial infarction (5.6%), decompensated cardiomyopathy (5.0%), myocarditis (0.8%), and other non-postsurgical indication (3.5%). From a surgical standpoint, the majority of ECMOs followed coronary artery bypass grafting (33.9%), valve surgery (15.4%), and mixed cases (8.7%). VA-ECMO followed aortic surgery in 103 cases (6.1%), 36 of which (2.1%) were for acute type A aortic dissection. Patients undergoing VA-ECMO had a mean age of 61.7 years and 68% were male. Baseline European System for Cardiac Operative Risk Evaluation score ranged between 6.2% and 25.7%. Follow-up reporting across the studies varied between 30-day and inhospital survival. Detailed characteristics of studies and patients are listed in Table 1.

Risk of bias for each study across each of the seven risk of bias domains is presented in Appendix Table 1. Overall, the studies reported either moderate or serious risk of bias. Given the overall high risk of bias along with the limited number of studies, all articles were retained for the purposes of this review. Most commonly, biases arose from (1) selection of participants for the study, and (2) subjective distribution of the participants within the study arms by either designated heart teams or according to surgeon preference and underlying causes.

Primary Endpoint

All 17 selected studies contributed to the analysis of inhospital all-cause mortality. In an overall analysis, 1,085 of 1,691 patients (64.2%) died within this time frame. No evidence of publication bias due to small study effect was observed (Supplemental Fig 2), and this was confirmed in Egger's test ($p = 0.37$). There was no difference in the analysis of all-cause mortality between peripheral and central cannulation, even with respect to the type of surgery (prespecified sensitivity analysis stratified by surgery type is available as Supplemental Fig 3). Corresponding mortality rates were 63.7% (624 of 980 patients) versus 64.8% (461 of 711 patients) for peripheral and central VA-ECMO, respectively. Risk ratio was 1.00 (95% CI: 0.94 to 1.08, $p = 0.92$, $I^2 = 0\%$; Fig 1). By means of meta-regression analysis, there was no evidence that higher prevalence of non-PCS patients ($p = 0.99$), left ventricle (LV) venting ($p = 0.71$), and distal perfusion ($p = 0.48$) strategies across single studies influenced the occurrence of the primary endpoint (Supplemental Figs 4–6).

Secondary Endpoints

A total of six studies enrolling 323 patients contributed to the analysis of cerebrovascular events. No statistically significant differences were found in regard to risk of CVE: 0.88 (95% CI: 0.46 to 1.68, $p = 0.69$, $I^2 = 0\%$), with corresponding event rates of 10.7% (23 of 214) versus 13.8% (15 of 109) for peripheral and central VA-ECMO, respectively (Fig 2A).

Eight studies (699 patients) provided data for the analysis of bleeding. Bleeding occurred in more than 40% of VA-ECMO patients; peripheral, as compared with central, cannulation was associated with a significant 35% reduction of the bleeding risk (0.65, 95% CI: 0.46 to 0.93, $p = 0.02$, $I^2 = 59\%$). Respective bleeding rates were 32.9% (141 of 429) using peripheral and 51.9% (140 of 270) using a central cannulation approach (Fig 2B).

Peripheral cannulation for VA-ECMO reduced the need for CVVH by nearly 25% (0.76, 95% CI: 0.60 to 0.97, $p = 0.03$, $I^2 = 0\%$) when compared with central cannulation. Accordingly, CVVH was used in 30.2% of cases in the peripheral cannulation group (70 of 232) as compared with

Table 1. Studies, Peripheral Extracorporeal Membrane Oxygenation Versus Central Extracorporeal Membrane Oxygenation, and Patients' Baseline Characteristics

