Editorial

What is extracorporeal cardiopulmonary resuscitation?

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Death, *be not proud*, *though some have called thee*;
Mighty and dreadful, *for thou art not so*;
John Donne, *Sonnet X*, *Holy Sonnets*

In 2016, in the USA, more than 350,000 and 209,000 peoples suffered, respectively, out-of-hospital cardiac arrest (OHCA) and in-hospital cardiac arrest (IHCA), with a survival rate of 12% and 24.9% (1). The percentage of survival is near zero when cardiac arrest is refractory to conventional cardiopulmonary resuscitation (CPR). The dismal prognosis of this pathological state prompted the scientific community to extend the increased knowledge in mechanical circulatory support (MCS) in resuscitating patients in refractory cardiac arrest. Indeed, the term 'refractory' applies to failure of obtaining ROSC in a setting where extracorporeal CPR (ECPR) is contemplated.

Even if the first application of extracorporeal circulation to treat cardiac arrest was in 1976 (2), it is only recently that this technique has gained a wider application in USA and Europe.

ECPR can be defined as the implantation of veno-arterial extracorporeal membrane oxygenation (VA-ECMO) in a patient who experienced a sudden and unexpected pulseless condition attributable to cessation of cardiac mechanical activity (1,3). ECPR is now recognized in Extracorporeal Life Support Organization (ELSO) (4) and American Heart Association (AHA) (5) guidelines as a technique that can be considered in selected patients in cardiac arrest.

Many prospective or retrospective studies showed a superiority of ECPR on conventional CPR in increasing the odd of survival and of a good neurologic outcome (6-11). A recent article (12) offers the opportunity for a deep thought about ECPR.

The work by Richardson *et al.* describes the outcomes, over a period of 12 years, of 1,796 patients receiving ECPR, extracting data from the ELSO registry (12).

This article is a unique insight into the field, because of the large number of patients and the long period considered.

The authors showed a remarkable increase of the number of ECPR performed during the study period, without any significant change in odds of survival. Overall hospital discharge rate was 29%. The authors identified Hispanic race, pulse pressure less than 20 mmHg before ECMO implantation and device-related complications as negative prognostic factors. As expected, age and comorbidity of the patients increased along with the wider application of the therapy, but without a significant association with mortality.

On the basis of ELSO registry a 10-fold increase of ECPR procedures has been registered in the last 10 years (13). Furthermore, this therapy is considered in the most recent guidelines on cardiac arrest in the context of an acute coronary syndrome (ACS) (14,15).

However, many areas of uncertainty still exist, and the role and the application of ECPR are today greatly debated.

We have identified some hot points of controversy: the lack of a clear and univocal definition of ECPR; the selection of patients to be treated with ECPR; the management of the post cardiac arrest phase; the possibility to treat the cause of cardiac arrest; the definition of outcomes.

To define ECPR is not a straightforward task: indeed, ECPR is more than ECMO implantation on a cardiac arrest patient.

From our standpoint, ECPR has two common trademarks: the abrupt presentation of a patient on cardiac arrest, whether IHCA or OHCA, to the ECMO team and the absolute uncertainty about its cause.

In the case of IHCA, further specifications are needed: cardiac arrest may happen as an unexpected event in patients admitted to the hospital for other causes, but could also be the natural evolution of an acute critical illness, in which ECPR could be interpreted as a late intervention for a moribund patient, possibly candidate to an earlier circulatory support system. Excluding patients in the intensive care unit (ICU) takes out of the scene the question about the 'abrupt presentation', these are patients who would have received ECMO earlier in an ideal setting.

The connotative aspect of sudden presentation implies that a centre providing ECPR should have available 24/7 a team experienced in emergent ECMO implantation on a patient in cardiac arrest during continuous chest compressions.

The uncertainty in the preliminary diagnosis drives the uncertainty in eligibility criteria.

AHA guidelines state that ECPR may be considered for selected patients when the suspected aetiology of cardiac arrest is potentially reversible during a limited period of mechanical cardiorespiratory support (5). This definition is conceptually correct, but in the real world applies on a very limited group of patients: those who received a diagnosis of myocardial infarction before or after the admission to hospital. In the majority of cases, mostly in OHCA, but in a remarkable percentage also in IHCA, the clinician has not, or at least confusing, data to decide whether cannulate or not.

On these premises, two main paths can be taken. The first possibility is the application at the moment of triage of different scores validated for MCS implantation for cardiogenic shock, but burdened by a low proportion of ECPR in the derivation or validation cohort (16-18). We strongly believe that the application of scores outside the original setting is not the right choice to decide the fate of a cardiac arrest patient.

Moreover, as the study of Richardson *et al.* has pointed out, even the patients with the higher risk scores have not a negligible survival (12).

