Editorial

Neurologic complications during V-V extracorporeal membrane oxygenation: still counting…

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In the last ten years, extracorporeal membrane oxygenation (ECMO) has emerged as a life-saving technique, with an extraordinary progress and positive results (1).

However, the burden of ECMO-related complications in determining the patients' prognosis is still high (2,3).

Recently, Lorusso *et al*. assessed neurological complications in a large cohort (4,988 patients), whose data have been extracted from the database of Extracorporeal Life Support Organization (ELSO) (4); they considered only patients on veno-venous (V-V) ECMO.

The percentage of patients who suffered from neurological injury was 7.1%, including: intracranial hemorrhage (42.5%), brain death (23.5%), ischemic stroke (19.9%) and seizures (14.1%).

They found a strong effect of neurological injury on patients' mortality, identifying in pre-ECMO cardiac arrest, hyperbilirubinemia, need for continuous renal replacement therapy (CRRT) as factors associated to increased odds of neurological injury.

This paper adds further knowledge to the field of brain damage during ECMO, as the same author previously published a paper focused on neurologic complications of veno-arterial (V-A) ECMO (5).

Brain damage during Extracorporeal Life Support (ECLS) includes: neurocognitive impairment in survived patients, global brain injury and focal brain injury. Neurocognitive impairment in survivors from ARDS is of high concern, as many studies showed high rate of cognitive decline in this subset of patients (6-8). The authors, on the basis of correlation between hypoxemia and neurocognitive sequelae, hypothesized that the cerebral hypoxia might explain this phenomenon. These findings, rather than denying the role of permissive hypoxemia, reinforce the need for a real-time brain monitoring, in order to identify the subset of patients who cannot tolerate low values of oxygen levels.

For both V-V and V-A ECMO patients, neurologic injury is an awful complication, not only for the strong role in determining the possibility to survive, but even for the devastating impact on the quality of life of survived but neurologically injured patients.

Many factors affect the onset of neurological damage (hypoxia, hypoperfusion, embolism, ischemia-reperfusion syndrome, differential hypoxia, coagulation derangements, metabolic and electrolyte disturbances) but it is actually impossible to identify, at a given point of clinical course, which mechanism determines that injury, and this fact hampers an effective preventive strategy.

The first issue we have to face with is the real possibility to monitor the brain. Hemodynamic, coagulation, respiratory monitoring are widely employed in patients on ECLS, but the real-time assessment of brain function is far from being an established practice.

In other words, *we wait for neurological complications*,

rather than to timely identify them.

There are no recommendations about standard brain monitoring during ECMO and the common clinical scenario is the identification of clinical signs and then the radiologic demonstration of an established injury.

If we wait for complications, we are substantially unaware about the status of brain during the support. On clinical grounds, the identification of signs of focal damage in an awake patient is easy, whereas determination and quantification of hypoxic encephalopathy is more complex.

In this perspective, new tools have to be evaluated as a near infrared spectroscopy (NIRS) (9)and continuous electroencephalographic (EEG) monitoring (10), in order to provide comprehensive assessment of cerebral blood flow and metabolism.

The routine application of real time neuromonitoring systems could allow us to prompt detection of brain insults prior to the establishment of irreversible damage.

As a matter of fact, a recent review demonstrates that the number of studies on neuromonitoring during ECMO is quite low, with heterogeneous cohorts and, surprisingly, with few studies evaluating the most promising techniques, such as NIRS and continuous EEG or amplitude-integrated EEG (11).

The level of sedation of ECMO patients is also a reason of concern: the need for sedatives is related to the first phase of stabilization and sometimes to the clinical expression of delirium and encephalopathy in the following days. Indeed, the failure-to-use of monitoring systems of the depth of sedation could lead to oversedation and, by inducing burst suppression, might affect the patients' outcomes, thereby limiting the beneficial effect on cerebral metabolism (12). In fact, in cardiac surgery with the employment of extracorporeal circulation, the duration of intraoperative burst suppression has been related with long-term mortality (12) and increased long-term risk for stroke, supporting the hypothesis of a non-transient effect (13-17). In this perspective, the value of early awakening facilitated by full ECMO support is to be further recognized.

If we are blind to central nervous system injuries at their onset, the same happens for peripheral nervous system and muscle function. Detection of critical illness neuropathy and myopathy is often late. Its incidence and prevalence in ECMO patients has not been, to the best of our knowledge, object of specific studies, but probably as high as in other critically ill patients. Furthermore, peripheral lesions can hide the recognition of central lesions or even mimic them (is diagnosis of critical illness myopathy and neuropathy specific enough to rule out a concomitant global neurologic damage in determining the clinical picture?).

Looking at the prognostic factors of neurological damage, if the pre-ECMO cardiac arrest obviously correlates with brain damage, renal and hepatic failure account probably for the metabolic component of neurologic insults. Moreover, it should be emphasized that liver damage is emerging as the major determinant of mortality in ECMO patients (18).

At the end of the day, assessment of neurological performance in patients on ECMO should distinguish between hemodynamic and coagulative and metabolic events. In all fields, we do think that there is room for improvements but we also have to acknowledge that the primary disorder itself can be associated with neurological events. This is the case of Acute Respiratory Distress Syndrome (ARDS) secondary to viral pneumonia, which has been associated with focal brain injury irrespective to ECMO (19).

The paper from Lorusso *et al*. gives an intriguing piece of informations, as these adverse events are not related to the duration of ECMO support. This reinforces the concept that background disorders and comorbidities plays an essential role rather than ECMO-driven coagulopathy and anticoagulation need. If waiting for conventional evaluation, we might miss patients suffering since days for hypoxic encephalopathy.

Again, it is not just a matter of oxygen, but nevertheless we do have to monitor oxygen as a driver of organ function, namely the brain, in the decision making for these patients.

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Footnote

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

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