Variables	Study First Author, Year [Reference]								
	Ranney, 2017 [10]	Biancari, 2017 [12]	Guihaire, 2017 [17]	Slottosch, 2017 [15]	Raffa, 2017 [4]	Khorsandi, 2016 [11]	Mazzeffi, 2016 [18]	Zhao, 2015 [45]	Saeed, 2014 [8]
Number of patients	131	148	92	139	86	15[b]	23	24	37
PCS	9, 6.9%	…	…	100, 72%	…	…	…	…	25, 67.5%
CABG	…	148, 100%	12, 13%	45, 45%	19, 22.1%	3, 20%	7, 30.4%	20, 83.3%	…
Valve	…	…	64, 69%	19, 19%	11, 12.7%	4, 26.6%	5, 21.8%	2, 8.3%	…
AAR (AAD)	…	…	12, 13%	…	…	2, 13.3%	…	…	…
LVAD	…	…	2, 2%	…	…	…	…	…	…
CABG + valve	…	…	…	16, 16%	18, 20.9%	4, 26.6%	…	…	…
CABG + other	…	…	…	8, 8%	1, 1.1%	…	…	…	…
Other[a]		…	2, 2%	12, 12%	37, 43%	2, 13.3%	11, 47.8%	2, 8.3%	…
Non-PCS		…	…	39, 28%	…	…	…	…	12, 32.5%
AMI	48, 36.6%	…	…	19, 14%	…	…	…	…	…
DCM	28, 21.3%	…	…	13, 9%	…	…	…	…	…
Myocarditis	…	…	…	5, 4%	…	…	…	…	…
Other	46, 35%	…	…	2, 1%	…	…	…	…	7, 19%
Age, years	56.4	65.4	65.4	58	65	64.3	57	61.9	59 vs 70[c]
Male, %	67.9%	78.4	59	76	65	73.3	60.9	79.2	60 vs 50[c]
Elective status, %	…	12.8	64	63	61.6	53.3	…	…	…
EuroSCORE II, %	…	19.2	6.2 vs 9.4[d]	…	6.5	19.62[e]	…	…	…
ECMO at surgery, %	…	51.4	86.9	40	55.8	…	…	37.5	…
AAC	16, 12.2%	19, 12.8%	…	…	…	…	…	…	…
Distal perfusion, %	10.8%	44.6	…	100	…	…	…	75%	100
LV venting, %	…	3.4	14.1	…	…	…	0	…	…
IABP, %	…	25.9	27.1	83	27.1	…	20	87.5	8.1
ECMO duration, days	4[f]	6.4	6[f]	4.8	5[f]	5.4[b]	3[f]	4.7	5.8 vs 6[c]
ECMO weaning, %	…	48.6	48	63	49	…	60.8	66.7	…
GI complications, %	6.1	10.8	…	25	14.3	…	…	20.8	…
CVE, %	14.5	22.2	3.2	25	11.9	18.7	…	37.5	16.2
CRRT, %	14.5	45.3	…	66	29.8	18.7	47.8	29.2	…
Reop for bleeding, %	11.1	41.9	19.5	36	46.4	33.3	…	…	62.1
VAC/limb ischemia, %	29.5	12.1	9.7	12	10.7	33.3	…	8.3	18.9
Early outcome	Inhospital	Inhospital	NA	30 d	Inhospital	Inhospital	30 d, inhospital	Inhospital	30 d

Variables	Loforte, 2014 [6]	Mikus, 2013 [14]	Unosawa, 2012 [16]	Pokersnik, 2012 [13]	Kanji, 2010 [7]	Rastan, 2010 [4]	Russo, 2010 [46]	Ko, 2002 [9]
Number of patients	228	14	47	49	50	517	15	76
PCS	155, 67.9%	…	…	49, 100%	37, 74%	…	3, 21%	…
CABG	68, 43.8%	5, 35.7%	19, 40.4%	…	…	193, 37.4%	1, 6.6%	37, 48.6%
Valve	50, 32.2%	6, 42.8%	8, 17%	…	…	74, 14.3%	1, 6.6%	14, 18.4%
AAR (AAD)	…	…	…	…	…	20, 3.8%	…	2, 2.6%
LVAD	…	…	…	…	…	…	…	2, 2.6%
CABG + valve	…	…	2, 4.2%	…	…	87, 16.8%	…	6, 7.8%
CABG + other	…	…	3, 6.3%	…	…	…	…	…
Other[a]	37, 23.8%[a]	3, 21.4%	15, 31.9%	…	…	143, 27.6%	1, 6.6%	15, 19.7%
Non-PCS	73, 32.1%	…	…	…	13, 26%	…	12, 80%	…
AMI	27, 11.8%	…	…	…	…	…	2, 13.3%	…
DCM	40, 17.5%	…	…	…	…	…	4, 26.6%	…
Myocarditis	6, 2.6%	…	…	…	…	…	2, 13.3%	…
Other	…	…	…	…	…	…	4, 26.6%	…
Age, years	58.3	53.1	64.4	65	46 vs 52[c]	63.5	44.7	56.8

(*Continued*)

