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CLINICAL CONTROVERSY

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# Extracorporeal CPR after the INCEPTION trial: No one steps twice into the same river

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**Abstract**

The use of veno-arterial extracorporeal membrane oxygenation as extracorporeal cardiopulmonary resuscitation in patients suffering out-of-hospital cardiac arrest, largely increased in the last decade despite evidence supporting this practice being limited to non-randomized studies. However, between 2020 and 2023, four randomized studies were published comparing extracorporeal cardiopulmonary resuscitation to conventional cardiopulmonary resuscitation with controversial findings that triggered great debates. In this controversy, we discuss merits and pitfalls, and provide a critical interpretation of the available evidence from randomized trials on the use of extracorporeal cardiopulmonary resuscitation, with a particular focus on the recent multi-center INCEPTION trial.

**KEYWORDS**

ECLS, ECMO, ECPR, extracorporeal cardiopulmonary resuscitation, extracorporeal life support, extracorporeal membrane oxygenation, OHCA, out-of-hospital cardiac arrest

## 1 | INTRODUCTION

The use of veno-arterial extracorporeal membrane oxygenation (ECMO) during cardiopulmonary resuscitation (CPR) in patients suffering out-of-hospital cardiac arrest (OHCA) is increasing. Such indication, termed as extracorporeal CPR (ECPR), aims to restore circulation during OHCA unresponsive to conventional CPR but with recovery chance. The

evidence supporting ECPR was limited to non-randomized studies,[1–3] however since 2020, four randomized clinical trials (RCT) have been released. In this controversy, we discuss merits and pitfalls of ECPR RCT, with a particular focus on the recent multi-center INCEPTION trial.

## 2 | RANDOMIZED TRIALS OF ECPR

The ARREST trial was the first RCT ($n = 30$) in the field of ECPR and suggested that ECPR improved survival and neurological outcomes compared to conventional CPR in patients with shockable rhythms.[4] EROCA was a pilot RCT ($n = 15$, eight with shockable rhythms) aiming to demonstrate that early transport would reduce time to ECPR; however, this was achieved in less than half of the patients. Most transported patients did not meet ECPR criteria and only five patients were placed on ECMO with no survivors with a favorable neurological outcome.[5] The EROCA trial was initiated in a system without prior ECPR experience as a feasibility study to identify successful transport criteria for ECPR initiation in the Emergency Department (ED). The Prague OHCA study randomized 264 refractory all-rhythms OHCA patients documenting an increased survival with favorable neurological outcome with ECPR, statistically significant at 30 days (30.6% vs. 18.2%) but not at 6 months (31.5% vs. 22.0%).[6] Importantly, patients with the longest CPR duration had statistically significant increased survival with favorable neurological outcomes with ECPR, demonstrating its added value to high-quality prolonged CPR. Moreover, in this RCT 11 patients assigned to conventional CPR crossed-over to ECPR, and five survived, favoring the control group in the intention-to-treat analysis.[6] The ARREST and Prague OHCA trials have a very similar intervention arm and therapeutic strategy and their combination of data demonstrated improved neurologically favorable survival with ECPR.[7,8]

## 3 | THE INCEPTION TRIAL IS A PRAGMATIC RCT—WHAT DOES IT MEAN?

The pragmatic implementation of ECPR was investigated in the INCEPTION trial, a multi-center RCT conducted in the Netherlands, which showed similar effects on survival with favorable neurologic outcomes at 30 days for ECPR and conventional CPR (20% vs. 16%, $p = 0.52$) among 134 patients with shock-refractory OHCA.[9] The INCEPTION trial differs substantially from ARREST and Prague OHCA. Ten cardiosurgical ECMO centers provided ECPR while following routine clinical practice. The centers did not have established ECPR programs before the trial started. No standardized protocols for EMS, ECMO, and post-resuscitation care were required. In-hospital ECPR initiation was left to the discretion of the participating hospitals. The average time to ECMO flow from ED arrival was 36 min, while in the ARREST and Prague OHCA was 7 and 10 min, respectively. Low volume of cases in centers and surprisingly short ICU care times (median ICU stay 1 day and median hospital stay 2 days for the ECPR group), demonstrate the very short attempts at post-ECPR care and highlight the differences in care compared to the systems in Minnesota and Prague.

Overall, the INCEPTION trial examined ECPR within a completely different setting—centers with no formal prehospital or hospital-based protocols, with very little experience with ECPR in OHCA.

The absence of standardization is an intrinsic property of pragmatic RCTs, which is used to increase generalizability and evaluate the effectiveness of interventions in conditions very close to real-life. However, this approach resulted in testing a complex intervention such as ECPR with a high level of heterogeneity with the risk of diluting its effect and failing to demonstrate a significant difference. To increase the power of detecting even minor effects, pragmatic RCTs generally enroll large sample sizes. In the INCEPTION trial, the sample size was relatively small ($n = 134$), and a 4% absolute difference in the primary outcomes did not reach significance (odds ratio 1.4; 95% confidence interval 0.5–3.5).[9] Previous trials,[4,6] performed at single centers with strictly controlled and standardized practices and experience on ECPR, could be instead considered explanatory trials. These trials assess whether an intervention is effective under optimal situations, limiting as much as possible biases and confounders but possibly overestimating the benefits. A complex procedure like ECPR could demonstrate its effectiveness in a trial with a specific combination of professionals, setting and patients, and no difference in less homogeneous or suboptimal settings, as it may have occurred in the INCEPTION trial.[9]

