Spinal cord infarction during venoarterial-extracorporeal membrane oxygenation support

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Abstract
Spinal cord infarction (SCI) is a rare disease among central nervous system vascular diseases. Only a little is known about venoarterial extracorporeal membrane oxygenation (VA-ECMO)-related SCI. Retrospective observational study conducted, from 2006 to 2019, in a tertiary referral center on patients who developed VA-ECMO-related neurovascular complications, focusing on SCI. During this period, among the 1893 patients requiring VA-ECMO support, 112 (5.9%) developed an ECMO-related neurovascular injury: 65 (3.4%) ischemic strokes, 40 (2.1%) intracranial bleeding, one cerebral thrombophlebitis (0.05%) and 6 (0.3%) spinal cord infarction. Herein, we report a series of six patients with refractory cardiogenic shock or cardiac arrest receiving circulatory support with VA-ECMO who developed subsequent SCI during ECMO course, confirmed by spine MRI after ECMO withdrawal. All six patients had long-term neurological disabilities. VA-ECMO-related SCI is a rare but catastrophic complication. Its diagnosis is usually delayed due to sedation requirement and/or ICU acquired weakness after sedation withdrawal, leading to difficulties in monitoring their neurological status. Even if no specific treatment exist for SCI, its prompt diagnosis is mandatory, to prevent secondary spine insults of systemic origin. Based on these results, we suggest that daily sedation interruption and neurological exam of the lower limbs should be performed in all VA-ECMO patients. Large registries are mandatory to determine VA-ECMO-related SCI risk factor and potential therapy.

Keywords Extracorporeal membrane oxygenation · Intra-aortic balloon pump · Spinal cord infarct · Neurological examination · Sedation withdrawal · Secondary spine insults of systemic origin

Introduction
Spinal cord infarction (SCI) is a rare disease among central nervous system vascular diseases. Causes of SCI can be idiopathic (28%), degenerative spine disease (15.8%), associated to aortic pathology with or without surgery (15.8%), epidural anesthesia (1.8%), arteriosclerosis (33.3%), cardiac embolism (3.5%), or secondary to an acute systemic hypoperfusion (1.8%) [1]. It is often associated with severe prognosis and permanent sequelae [1, 2]. Coronary angiography and intra-aortic balloon pump (IABP) may cause SCI [3–5], as well as venoarterial-extracorporeal membrane oxygenation (VA-ECMO). This latter condition has only been reported as small case series; one patient with refractory cardiac arrest due to myopericarditis [6], and a short case series of three patients with a combination of VA-ECMO and IABP [7]. These SCI were documented by MRI after circulatory support withdrawal, and multifactorial origin was retained by the authors to explain the pathophysiological process that led to ischemia (hypoperfusion, vasoconstriction, thromboembolism of Adamkiewicz artery, etc.…). In this study, we retrospectively identified in our database six cases of SCI (documented by MRI) after VA-ECMO (+IABP) withdrawal, and discussed its potential risk factors. Characteristics of patients are resumed in Table 1.
Table 1  Patients’ characteristics at admission, during ICU stay and at follow-up