Table 1. Continued

Variables	Loforte, 2014 [6]	Mikus, 2013 [14]	Unosawa, 2012 [16]	Pokersnik, 2012 [13]	Kanji, 2010 [7]	Rastan, 2010 [4]	Russo, 2010 [46]	Ko, 2002 [9]
Male, %	67.9	64.3	35	33	72	71.5	66.6	63
Elective status, %	…	64.2	53.1	100	…	36.7	…	…
EuroSCORE II, %	25.7[e]	…	9.72[e]	…	…	21.6[e]	…	…
ECMO at surgery, %	88.5	85.7	70.2	…	…	41.9	…	51.3
AAC	…	…	…	Yes	…	62, 11.9%	…	…
Distal perfusion, %	65.8	100	100[g]	Frequently	…	23.4	66.6	26.3
LV venting, %	…	100[h]	0	…	…	…	6.6	2.6
IABP, %	100	92.8	83	60.6 vs 56.3[d]	73 vs 71[c]	74.1	80	69
ECMO duration, days	10.9	5	2.6	3.8 vs 4.3[d]	3 vs 2.5[c]	3.28	11.5	4.1
ECMO weaning, %	46.9	50	55.3	63.6, 45.5, 55.6[i]	…	63.3	80[j]	60.5
GI complications, %	…	…	…	…	…	18.8	…	…
CVE, %	15.7	14.2	…	6.1	10	9	0	3.9
CRRT, %	49.5	57.1	31.9	32.6	…	65	…	36.8
Reop for bleeding, %	48.4 vs 62.7[c]	64.2	42.5	78.8 vs 56.3[d]	44	58	26.6	46
VAC/limb ischemia, %	5.7	0	10.6	…	14	19.9	…	17.1
Early outcome	Inhospital	Inhospital	Inhospital	Inhospital	30 d	Inhospital	Inhospital	Inhospital

[a] Including thoracic organs transplantation. [b] One patient had right ventricular assist device. [c] Peripheral extracorporeal membrane oxygenation (ECMO) versus central ECMO. [d] Survivors versus nonsurvivors. [e] Logistic European System for Cardiac Operative Risk Evaluation (EuroSCORE). [f] Median. [g] Distal limb perfusion perfomed in 100% of cases after year 1999. [h] All in cECMO. [i] According to centrifugal pump and oxygenator combination. [j] Weaning or bridging.

Continuous variables are mean and categoric variables are percentage.

AAC = axillary arterial cannulation; AAD = acute aortic dissection; AAR = ascending aorta replacement; AMI = acute myocardial infarction; CABG = coronary artery bypass graft surgery; CRRT = continuous renal replacement therapy; CVE = cerebrovascular event; d = days; DCM = decompensated cardiomyopathy; ECMO = extracorporeal membrane oxygenation; GI = gastrointestinal; IABP = intra-aortic balloon pump; LV = left ventricular; LVAD = left ventricle assist device; PCS = postcardiotomy shock; Reop = reoperation; VAC = vascular access complications; vs = versus.

patients having central cannulation where the incidence of CVVH reached 45.5% (71 of 156; Fig 2C). With six studies and 537 patients included, there were no differences in the risk of limb complications between peripheral and central VA-ECMO: 1.68 (95% CI: 0.63 to 4.46, $p = 0.30$, $I^2 = 53\%$; Fig 2D). Similarly, no differences between cannulation approaches were observed in the analysis of sepsis: 0.71 (95% CI: 0.27 to 1.88, $p = 0.50$, $I^2 = 11\%$; Fig 2E).

Lastly, peripheral cannulation as compared with central cannulation was associated with a significantly reduced number of transfusions administered (Fig 3). Number of transfused packed red blood cells was significantly lower (by more than 7 units) with peripheral cannulation: weighted mean difference −7.17 (95% CI: −9.94 to −4.40, $p < 0.00001$, $I^2 = 36\%$) as compared with central cannulation. Similarly, the number of units of fresh frozen plasma administered was significantly lower (by nearly 3 units) when peripheral cannulation was used as compared with central cannulation: −2.73 (95% CI: −4.16 to −1.29, $p = 0.0002$, $I^2 = 33\%$). Number of transfused units of platelets was similarly reduced with peripheral cannulation: −5.09 (95% CI: −6.77