In this issue of Artificial Organs, a meta-analysis combining these four RCTs demonstrated higher survival with favorable neurological outcome with ECPR compared to conventional CPR (27% vs. 18%; odds ratio = 1.72; 95% confidence interval, 1.09–2.70; $p$-value = 0.02).[10] Very frequently in critical care medicine, multi-center RCTs do not replicate positive single-center RCTs, with relevant unintended consequences. Healthcare authorities may justify avoiding the costs of this potentially lifesaving procedure, clinicians may lose interest and enthusiasm, and industries limit investments in this field. Citizens' expectations may also be affected as INCEPTION trial results reached the lay press headlining "*CPR with heart-lung machine has no added value (and is too expensive)*".[11] INCEPTION trial results also disappointed experts and clinicians already

applying ECPR, while the skeptics used this trial to argue against its use. Nevertheless, multi-center RCTs are fundamental to understand the benefits and weaknesses of interventions. Given the resources needed to conduct RCTs, information to guide clinical practice must also be extrapolated from neutral studies. Indeed, also the INCEPTION trial conveys valuable information to improve the delivery of ECPR.

## 4 | ECPR IS A COMPLEX INTERVENTION

ECPR is complex and consists of several interacting components managed by different professionals whose expertise may vary, especially when involving several centers. In addition, various strategies are available for pre-hospital resuscitation, post-resuscitation care, prognostication and life-sustaining therapy withdrawal, temperature control, coronary angiography, ventilatory and circulatory supports. All these potential confounders were not controlled by study design in the INCEPTION trial, while single-center RCTs were intrinsically more homogeneous. Along the same lines, high-performing systems have optimized logistics and pathways, mainly reflected by low-flow times, a critical aspect for the success of ECPR.[1,12] In the INCEPTION trial, time between hospital arrival and cannulation initiation and between cannulation initiation and ECMO flow were 16 and 20 min.[9] Such delays reflect the overall system efficacy, logistics, team experience, and caseload. Of note, these intervals were considerably longer than the ARREST and Prague OHCA trials,[4,6] where immediate cannulation after arrival was performed.

An analysis of the Extracorporeal Life Support Organization (ELSO) registry suggested that survival after ECPR was associated with modifiable post-resuscitation practices and center volume.[13] Likewise, low volume per center, absence of standardization, and delays in how ECPR was provided in the INCEPTION trial may have contributed to its reduced effect, being, per definition, a time-dependent intervention.

## 5 | THE CONTROL GROUP

Registry studies of patients with OHCA report very poor outcomes after prolonged resuscitation.[14,15] 90% of patients with good neurological outcome achieved ROSC with conventional CPR after 20 min and 99% within 37 min.[14] No additional survivors had favorable neurological outcomes after 47 min.[14] In the control group of the INCEPTION trial, 31% of patients had ROSC and 16% survived with favorable neurological outcome despite 49 min of CPR.[9] Similarly, in the control group of the Prague OHCA study, 44% of patients had ROSC and 22% survived with favorable neurological outcome despite 46 min of CPR.[6] The potential efficacy of ECPR may have been blunted because of the study design. In the ARREST trial randomization occurred in the hospital after prolonged CPR (>45 min) and just one patient sustained ROSC and subsequently died in the control group.[4] Different pre-hospital CPR strategies (e.g., routine intra-arrest transport or continued on-scene resuscitation) and different skills (e.g., on-scene physician presence) may achieve different outcomes in patients with refractory OHCA.[16] Therefore, the effect of ECPR might seem to diminish in systems with high rates of successful conventional CPR. Still, even in such systems, ECPR offers a rescue chance with a reasonable odd of favorable survival, as demonstrated in the Prague OHCA study. Consequently, a larger sample size might have been required to demonstrate a statistically significant difference in the INCEPTION trial.

## 6 | CONCLUSIONS AND FUTURE DIRECTIONS

ECPR is a complex but powerful lifesaving procedure, especially in patients presenting with shockable rhythms, when applied within an optimal window of time (i.e., 60 min), that the underline hypoperfusion during CPR has not caused irreversible damage to the brain. Rather than the ineffectiveness of ECPR, the INCEPTION trial revealed the complexity of pragmatically implementing ECPR without detailed system adjustments. While large, international RCTs could improve our understanding, centers already successfully offering ECPR are unlikely to consider there is equipoise. Limits in healthcare systems (e.g. bystander interventions) must be identified and optimized before implementing and testing ECPR.

Referring refractory OHCAs to a single, metropolitan, high-volume, and high-expertise ECPR-capable cardiac arrest center might achieve better outcomes. Whether this approach is compatible with making ECPR widely accessible remains to be demonstrated. Moreover, defining how novel centers should set up their ECPR programs and the optimal minimum of patients required to gain enough experience needs to be determined.

### AUTHOR CONTRIBUTIONS

All authors contributed to the design and to the analysis of the randomized trials results and to the writing of the manuscript. The manuscript has been approved by all authors.

## CONFLICT OF INTEREST STATEMENT

R. Lorusso is consultant for Medtronic, LivaNova, Getinge, and Abiomed; he is member of the Medical Advisory Board of Eurosets and Xenios. Remaining authors have no conflict of interest to declare.

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