The second way could be a strict application of prognostic criteria validated from studies on cardiac arrest, including or not ECPR: witnessed arrest, bystander ECPR, end-tidal CO_2, no-flow time, low-flow time, shockable rhythm, quality of CPR (19-22).

In our experience, no one of these parameters may be considered reliable in the few minutes in which a team is forced to draw a conclusion about the eligibility of a patient.

We are aware that a strict application of exclusion criteria might lead to better outcomes (23), but one must recognize that such criteria are today not univocal and many patients who could possibly take advantage from this procedure would be irremediably lost. As a direct consequence, one can conclude that contraindications to ECPR, like aortic disease, can be often identified only after cannulation.

Given the above, the unreliability of current prognostic factors should push the team to cannulate, unless cardiac arrest did not represent the evolution of a chronic incurable disease or accompanied by lesions incompatible to survival.

In evaluating the outcome of ECPR, another issue should be raised: it is our opinion that a correct analysis of the results, at this preliminary stage, should include only ECPR correctly performed.

In other words, should we validate the failure of cannulation or a cannulation time taking more than 10 min a negative outcome of ECPR, or rather a not-performed ECPR?

In this stage, ECPR deserves a *per se* evaluation. Once ECMO has been implanted, the patient usually reaches a hemodynamic stabilisation. However, the patient who has suffered cardiac arrest with prolonged CPR experiences a global derangement of organ function, encompassed in the term of post cardiac arrest syndrome (24,25), including brain injury, myocardial dysfunction and systemic inflammatory response.

Hallmark of this pathological state is the ischemia-reperfusion syndrome. During cardiac arrest, the reduced oxygen delivery to peripheral tissues determines the onset of an oxygen debt, that is a powerful stimulus to endothelial activation, systemic inflammatory syndrome and uncontrolled coagulation activation (24). The entity of oxygen debt is predictive of subsequent multiple organ failure.

The stabilisation of haemodynamics is mostly secondary to the regulation of ECMO flow.

In the paper of Richardson *et al.* (12), median values of ECMO flow increased from 3 litres per minute (LPM) in 2002 to 3.6 LPM in 2014.

This finding may account for an increased awareness about the role of full ECMO support in the immediate post cardiac arrest phase, but these values are still well above the normal cardiac output of a normotype patient.

The regulation of ECMO flow is a two-front war. From one side, the need for restoration of systemic perfusion pushes toward higher flows but, on the other, the risk of left ventricular (LV) distension, endoventricular stasis and pulmonary oedema frightens the clinician (26,27). To the best of our knowledge, even if no studies have compared different strategies of ECMO flow regulation after cardiac arrest (hyperflow, normal flow, partial assistance), we strongly advise that the opportunity of setting the pump flow to values allowing for a rapid lactate clearance, restoration of urine output, resolution of metabolic acidosis should be carefully considered (28). The existence of effective systems of percutaneous LV venting should give the response to the case of profound cardiac depression and LV distension by a high, ECMO-dependent, afterload (29-31).

Lastly, the possibility to deliver a specific therapy for cardiogenic causes of cardiac arrest, like massive pulmonary embolism or myocardial infarction is a topic greatly debated.

The role for interventions is not straightforward. Rushing and transport the patient to cath lab or radiology without prior stabilisation is cumbersome and harmful. Moreover, when a coronary cause of cardiac arrest is identified, the risk of bleeding associated to unavoidable antiplatelet and anticoagulant therapy might be too high (32,33).

Even if European Society of Cardiology (ESC) and AHA guidelines support myocardial revascularization in patients in cardiogenic shock or acute heart failure secondary to acute myocardial infarction (AMI) (14,15), these recommendations are not specifically referred to the patient resuscitated from cardiac arrest with ECPR. Similarly, guidelines on pulmonary embolism recommend systemic fibrinolysis or surgical embolectomy in shocked patients (34). On top of that, the intra-hospital transport of a patient immediately after ECMO implantation is carried out with a considerable harm.

Recently, Kuroki *et al.* (35) reported the outcomes of 119 ECPR patients, in which the group of patients with a probable cardiogenic cause of CA underwent coronary angiography and, if indicated, percutaneous coronary revascularisation. The group of patients with shorter cardiac arrest to ECMO time and cardiac arrest to cath-lab time had an increased odd of survival with a good neurological outcome. In this regard, we have two objections. The first argument is the reliability of diagnosis of CA secondary to ACS in OHCA setting: in the real world, an ECG before OHCA is not always available and is not sufficient to make a diagnosis of AMI. Excluding IHCA patients who undergo CA during a coronary procedure, the diagnosis is otherwise presumptive, and the decision to perform a high-risk procedure on these patients should be weighted.

Finally, considering the global derangement of coagulation system after CA and the high risk of bleeding invariably associated to ECMO (33,36), how is the balance of risks and benefits regarding the need for fibrinolysis for PE or anticoagulation after coronary stenting?

