ESC European Society of Cardiology

European Heart Journal (2018) **39**, 4205–4207
doi:10.1093/eurheartj/ehy507

EDITORIAL

Extracorporeal cardiopulmonary support in acute high-risk pulmonary embolism: still waiting for solid evidence

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Online publish-ahead-of-print 19 September 2018

This editorial refers to 'Outcomes after extracorporeal membrane oxygenation for the treatment of high-risk pulmonary embolism: a multicentre series of 52 cases'†, by N. Meneveau *et al.*, on page 4196.

Acute pulmonary embolism

Arterial and venous thrombo-embolic conditions are estimated to account for one in four deaths worldwide and are the leading cause of overall mortality.[1] Venous thrombo-embolism (VTE) includes deep-vein thrombosis and acute pulmonary embolism (PE) whose combined incidence rate is variable from 115 to 269 cases and with mortality rates from 9.4 to 32.3 cases per 100 000 people.[1] Despite the fact that both the incidence and mortality rates for VTE are decreasing in developed countries, the management of specific patient subsets such as those with high-risk PE is still challenging.[2,3] According to the 2014 European Society of Cardiology (ESC) PE guidelines,[3] high-risk PE is defined by cardiac arrest, or persistent hypotension (i.e. systolic blood pressure < 90 mmHg or a systolic pressure drop by 40 mmHg, for >15 min, if not caused by new-onset arrhythmia, hypovolaemia, or sepsis) accompanied by signs of end-organ hypoperfusion. High-risk PE is a medical emergency; it accounts for ~5% of all acute PE cases, and hospital mortality ranges from 15% to 50% according to specific patient features and treatment strategies.[4] In addition, non-hypotensive patients with acute PE and designated at intermediate risk according to clinical variables, myocardial injury biomarkers, and right ventricular dysfunction deserve intensive monitoring due to possible progression to advanced right heart failure and high-risk status despite initial treatment strategies.[2–4]

The initial management of high-risk PE patients, in addition to anticoagulation, includes haemodynamic and respiratory support by cautious volume expansion, diuretic treatment, pharmacological inotropic therapy, and oxygen administration.[3] Interestingly, the 2014 ESC PE guidelines also report that 'experimental evidence suggests that extracorporeal cardiopulmonary support can be an effective procedure in massive PE' based on case reports and patients series.[3] The supportive therapy will bridge the patient to the cornerstone of the management of high-risk PE patients, which is reperfusion therapy. Reperfusion includes full-dose systemic thrombolysis, surgical pulmonary embolectomy (in the case of contraindication or failure of thrombolysis), and percutaneous catheter-directed treatments (in the case of unavailability of surgical embolectomy).

The study of Meneveau *et al.*[5] published in the current issue of the *European Heart Journal* provides useful information on the potential role of extracorporeal membrane oxygenation (ECMO) for the supportive treatment of high-risk PE patients.

Extracorporeal membrane oxygenation

ECMO is a rapidly growing procedure for both respiratory and cardiac failure in adult patients.[6] Relevant advances in technology, have made ECMO devices easier to implement, safer, and more effective.[7] However, the increased use of ECMO and the expanded availability of ECMO-related literature have still not provided sufficient evidence in different aspects of this procedure including indications, appropriateness in the individual patients, thresholds for initiation, type of ECMO to implement, duration, and weaning procedures.

ECMO is a circuit that oxygenates and removes carbon dioxide from blood through an extracorporeal gas exchange device constituted by a semi-permeable membrane that separates a blood compartment from a gas compartment, allowing only gas molecules to diffuse between compartments. Special cannulas for blood drainage and reinfusion are positioned in central vessels. An external pump

The opinions expressed in this article are not necessarily those of the Editors of the *European Heart Journal* or of the European Society of Cardiology.

† doi:10.1093/eurheartj/ehy464.

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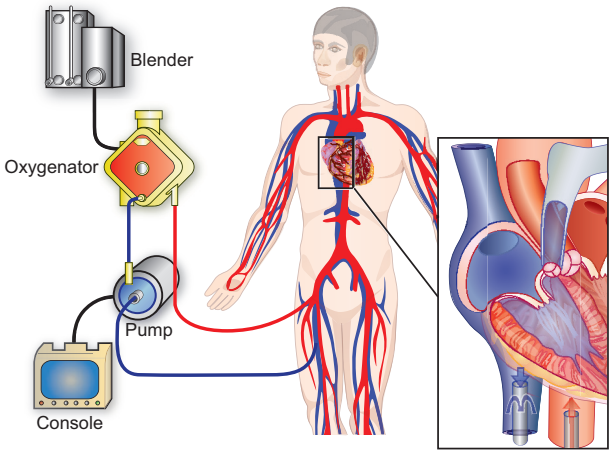

Potential indications for Venous-Arterial extracorporeal membrane oxygenation in case of Cardiac Failure