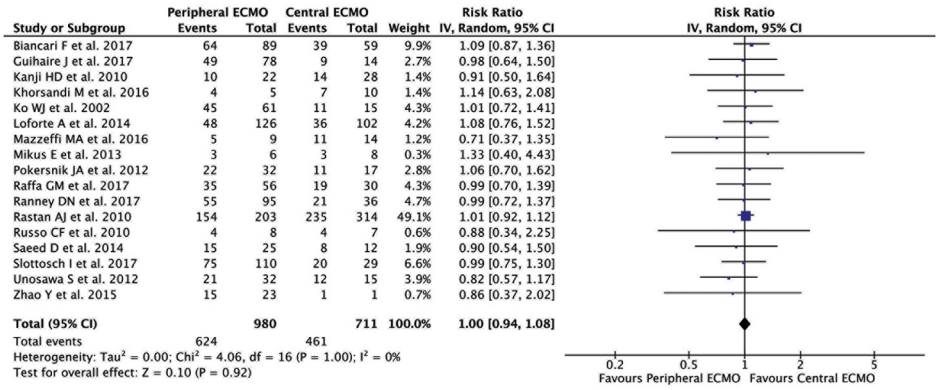

Fig 1. Forest plot of the comparison between peripheral and central venoarterial extracorporeal membrane oxygenation (ECMO) for inhospital survival. (CI = confidence interval; IV = inverse variance; RR = risk ratio.)

