Editorial Commentary

# Autopsy and clinical discrepancies in patients undergoing extracorporeal membrane oxygenation: a case series—a step towards understanding "Why"?

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Veno-arterial extracorporeal membranous oxygenation (VA-ECMO) is a form of temporary mechanical circulatory support that is used as a salvage technique in cardiac arrest and cardiogenic shock. The setting up of an ECMO is often a difficult decision that is taken in an emergency environment, in hemodynamically unstable patients. Despite all advances that veno-arterial ECMO has witnessed over the past 50 years (1), its related mortality is still very high. Referring to the Extracorporeal Life Support Organization (ELSO) registry, VA-ECMO cardiac patients have overall survival to discharge of only 43% (2).

These low survival rates drive us to investigate why more than half of them die, in order to better understand and ameliorate the management of patients under ECMO. In 2013, Zangrillo and colleagues have published a meta-analysis focusing on outcomes and complications of ECMO in adult patients in peer-reviewed studies. The survival rate was 46% (3). Their work also shed a light on the most common complications under ECMO; renal failure requiring continuous veno-venous hemofiltration (occurring in 52%), bacterial pneumonia (33%), any bleeding (33%), oxygenator dysfunction requiring replacement (29%), sepsis (26%), hemolysis (18%), liver dysfunction (16%), leg ischemia (10%), venous thrombosis (10%), central nervous system complications (8%), gastrointestinal bleeding (7%), aspiration pneumonia (5%), and disseminated intravascular coagulation (5%).

The role of autopsy after cardiac surgery in discovering clinically occult lesions has been demonstrated in many studies. In a series of 147 autopsies post cardiac surgery, Zehr and colleagues highlighted that autopsy found more than 20% of discrepancies compared to premotum clinical impression (4). Another is that of Němec and colleagues who analyzed 158 autopsied patients post cardiac surgery according to Goldman criteria, and found that missed major diagnosis (class I and II) was found in 21 patients (13.3%) (5). Rastan and colleagues demonstrated a discrepancy rate of 23.1% in a series of 468 autopsies post cardiac surgery, clinically unrecognized postoperative complications were found in 364 cases (77.8%) (6). Thus despite the decline in its use (7) notably in Europe nowadays, autopsy remains an essential tool in understanding and assessing the perioperative course.

This tool was used as well to assess discrepancies between premortem and postmortem diagnosis in patients under ECMO. Blanco and colleagues found a rate of 53.7% of major discrepancies in a series of 54 autopsies that were performed in 139 pediatric no survivors who required ECMO support in the pediatric and cardiac ICU (8).

Rastan and colleagues followed their first work by a second one investigating discrepancies in patients after post cardiotomy ECMO circulatory support (9). Clinically unrecognized postoperative complications were found in 59 patients (75.6%) without classifying their degrees, many of

which are thromboembolic events that were not diagnosed by premortem clinical evaluation.

Regarding this work, Jia and colleagues (10) performed a retrospective analysis of 19 patients who mainly underwent VA-ECMOs (18/19 patients); also referred as extracorporeal life support (ECLS). One patient had veno-venous ECMO (VV-ECMO) for common acquired pneumoniae, this technique is used for refractory respiratory failure.

The authors found clinically unrecognized findings on autopsy in all patients, of which more than half of the discrepancies (56.6%) found at autopsy were major (grade I/II) according to modified Goldman criteria (11). The main one being clinically undiagnosed myocardial infarction.

We do realize that the evaluation of these patients, who are often sedated, is very challenging. Troponins are usually high after cardiac surgery, rendering their interpretation sometimes difficult. And ultrasonography usually shows a 'rested' heart; which remains one of the goals of ECMO therapy.

The authors also found an underestimation of neurological complications in ECMO patients. The complex context of the patients' presentation and possible initial deep sedation may make it difficult to detect concomitant neurological conditions or complications. Also, one must not forget the 'practical' difficulties that we all face when it comes to transferring these patients outside the ICU, to have an MRI or a CT scan for e.g.

These findings correlate with earlier reports published in the literature. We'd like to highlight the prospective study of Mateen and colleagues (12) that found neurological complications in 50% of the patients receiving VA-ECMO as a last resort life support option. Nine of 10 brains studied at autopsy demonstrated hypoxic-ischemic and hemorrhagic lesions of vascular origin although that diagnosis was rarely clinically made.