Myocardial infarction–associated cardiogenic shock
Myocarditis-associated cardiogenic shock
Post-cardiotomy cardiogenic shock
Bridge to ventricular assist devices implantation
Prevention of acute right ventricular failure after left ventricular assist devices implantation
Bridge to heart transplantation
Primary graft failure after heart transplantation
Pulmonary hypertension and acute or decompensated right heart failure
High-risk acute pulmonary embolism (supportive)?
Extracorporeal cardiopulmonary resuscitation
Sepsis-associated cardiac failure

Take home figure Schematic representation of veno-arterial extracorporeal membrane oxygenation (ECMO): venous blood is drained from a cannula inserted through the femoral vein into the inferior vena cava and oxygenated blood is reinfused by a cannula inserted through the femoral artery into the thoracic descending aorta. According with the level of cardiac function, the location of the border between antegrade blood flow and retrograde blood flow from the aortic cannula will vary, and the reinfused oxygenated blood may not reach the cerebral and coronary vascular beds.

provides the dynamic force to drain the deoxygenated blood, to pass it through the membrane oxygenator, and to reinfuse it back to the patient. According to the central vessels engaged by the drainage and reinfusion cannulas, ECMO is defined as veno-venous or veno-arterial: veno-venous ECMO provides a gas exchange function[8] only, while veno-arterial ECMO provides both gas exchange and circulatory support (*Take home figure*).[9]

Veno-venous ECMO is mainly indicated in cases of severe respiratory failure and can be configured with two distinct access points or using single cannulas with two lumens inserted typically into an internal jugular vein which can achieve both drainage and reinfusion.[7] Indications of veno-venous ECMO for severe respiratory failure, when gas exchange is refractory to conventional ventilation, include acute respiratory distress syndrome, acute hypercapnic respiratory failure, bridge to lung transplantation, and primary graft dysfunction post-lung transplantation.[7]

Veno-arterial ECMO is usually indicated in cases with severe impairment of cardiac function, and the preferred approach includes femoral venous drainage and femoral arterial reinfusion. However, this strategy may increase the left ventricular afterload and may limit the amount of well oxygenated blood reaching the aortic arch and perfusing the coronary and cerebral circulations. These drawbacks are particularly relevant in cases of concomitant impaired lung gas exchange and delivery of deoxygenated blood to the aortic arch. Arterial reinfusion sites closer to the aortic arch (e.g. the subclavian arteries) may limit this problem.[10] Indications for veno-arterial ECMO in cardiopulmonary diseases include the following conditions (*Take home figure*): myocardial infarction-associated cardiogenic shock, myocarditis-associated cardiogenic shock, post-cardiotomy cardiogenic shock, bridge to ventricular assist devices (VAD) implantation, prevention of acute right ventricular failure after left VAD implantation, bridge to heart transplantation, primary graft failure after heart transplantation, pulmonary hypertension and acute or decompensated right heart failure, high-risk acute pulmonary embolism, extracorporeal cardiopulmonary resuscitation, and sepsis-associated cardiac failure.[9]

Veno-arterial ECMO for the supportive treatment of high-risk pulmonary embolism patients

Some patients with acute high-risk PE remain clinically unstable despite the initial supportive therapy and may require additional measures either before, during, or after reperfusion treatments and in cases with no reperfusion strategies. Until recently, case reports and small case series have supported the role of veno-arterial ECMO to improve the cardiopulmonary conditions of these unstable subjects.[11]

Meneveau *et al.*[5] report a series of 180 high-risk PE patients in a multicentre, retrospective and observational study. A total of 128 patients were treated without ECMO and their 30-day mortality was 43% as compared with 61.5% in those treated with ECMO (P = 0.008), who had, as expected, a more severe presentation. Among patients with ECMO, the 30-day mortality was 77.7% in those without a reperfusion strategy, 76.5% in those with associated thrombolysis, and 29.4% when ECMO was performed after surgical embolectomy (P = 0.008). Of note, among patients with ECMO, 38.5% had an in-hospital major bleeding event, without a significant difference across groups. The authors conclude that ECMO in patients with failed fibrinolysis and in those with no reperfusion strategies seems to be associated with a particularly unfavourable prognosis. ECMO does not appear justified as a stand-alone treatment strategy in PE patients, but shows promise as a complement to surgical embolectomy.

The interpretation of the results of this important study requires the analysis of the relevant limitations, which the authors have correctly discussed. The retrospective nature of the study has not

allowed uniform decision-making about the treatment strategies adopted, including ECMO.

Therefore, the treated groups are not homogeneous, and any statistics should be regarded with caution. Nevertheless, the reduced mortality observed in patients with high-risk PE and treated with surgical embolectomy (with supportive post-operative ECMO) represents a relevant finding in favour of the surgical approach. In this case, the exact role of ECMO in achieving these favourable results is not clear without a comparative non-ECMO surgical group.

The most relevant finding of this study is the apparent lack of efficacy of veno-arterial ECMO in the majority of high-risk PE patients and a potential for a detrimental effect due to major bleeding events observed in 38.5% of ECMO cases. This information will probably be captured in the updated version of the ESC PE guidelines, which will be available in the summer of 2019.

Conflict of interest: none declared.

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