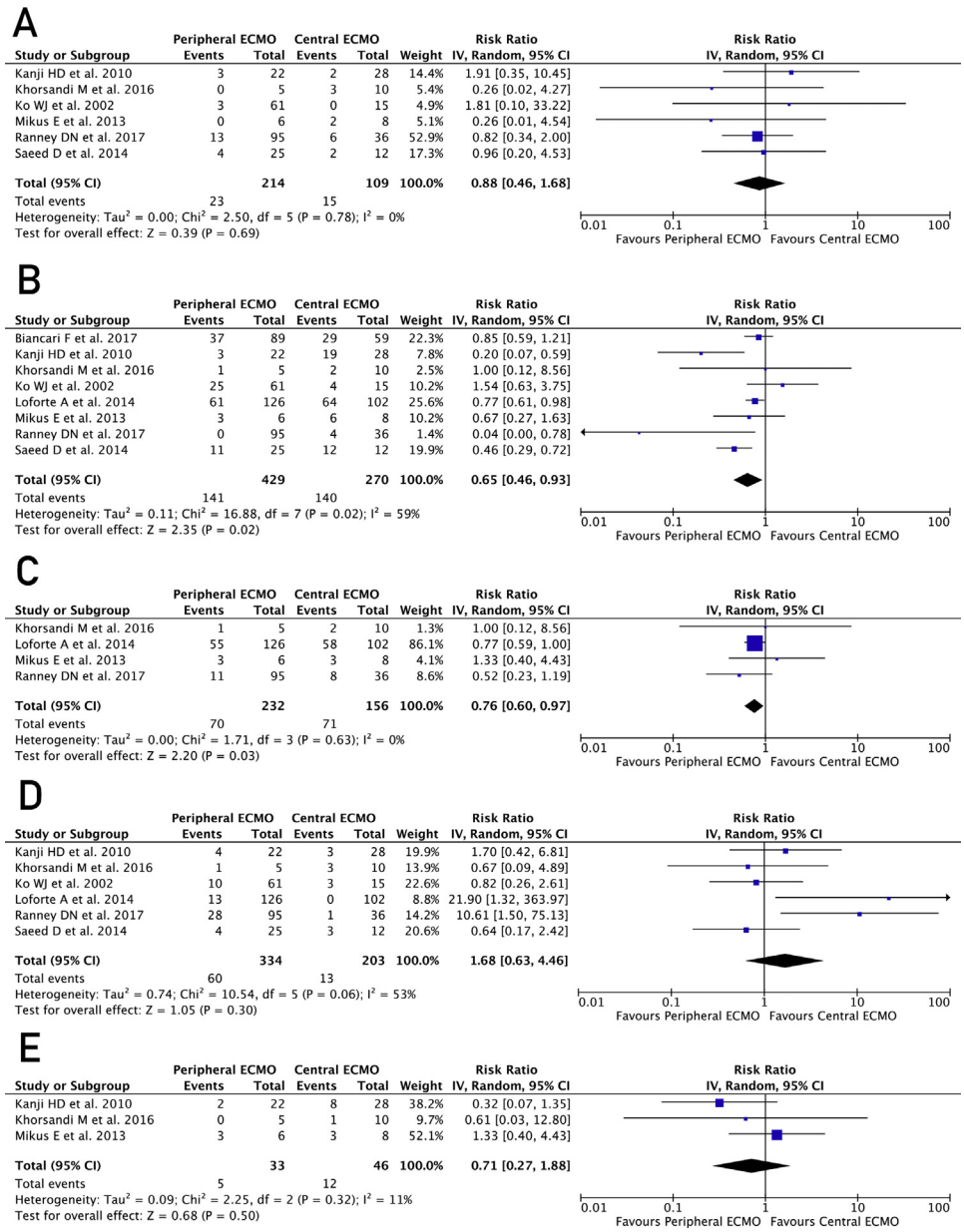

Fig 2. Forest plot of the comparison between peripheral and central venoarterial extracorporeal membrane oxygenation (ECMO) in regard to (A) risk of cerebrovascular events, (B) bleeding requiring reoperation, (C) continuous venovenous hemofiltration, (D) limb complications, and (E) sepsis. (CI = confidence interval; IV = inverse variance; RR = risk ratio.)

to −3.40, $p < 0.00001$, $I^2 = 0\%$), by more than 5 units on average.

Comment

To the best of our knowledge, the current meta-analysis represents the first attempt to address the difference in inhospital outcomes between central and peripheral cannulation in patients supported with VA-ECMO. The published articles analyzed, enrolling nearly 1,700 patients, have been strictly selected confirming that, although being a relevant and a greatly debated issue, the data available on this topic are very limited. Our main findings were, first, that among patients with PCS and non-PCS, no differences in 30-day inhospital mortality were observed between peripheral and central cannulation. This observation was also confirmed in a subgroup analysis including only PCS cases and according to type of surgery. Second, there was no difference between the two VA-ECMO configurations with respect to CVE, sepsis, acute renal injury requiring dialysis, and of particular note, in limb complications. Finally, central cannulation had increased surgical revision for bleeding, as well as use

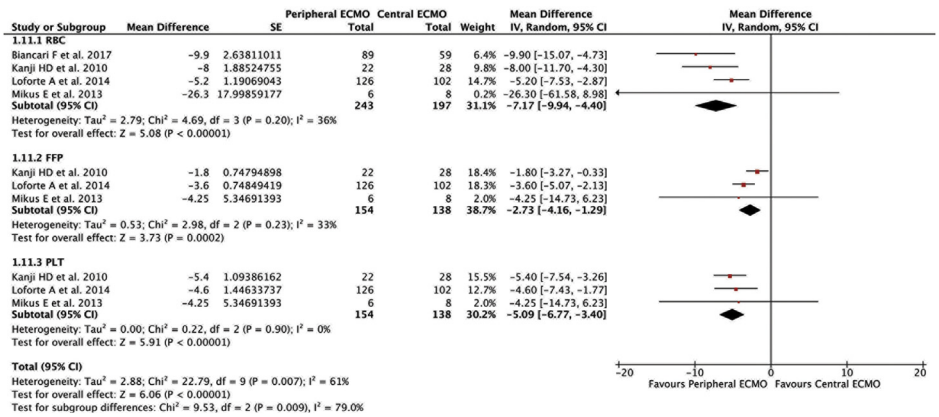

Fig 3. Forest plot of the comparison between peripheral and central venoarterial extracorporeal membrane oxygenation (ECMO) in regard to the risk of transfusions of red blood cells (RBC), fresh frozen plasma (FFP), and platelets (PLT). (CI = confidence interval; IV = inverse variance; RR = risk ratio.)

of CVVH, and a higher rate of transfusion of blood products.

Use of ECMO use is increasing, represents a resource-consuming treatment and, in many cases, is seen as a last resort for patients who otherwise would inevitably die [1, 2, 23–25]. Postcardiotomy shock was the most frequent indication for VA-ECMO implantation in the United States until 2011 [23–25], and the current European Society of Cardiology guidelines recommend ECMO (class of recommendation IIb, level of evidence C) for the management of cardiogenic shock in ST-segment elevation myocardial infarction [26]. However, despite growing worldwide experience, inhospital outcomes have not shown substantial progress [2, 27]. Furthermore, little is known about the cost-benefit ratio in these patients, especially in adult population [28].