A more comprehensive retrospective observational study by Le Guennec and colleagues (13) of 878 VA-ECMO-treated patients, found that 65 (7.4%) developed an ECMO-related brain injury: 42 (5.3%) ischemic strokes and 20 (2.8%) intracranial bleeding.

The rapid identification of risk factors for neurological complications, their prevention and treatment in early specific charge appear essential in order to improve the prognosis in these patients.

In fact, approximately 1% of adult patients who undergo cardiac surgery develop post-cardiotomy cardiogenic shock (PCCS) and require mechanical circulatory support beyond the conventional medical or mechanical treatments. In-hospital survival ranged from 24.8% to 52% (14).

In another recent meta-analysis of VA-ECMO in refractory (PCCS) by Khorsandi and colleagues showed that survival to discharge rate was only 30.8% under such scenarios (15).

Most of the VA-ECMO implantations (13 patients) were performed during cardiac surgical procedures—11 were post cardiopulmonary bypass (PCB), 2 were post coronary artery bypass grafting surgery (CABG). In these situations, the main cause of VA-ECMO implantation is failed weaning from cardiopulmonary bypass. It would have been interesting to give more details about the type surgery undergone by these 13 patients. It is obvious that the duration of aortic cross clamping, the type and the technique of cardioplegia might influence the occurrence of myocardial ischemia, and ventricular remodeling, which were found at autopsy but not clinically.

In the article, 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.

Central VA-ECMOs are often implanted in the operating room by sternotomy and opening of the pericardial sac. This invasive method allows the operator to assess any myocardial or respiratory lesions. It can also be assumed that the conditions under which the ECMO is implanted in the operating room allow the health care team to ensure a high level of monitoring of vital parameters such as blood pressure, continuous ECG, oxygen saturation monitoring and possibly pulmonary arterial pressure.

In contrast, peripheral VA-ECMOs are implanted in a life-threatening emergency situation. Under such circumstances cardiac, neurological or mesenteric damages prior to ECMO implantation could be poorly documented.

In this study 4 central ECMO were converted to peripheral and 1 peripheral ECMO was converted to central. Switching from peripheral to central is often done when ECMO related malperfusion syndrome or limb ischemia is detected. On the other hand, switching from central to peripheral cannulation can be due to major bleeding, or the need for patient awakening.

The authors do not specify the causes that led to the change in the type of cannulation, but were able to define

 

2 subgroups (converted *vs.* peripheral VA-ECMOs) where discrepancies in the peripheral ones were statistically more significant than central cannulation. Axillary *vs.* femoral EMCOs were not compared.

This is the first report in favor of central ECMOs. A recent meta-analysis by Raffa and colleagues showed no statistical differences between peripheral and central VA-ECMO with regard to cerebrovascular events, limb complications, or sepsis rates (16).

In peripheral retrograde VA-ECMOs, a 'Watershed' zone where ECMO retrograde flow meets the left ventricle (LV) anterograde flow is usually formed somewhere between the aortic root and the diaphragm. The oxygenation of the blood coming out from the LV depends on the respiratory status of the patient. So, in case of a watershed zone in the ascending aorta in a patient with respiratory failure, the coronary arteries might be supplied for hours or days with insufficiently oxygenated blood. This might be one of the reasons behind the higher rate of discrepancies between central and peripheral ECMOs (17).

One of the biases in this study is the criteria upon which the coroner chose which patients to be autopsied. Apparently, that was affected by the medical team recommendations where the cause of the death wasn't clinically relevant. This could be the reason why only 19 patients out of the 53 ones who died under ECMO and referred to the coroner were eventually autopsied.

In conclusion, although this study is a monocentric, retrospective and observational one, it stands out because of its rarity in the medical literature. We congratulate the authors for the quality of their work. It underlines the importance of autopsy to assess the causes of death in patients undergoing ECMO. Myocardial ischemia and neurological lesions represented major complications clinically undiagnosed compromising thus the survival or the good clinical evolution of the patient. Total body CT scan and coronary artery angiogram can help to the diagnosis of complications, even if the transport of this type of patient is sometimes difficult. The high rate of these major discrepancies might mean that current clinical practice might be insufficient in such cases. Bigger series are needed to have more precise data, in order to develop our protocols, in the aim of enhancing quality and reducing overall morbidity and mortality.

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## Footnote

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

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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