Last but not least, what are we doing all this work for? In this scenario, ethical problems should be addressed (37) and, as often happens, the technical progress went faster and surprised us ethically unprepared to deal with this issue, acknowledging the value of life and that our thoughts should be kept to a minimum when the clock is faster than our mind.

Traditionally, the considered outcomes of ECPR are death, neurological damage and multiorgan failure despite successful resuscitation. From our standpoint, other possible scenarios can be depicted. The first one is that patients after ECPR evolve to brain death, and the end-organs perfusion ensured by ECMO can make these patients suitable for organ donation (11), when cardiac death without extracorporeal support does not lead for candidacy. The second question is that a patient neurologically intact, in whom cardiac recovery does not take place, may become candidate to heart transplantation (HTx) or durable MCS, like LV assist device (LVAD) or total artificial heart (TAH).

Therefore, the possibility of the consideration of a composite outcome (38) should be evaluated: survival, survival with a good neurological performance, organ donation, bridge to durable MCS or HTx.

In conclusion, ECPR has demonstrated in many retrospective studies its superiority on conventional CPR in the treatment of refractory cardiac arrest. Further studies probably will increase our knowledge but we doubt that randomised controlled trials (RCT) will straighten the question out.

This situation is analogue to MCS use in cardiogenic shock, where the organisation of a RCT on a life-saving technique is ethically unacceptable, beyond the well-known statistical obstacles in the attainment of a sample size sufficient to infer on mortality (39). Therefore, from our point of view, an increase of our knowledge could be obtained only through a clear definition of ECPR and related questions, allowing for a correct interpretation of our present and future data.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Mozaffarian D, Benjamin EJ, Go AS, et al. Heart disease and stroke statistics--2015 update: a report from the American Heart Association. Circulation 2015;131:e29-322.
2. Mattox KL, Beall AC. Resuscitation of the moribund patient using portable cardiopulmonary bypass. Ann Thorac Surg 1976;22:436-42.
3. Soar J, Nolan JP, Böttiger BW, et al. European Resuscitation Council Guidelines for Resuscitation 2015. Section 3. Adult advanced life support. Resuscitation 2015;95:100-47.
4. ELSO ECPR Supplement to the ELSO General Guidelines Extracorporeal Life Support Organization (ELSO) Guidelines for ECPR Cases. 2013. Available online: https://www.elso.org/Portals/0/IGD/Archive/FileManager/6713186745cusersshyerdocumentselsoguidelinesforecprcases1.3.pdf
5. Link MS, Berkow LC, Kudenchuk PJ, et al. Part 7: Adult Advanced Cardiovascular Life Support. Circulation 2015;132:S444-64.
6. Dennis M, McCanny P, D'Souza M, et al. Extracorporeal cardiopulmonary resuscitation for refractory cardiac arrest: A multicentre experience. Int J Cardiol 2017;231:131-6.
7. Fjølner J, Greisen J, Jørgensen MRS, et al. Extracorporeal cardiopulmonary resuscitation after out-of-hospital cardiac arrest in a Danish health region. Acta Anaesthesiol Scand 2017;61:176-85.
8. Ha TS, Yang JH, Cho YH, et al. Clinical outcomes after rescue extracorporeal cardiopulmonary resuscitation for out-of-hospital cardiac arrest. Emerg Med J 2017;34:107-11.
9. Spangenberg T, Meincke F, Brooks S, et al. "Shock and Go?" extracorporeal cardio-pulmonary resuscitation in the golden-hour of ROSC. Catheter Cardiovasc Interv 2016;88:691-6.
10. Mazzeffi MA, Sanchez PG, Herr D, et al. Outcomes of extracorporeal cardiopulmonary resuscitation for refractory cardiac arrest in adult cardiac surgery patients. J Thorac Cardiovasc Surg 2016;152:1133-9.
11. Ortega-Deballon I, Hornby L, Shemie SD, et al. Extracorporeal resuscitation for refractory out-of-hospital cardiac arrest in adults: A systematic review of international practices and outcomes. Resuscitation 2016;101:12-20.
12. Richardson AS, Schmidt M, Bailey M, et al. ECMO Cardio-Pulmonary Resuscitation (ECPR), trends in survival from an international multicentre cohort study over 12-years. Resuscitation 2017;112:34-40.
13. ELSO. ECLS Registry Report: International Summary. 2017. Available online: https://www.elso.org/Registry/Statistics.aspx
14. Steg PG, James SK, Atar D, et al. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur Heart J 2012;33:2569-619.
15. O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013;61:e78-140.
16. Schmidt M, Burrell A, Roberts L, et al. Predicting survival after ECMO for refractory cardiogenic shock: The survival after veno-arterial-ECMO (SAVE)-score. Eur Heart J 2015;36:2246-56.
17. Kim KI, Lee HS, Kim HS, et al. The pre-ECMO simplified acute physiology score II as a predictor for mortality in patients with initiation ECMO support at the emergency department for acute circulatory and/or respiratory failure: a retrospective study. Scand J Trauma Resusc Emerg Med 2015;23:59.
18. Muller G, Flecher E, Lebreton G, et al. The ENCOURAGE mortality risk score and analysis of long-term outcomes after VA-ECMO for acute myocardial infarction with cardiogenic shock. Intensive Care Med 2016;42:370-8.
19. Goldberger ZD, Chan PS, Berg RA, et al. Duration of resuscitation efforts and survival after in-hospital cardiac arrest: an observational study. Lancet 2012;380:1473-81.
20. Wibrandt I, Norsted K, Schmidt H, et al. Predictors for outcome among cardiac arrest patients: the importance of initial cardiac arrest rhythm versus time to return of spontaneous circulation, a retrospective cohort study. BMC Emerg Med 2015;15:3.
21. Levine RL, Wayne MA, Miller CC. End-tidal carbon dioxide and outcome of out-of-hospital cardiac arrest. N Engl J Med 1997;337:301-6.
22. Debaty G, Babaz V, Durand M, et al. Prognostic factors