Postcardiotomy shock and non-PCS are the clinical scenarios where central and peripheral cannulation strategies may both be deployed routinely. The location of ECMO implantation for PCS is mostly represented by the operating theater at the time of surgery (Table 1). In PCS, VA-ECMO is frequently needed for failure from cardiopulmonary bypass weaning and, usually, a central configuration can be easily instituted utilizing the cannulas already in place for previous cardiopulmonary bypass. A peripheral strategy using the femoral, or less frequently axillary or subclavian [10, 29], artery and femoral or jugular vein can be performed with percutaneous access [4, 9] or by surgical cut-down or ministernotomy. Advantages of the axillary cannulation include less atherosclerosis, less differential hypoxemia, and greater mobility on ECMO [3, 29]. The disadvantage is that it requires a cut-down technique that may not be feasible in emergency circumstances. Details on cannulation strategy to establish a proper ECMO flow have been reported elsewhere [3].

Central and peripheral cannulation carry advantages and disadvantages (Table 2): the central one directs an antegrade flow stream into the aorta with better cardiac unloading. The peripheral technique is a faster, particularly with regard to femoral arterial access, and less invasive technique for ECMO institution, concomitantly allowing sternal closure, which may be beneficial in terms of bleeding and infectious complications. In PCS, central VA-ECMO may also be instituted with the chest closed—the ECMO cannulas may be tunneled to exit at the subxyphoid region (Fig 4A)—allowing patient extubation and mobilization after surgery in case of prolonged support or bridge to more advanced therapies. However, the course of the cannulas, through the mediastinum toward the subxyphoid exit points, may provoke cardiac compression during a weaning attempt. Therefore, in case of expected short temporary support and expeditious cardiac recovery, cranial exit ports might be also considered by extending the upper incision with a Y toward the head (Fig 4B). This approach, avoiding cardiac compression by the cannulas, allows an unrestricted cardiac loading during ECMO weaning, making the evaluation of hemodynamics more reliable.

In this meta-analysis, the peripheral cannulation was the cannulation strategy most commonly adopted (57.7%) and, notably, in some series, it was the only one [30–32]. Whenever performed, the open access was chosen in the majority of the cases [9, 30–32].

The evaluation of hemodynamic performance of VA-ECMO according to cannulation strategy is lacking in the literature. Saeed and colleagues [8] compared the immediate changes in hemodynamics, arterial blood gas value, and end-organ function of patients on either peripheral ECMO or central ECMO support with no particular advantage of one cannulation technique over the other. The lactate levels during ECMO support have been shown to have a predictive role in mortality [33, 34], especially when the serial lactate measurements and lactate clearance are evaluated [15]. The majority of the studies included in this meta-analysis reported the differences in the lactate levels between survivors and nonsurvivors. Similarly, Kanji and colleagues [7] showed no differences in the peripheral and central cannulations in the mean peak lactate level as a marker for the end-organ and limb perfusion. Of note, in a series of 517 patients reported by Rastan and colleagues [4], a worse survival (13.9% versus 22.4%) occurred among patients who received a percutaneous femoral vein approach (23%) suggesting a suboptimal venous drainage and compromised ECMO flow as opposed to central right atrial drainage.

Table 2. Advantages and Disadvantages of Central Versus Peripheral Cannulation in Patients Undergoing Postcardiotomy Extracorporeal Membrane Oxygenation

	Advantages	Disadvantages
Central cannulation (aortic/atrial)	Use of originally (CPB) implanted cannulas	Opened sternum (chest closed possible)
	Antegrade flow	High bleeding risk
	Better drainage (bigger right atrium cannulas)	Cardiac compression (if exit port subxyphoid)
	Long-lasting support (subclavian artery use)	Resternotomy to remove cannulas
	Higher ECMO flow (better unloading through RA drainage)	More infection (sepsis)
	Patient mobilization (particularly with subclavian artery access)	Higher rate of cerebral emboli
	More options (and more easily) for LV venting	Higher risk of closed aortic valve
	No harlequin (or north/south) syndrome	
Peripheral cannulation (percutaneous)		
Femoral artery	No surgical incision	Leg ischemia
	Reduced bleeding risk	Retrograde flow (LV afterload increase)
	Closed sternum	Not suitable for long-lasting support
	No cardiac compression	Lower ECMO flow
	Easier switch to VAD implant	Vascular complication[a]
	No resternotomy for cannulas removal	Reduced options for LV venting (percutaneous)
Peripheral cannulation (open)		
Femoral artery	Visualization of peripheral vessel and appropriate cannulation site	Lower limb compartment syndrome[b]
	Reduced bleeding than central access	Retrograde flow (LV afterload increase)
	Closed sternum	Less suitable for prolonged support[c]
	No cardiac compression	Lower ECMO flow (limited right chamber unloading)
Axillary artery	Avoidance of leg ischemia	Upper limb compartment syndrome
	Avoidance of harlequin (north/south) syndrome	Upper limb HPS (with graft interposition)
	Patient mobility if prolonged support (bridge-to) required	Higher bleeding risk (site of cannulation)
	Visualization of peripheral vessel and appropriate cannulation site	Higher cerebral embolic risk
	Reduced bleeding than central access	Lower ECMO flow (limited right chamber unloading)
	Closed sternum	Retrograde flow[d]
	No cardiac compression	Higher rate of vascular complications
		Time-consuming

