EDITORIAL

Arteriovenous extracorporeal membrane oxygenation for cardiac arrest/cardiogenic shock

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‘For now they kill me with a living death’ (Shakespeare, *King Richard III*).

Refractory cardiac arrest is ultimately unsurvivable and cardiogenic shock following cardiac arrest carries a severe mortality. It is for these extremely vulnerable patients that veno-arterial extracorporeal membrane oxygenation (VA-ECMO) might be considered given its immediate effects on systemic perfusion [1] and the lack of efficacy of alternate therapies. The Extracorporeal Life Support Organization (ELSO) registry has 2885 records for adult cardiogenic shock and/or cardiac arrest patients receiving VA-ECMO during ongoing resuscitation (ECPR) in the 2016 report [2].

The time constraints surrounding the decision to start VA-ECMO mean that often there is insufficient information available in regards to the two main prognostic issues: reversibility of the myocardial injury and severity of any neurological insult. Commencing VA-ECMO is therefore often a bridge-to-decision as well as a bridge-to-treatment. The rationale to apply a rescue treatment that may lead to survival must be carefully balanced against the potential to generate survivors with devastating neurological sequelae and the significant resources involved in providing the treatment.

Clinical examination, echocardiography and laboratory tests (pH, lactate, venous oximetry, coagulation parameters) at the time of considering VA-ECMO can establish the failure of ongoing haemodynamic support but not the potential for cardiac recovery, and cardiac biomarkers are

unreliable [3]. Accepted criteria for neurological prognostication [4] are rarely applicable in the acute situation when VA-ECMO is contemplated. The degree and duration of poor systemic perfusion are obviously linked to any neurological insult that therefore shares common prognostic variables [5]. Brain death has been reported in 25% of patients subjected to VA-ECMO for refractory cardiac arrest [6]. A brain CT early after initiation of VA-ECMO, while logistically challenging, adds prognostic information and serial neurological evaluations, neurological biomarkers and assessing somatosensory evoked potentials are important in the first few days of VA-ECMO support [4].

Equally concerning as the limited quality of evidence to support indications for VA-ECMO is the heterogeneity of reported exclusion criteria. The 2013 ELSO Guideline lists prolonged cardiopulmonary resuscitation without adequate tissue perfusion as an absolute contraindication to VA-ECMO but the lack of detail makes this statement difficult to implement. Published case series suggest that time to commencing VA-ECMO is critical to its success and should be limited to 30–60 min after cardiac arrest [7, 8] whereas age, an independent predictor of in-hospital mortality, is arbitrarily defined [9]. Furthermore, while ECMO pump devices, tubing and cannulation procedures are becoming increasingly sophisticated and more compact mobile systems are available [10], the use of VA-ECMO is still associated with significant morbidity [11].

The 2015 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science with Treatment Recommendations state that ECPR is a reasonable rescue therapy for selected patients (weak recommendation, very low quality evidence). Substantial investments in logistics and staffing are required and even experienced ECMO units caution against expanded use [12].

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The characteristics and outcomes of 94 patients receiving VA-ECMO for cardiogenic shock post-cardiac arrest reported in a recent article in *Intensive Care Medicine* [13] are important to make experience in a well-established ECMO centre available to the wider intensive care community, especially since this category of patients has not been reported previously. In particular, efforts to establish risk prediction algorithms are laudable. The present report complements earlier cohort studies from which the ENCOURAGE and SAVE scores were derived. The performance of the SOFA score in predicting outcome is interesting and very relevant clinically. The results overall are encouraging with survivors showing good neurological outcomes.

The lack of detail for haemodynamic characteristics and interventions at the time of VA-ECMO implantation, certainly acknowledged by the authors and common for case series involving patients retrieved outside the ECMO unit, is unfortunate. Such information is needed to inform potential consensus guidelines for patient selection and to allow meaningful meta-analyses. It could also help explain some apparent inconsistencies in outcome predictors that in this study did not include cardiac

arrest variables, age, and lactate as reported earlier [7–9], albeit not specifically in patients with cardiogenic shock following cardiac arrest.

Three ongoing randomised controlled trials (RCT) are currently registered at clinicaltrials.gov investigating VA-ECMO for refractory cardiac arrest (NCT01605409, NCT01511666) and cardiogenic shock (NCT02301819). In the absence of published RCTs, clinical decision making can only be guided by retrospective reviews of prospectively collected data. Such reports are prone to indication bias and reporting bias that overinflate the benefits. For example, VA-ECMO implantation is frequently performed in the angiography suite which in itself might be a marker of patient selection and percutaneous techniques furthermore seem to be associated with better outcomes [14]. It is essential that the cumulative evidence is systematically reviewed and presented as done by Ouweneel and colleagues [15] in a meta-analysis recently published in *Intensive Care Medicine*. The meta-analysis supports the results by de Chambrun et al. [13] of improved survival using VA-ECMO in patients with cardiogenic shock after acute myocardial infarction as well as in refractory cardiac arrest, with improved

Fig. 1 Trial sequential analysis (TSA) for a relative risk reduction of mortality (left-hand graph) or unfavourable neurological outcome (right-hand graph) of 30% by VA-ECMO in refractory cardiac arrest and in cardiogenic shock following acute myocardial infarction using data from all studies included by Ouweneel et al. [15]. Eleven studies including 2973 patients demonstrated a 50% relative risk reduction for death. A required diversity-adjusted information size of 6635 patients was calculated on the basis of a more moderate relative risk reduction of 30%, using a type I error of 5% and the O'Brien-Fleming α spending function, a power of 80% ($\beta = 0.20$) and a diversity (D^2) of 67% calculated from the included studies. The cumulated Z-score curve (blue line), i.e. the log of the pooled intervention effect divided by its standard error, crosses the trial sequential monitoring boundary (red solid line) indicating a survival benefit from using VA-ECMO when the analysis is adjusted for repetitive testing on accumulating data. The cumulated Z-score curve is still far away from the inner wedge (dashed red line) indicating when further inclusion of patients would be futile to confirm or refute a 30% relative risk reduction for death. The TSA for unfavourable neurological outcome shows that the cumulated Z-score curve based on 1694 patients is far away from the sequential monitoring boundary and an indicative number of 12,579 patients would be needed to ascertain such treatment effect. More information is needed to extend the sequential monitoring boundary and the information fraction is too small to generate any futility borders. (Figure redrawn from output generated using TSA viewer Version 0.9 Beta, Copenhagen Trial Unit, 2011)

neurological outcomes reported in the latter category. Several important limitations inherent to the included studies are addressed in the systematic review.

The multiplicity of significance testing in a meta-analysis might generate spurious results. Trial sequential analysis (TSA) is a tool to adjust thresholds for statistical significance for multiple testing, similar to alpha spending rules for interim analyses in RCTs. It also provides an estimate of the information size required as well as boundaries for futility to guide future trials. With the proviso that cardiac arrest/cardiogenic shock represents a continuum of disease, the studies reported by Ouweneel and colleagues [15] were pooled in a TSA and analysed for a relative risk reduction for death/poor neurological outcome by 30% (Fig. 1). Interestingly such analysis confirms the survival benefit, but not improved neurological outcome, while indicating that the necessary information size for mortality is approximately twice that reported so far, and considerably larger for neurological benefit. Notwithstanding the inherent bias(es) in the included studies, it would hence appear that VA-ECMO may be a reasonable therapeutic option but that much more robust evidence is urgently needed. The medical community, the patients and their families deserve better guidance in desperate times.

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Compliance with ethical standards

Conflicts of interest

On behalf of both authors, the corresponding author states that there is no conflict of interest.

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