for extracorporeal cardiopulmonary resuscitation recipients following out-of-hospital refractory cardiac arrest. A systematic review and meta-analysis. Resuscitation 2017;112:1-10.
23. Anselmi A, Flécher E, Corbineau H, et al. Survival and quality of life after extracorporeal life support for refractory cardiac arrest: A case series. J Thorac Cardiovasc Surg 2015;150:947-54.
24. Binks A, Nolan JP. Post-cardiac arrest syndrome. Minerva Anestesiol 2010;76:362-8.
25. Callaway CW, Donnino MW, Fink EL, et al. Part 8: Post–Cardiac Arrest Care. Circulation 2015;132:S465-82.
26. Soleimani B, Pae WE. Management of left ventricular distension during peripheral extracorporeal membrane oxygenation for cardiogenic shock. Perfusion 2012;27:326-31.
27. Rupprecht L, Flörchinger B, Schopka S, et al. Cardiac decompression on extracorporeal life support: a review and discussion of the literature. ASAIO J 2013;59:547-53.
28. Pappalardo F, Montisci A. Veno-arterial extracorporeal membrane oxygenation (VA ECMO) in postcardiotomy cardiogenic shock: how much pump flow is enough? J Thorac Dis 2016;8:E1444-8.
29. Cheng A, Swartz MF, Massey HT. Impella to unload the left ventricle during peripheral extracorporeal membrane oxygenation. ASAIO J 2013;59:533-6.
30. Pieri M, Contri R, Winterton D, et al. The contemporary role of Impella in a comprehensive mechanical circulatory support program: a single institutional experience. BMC Cardiovasc Disord 2015;15:126.
31. Pappalardo F, Schulte C, Pieri M, et al. Concomitant implantation of Impella ® on top of veno-arterial extracorporeal membrane oxygenation may improve survival of patients with cardiogenic shock. Eur J Heart Fail 2017;19:404-12.
32. Adrie C, Monchi M, Laurent I, et al. Coagulopathy after successful cardiopulmonary resuscitation following cardiac arrest: Implication of the protein C anticoagulant pathway. J Am Coll Cardiol 2005;46:21-8.
33. Kim J, Kim K, Lee JH, et al. Prognostic implication of initial coagulopathy in out-of-hospital cardiac arrest. Resuscitation. Resuscitation 2013;84:48-53.
34. Konstantinides SV, Torbicki A, Agnelli G, et al. 2014 ESC guidelines on the diagnosis and management of acute pulmonary embolism. Eur Heart J 2014;35:3033-69, 3069a-k.
35. Kuroki N, Abe D, Iwama T, et al. Association between delay to coronary reperfusion and outcome in patients with acute coronary syndrome undergoing extracorporeal cardiopulmonary resuscitation. Resuscitation 2017;114:1-6.
36. Cheng R, Hachamovitch R, Kittleson M, et al. Complications of extracorporeal membrane oxygenation for treatment of cardiogenic shock and cardiac arrest: a meta-analysis of 1,866 adult patients. Ann Thorac Surg 2014;97:610-6.
37. Ocegueda-Pacheco C, Varon J. ECPR: Are we ready for primetime? Resuscitation 2016;103:A6-7.
38. Maj G, De Bonis M, Pieri M, et al. Extracorporeal life support for refractory cardiac arrest: what is a good outcome? Intensive Care Med 2012;38:2083-5.
39. Thiele H, Allam B, Chatellier G, et al. Shock in acute myocardial infarction: The Cape Horn for trials? Eur Heart J 2010;31:1828-35.

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