[a] During cannulation or after decannulation. [b] In majority of cases distal perfusion required. [c] Reduced patient mobility. [d] Left ventricle afterload increase, but less than femoral access.

CPB = cardiopulmonary bypass; ECMO = extracorporeal membrane oxygenation; HPS = hyperperfusion syndrome; LV = left ventricular; RA = right atrium; VAD = ventricular assist device.

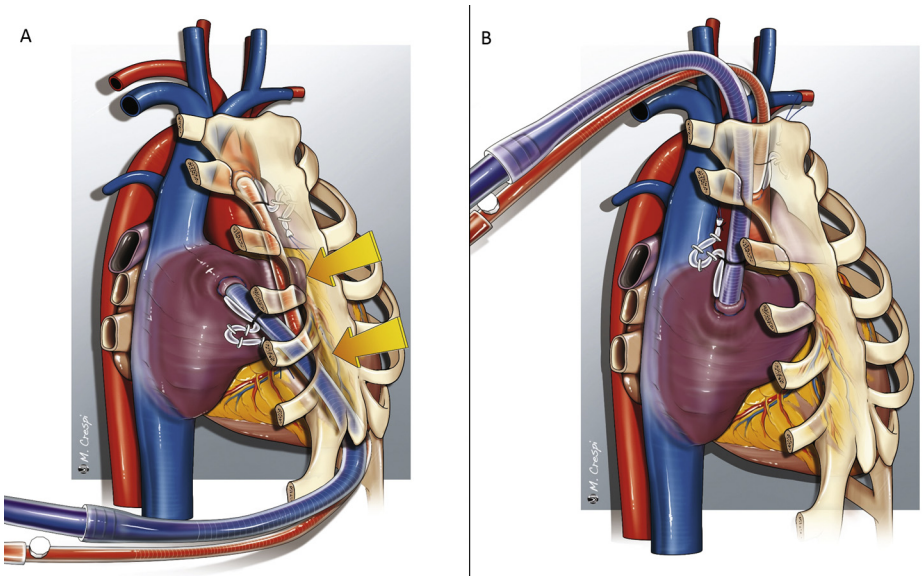

Fig 4. Closed chest central venoarterial extracorporeal membrane oxygenation achieved through (A) subxyphoid and (B) jugular exit sites.

Left ventricle unloading is another major issue during VA-ECMO [35]. Left ventricle dilation due to lack of contractility, high afterload, and retrograde flow toward the aortic valve during VA-ECMO requires careful monitoring and, sometimes, counteractions because of the risk of delayed myocardial recovery as well LV thrombus and pulmonary edema [35]. Six of 17 studies (Table 1) addressed the importance of LV venting during PCS although it was adopted in the minority of patients. Central VA-ECMO, despite better right-side heart drainage and an antegrade ECMO flow, may still face insufficient LV unloading. Central ECMO may enhance additional catheter/cannula placement through direct cannulation of vessels or chambers, whereas peripheral configuration, without open chest, may call for alternative solutions [35]. The appropriate or most effective methods for LV venting is still controversial. Intraaortic balloon counterpulsation, although controversial [35, 36], may play a role in LV unloading [37]. In some PCS series, the lack of intraaortic balloon pump use was linked to a trend to reduced survival [4, 38], whereas in other experiences no difference among survivors and nonsurvivors was also found [13, 16, 31]. Alternative approach in LV unloading—such as Impella (Abiomed, Danvers, MA), pulmonary artery venting, or other methods—have been also reported [35, 39]. The role, effects, and interaction between various LV venting and central or peripheral ECMO configuration are still unknown and warrant further investigations.

Complications in patients on VA-ECMO are frequent and strongly affect the ultimate outcome [2, 4]. The results of this meta-analysis favor peripheral VA-ECMO in terms of reoperation for bleeding and number of transfusions of red blood cells, fresh frozen plasma, and platelets. Bleeding, transfusion, and revision for bleeding remain major problems in ECMO patients, and although these may also occur in the peripheral configuration [4], the severity of these complications in central VA-ECMO tends to be worse. Open sternotomy to avoid tamponade and right ventricle compression as well as to allow cardiac edema to resolve, the use of cannulas inserted during the previous cardiopulmonary bypass course, and avoiding limb ischemia due to femoral artery cannulation are the major reasons to choose central cannulation. However, this meta-analysis showed that the risk of limb ischemia and vascular access complications were comparable between the two techniques of cannulation. Small cannula size, distal perfusion cannulas [40], and insertion of a vascular graft are commonly advocated [4, 5, 7] to avoid such a complication.

In relation to the peripheral approach, open cannulation appears to be associated with fewer complications than full percutaneous access [9, 31]. In this meta-analysis, 10 of 15 studies report the use of distal perfusion cannula, and in only three reports [4, 9, 10], it was adopted in less than 30% of the patients. Peripheral complications in central VA-ECMO may include embolic phenomena [7], although the use of vasoconstrictors in these hypovolemic and vasoplegic patients may also play a role. Loforte and colleagues [6] showed that central cannulation in PCS resulted in increased bleeding and CVVH rates compared with peripheral access (62.7% versus 48.4%, and 56.8% versus 43.6%, respectively). The latter, also confirmed by our analysis, may suggest the high rate of acute volume-depletion events and need for transfusion in the central setting that led to acute renal injury. Kanji and colleagues [7] investigated the incidence of limb ischemia, perfusion (peak lactate levels), CVE, thrombus, and sepsis in the peripheral versus central ECMO over 5 years, showing no difference. Of note, the investigators report 11% with limb ischemia in the central cannulation cohort. A high rate of neurologic complications was observed in the series by Ko and colleagues [9]

treated with open femoral ECMO, probably due to the pre-ECMO clinical condition of the patients.

The use and impact of axillary or subclavian artery cannulation, which should provide several advantages by allowing a "pseudo-central" flow as compared with femoral artery or ascending aorta cannulation, has been recently investigated [10, 41, 42]. A trend toward more frequent implant in the operating room as compared with aorta or femoral artery (93.8%, 80.6%, and 32.9%, respectively), a significant higher rate of vascular complication (particularly fasciotomy and amputation), and bleeding at the cannulation site (37.5%, 30.6%, and 13.9%, respectively) has been recently reported [10]. A trend, but not a significant one, toward higher incidence of CVE was also observed (18.8%, 16.7%, and 12.7%, respectively) [10]. The actual incidence, and related techniques to avoid or reduce upper limb hyperperfusion syndrome, was not described [43, 44]. Today, the use of the axillary or subclavian arteries appears therefore advisable in patients with inaccessible femoral arteries or for patients in whom prolonged support (with need for patient awakening, endotracheal extubation, and mobility) is expected. However, that should take into account the potentially higher risk of complications as compared with central or femoral artery cannulation [10].

The small number of patients and the retrospective nature of the studies included represent the major limitations of this meta-analysis. Only four studies reported the outcomes of interest in non-PCS patients [6, 8, 10, 15] and were deliberately included, although addressing a different patient population. This potential selection bias, however, did not influence the primary endpoint as shown in the further subgroup analysis including only PCS patients. We also acknowledge the lack of some critical information, for example, the timing of ECMO starting and distal perfusion and the weaning protocols (see Supplemental Figs 5 and 6 and Appendix Table 2). Finally, all the analysis were made according to the initial cannulation strategy, and deviations from the planned cannulation strategy ECMO (because of flows, need for adequate LV venting, and limb complication) or any changes were not considered.

In conclusion, from the available data in the literature, central versus peripheral access for VA-ECMO in PCS or non-PCS did not show any significant difference in relation to inhospital survival. Peripheral access was associated with reduced bleeding, transfusion, and CVVH rates. No other substantial differences were found regarding other ECMO-related complications. Owing to the paucity and limitation of available data, however, further investigations are required to elucidate the risk-benefit profiles of central and peripheral accesses in VA-ECMO.

Dr Brodie is currently the co-chair of the Trial Steering Committee for the VENT-AVOID trial sponsored by ALung Technologies and was previously on the medical advisory board of ALung Technologies and Kadence (Johnson & Johnson). All compensation for these activities is paid to Columbia University.

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