|                          | Case 1                   | Case 2                   | Case 3                   | Case 4                   | Case 5                   | Case 6                   |
|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| Age, years               | 35                       | 48                       | 56                       | 62                       | 43                       | 62                       |
| Sex                      | Male                     | Male                     | Male                     | Male                     | Male                     | Male                     |
| Premorbid condition      | Cocaine Tobacco          | Type II diabetes mellitus| Tobacco Coronary heart disease| Tobacco Ischemic dilated cardiomyopathy| None| Ischemic dilated cardiomyopathy |
| Reason for VA-ECMO       | Refractory cardiac arrest (cocaine-induced vasospasm) | Septic cardiomyopathy | Ischemic cardiogenic shock | Primary heart graft dysfunction | Ischemic cardiogenic shock | Cardiogenic shock |
| Pre-ECMO SAPS II score   | 64                       | 86                       | 84                       | 52                       | 85                       | 34                       |
| Pre-ECMO SOFA score      | 14                       | 17                       | 16                       | 16                       | 9                        | 10                       |
| Duration of VA-ECMO support, days | 4                       | 29                       | 2                        | 47                       | 4                        | 13                       |
| Survival to hospital discharge | Yes                   | Yes                      | Yes                      | No                       | Yes                      | Yes                      |
| ICU length of stay (days) | 90                      | 74                       | 6                        | 51                       | 9                        | 30                       |
| Organ support during ICU stay | Yes                  | Yes                      | No                       | Yes                      | Yes                      | No                       |
| Renal replacement therapy | Yes                     | Yes                      | No                       | Yes                      | Yes                      | No                       |
| Mechanical ventilation duration (days) | 78                     | 51                       | 3                        | 51                       | 8                        | 1                        |
| ECMO cannulation site    | Femoral                  | Femoral                  | Femoral                  | Femoral                  | Femoral                  | Femoral                  |
| ECMO flow rate at initiation (L/min) | 4.23                   | 3.9                      | 4                        | 3.8                      | 3.1                      | 4.1                      |
| IABP                     | No                       | No                       | No                       | No                       | Yes                      | Yes                      |
| Coronary angiography before SCI | Yes                  | Yes                      | Yes                      | Yes                      | No                       | No                       |
| Localization (artery)    | Radial                   | Femoral                  | Femoral                  | NK                       |                         |                          |
| Critical illness polyneuropathy at sedation withdrawal that could have delayed SCI diagnosis | Yes | Yes | No | Yes | No | No |
| Delay between awakening and SCI diagnosis (days) | 36 | 48 | 0 | 33 | 0 | NA* |
| Biology at ECMO start    | pH                       | 7.23                     | 7.26                     | 7.50                     | 7.20                     | 6.87                     | 7.63                     |
|                          | PaCO₂, mmHg              | 23.5                     | 31.8                     | 31.3                     | 33                       | 70                       | 31.8                     |
|                          | PaO₂, mmHg               | 375                      | 73                       | 68.8                     | 142                      | 40                       | 61.7                     |
|                          | Lactate, mmol/L          | 4.4                      | 9                        | 0.9                      | 12.5                     | 15                       | 1                        |
|                          | Platelets count, 10⁹/µL | 234                      | 45                       | 73                       | 260                      | 100                      | 51                       |
|                          | APTT (patient/reference) ratio | 1.9                 | 1.2                      | 1.7                      | 1.7                      | ND                       | 2.48                     |
Methods

We screened for VA-ECMO-related neurovascular complications a 13-year period (2006–2019) in the Intensive Care Unit (ICU) at La Pitié-Salpêtrière Hospital in Paris, France. During this period, among the 1893 patients requiring VA-ECMO support, 112 (5.9%) developed an ECMO-related neurovascular injury: 65 (3.4%) ischemic strokes, 40 (2.1%) intracranial bleeding, 1 cerebral thrombophlebitis (0.05%) and 6 (0.3%) spinal cord infarction.

Anticoagulation protocol, membrane oxygenator and its circuitry management are reported in the appendix (online supplement). Anticoagulation was performed according to this protocol in all patients. Patients were sedated with propofol infusion.

Case 1

A 35-year-old man presented with refractory cardiac arrest after cocaine consumption. VA-ECMO was inserted during chest compression (no- and low-flow duration of 0 and 45 min, respectively). Coronary angiography was normal. Patient’s cardiac condition improved rapidly, and VA-ECMO was removed on day 4. Since the patient required prolonged sedation, the first neurological assessment was performed on day 23. At that time, he was found to have a normal sensory examination, but suffered from ICU acquired weakness. Seven weeks later, motor strength improved at the upper limbs, but because of lower limbs weakness persistence, a spinal cord MRI (Fig. 1a, b) was performed, 55 days after VA-ECMO withdrawal. A longitudinal anterior high T2-weighted signal with owl-eyes sign extending from T1 to the conus medullaris was observed, consistent with anterior spinal artery infarction. After extubation, the patient was discharged from ICU at day 90. At 1-year follow-up, patient had to use wheelchair and to catheterize his own urinary tract to manage the neurogenic bladder.

Case 2

A 48-year-old man presented with septic shock and acute respiratory distress syndrome due to pneumococcal pneumonia. Echocardiography showed severe biventricular dysfunction, with left ventricular ejection fraction of 20%. He developed refractory cardiogenic shock, and VA-ECMO was placed. Coronary angiogram showed no abnormality, and diagnosis of septic cardiomyopathy was retained. Cardiac condition started to improve at day 4 and VA-ECMO was removed on day 7. A few minutes after VA-ECMO removal, the patient presented cardiac arrest. VA-ECMO was reimplanted. Patient was extubated on day 11 and suffered ICU acquired weakness. His cardiac condition slowly improved, and 1 month later, VA-ECMO was removed. Motor strength started to improve within the upper limbs, with persistence of lower limbs sensorimotor deficiency. Spinal cord MRI (Fig. 1c, d) was performed, which showed a longitudinally extensive anterior high T2-weighted signal extending from T9 to the conus medullaris, confirming SCI diagnosis. One-year follow-up showed no neurologic recovery.
Case 3

A 56-year-old man had refractory cardiac arrest complicating acute myocardial infarction. Implantation of VA-ECMO was performed during chest compression (no- and low-flow duration of 0 and 50 min, respectively). Coronary angiography showed occlusion of the circumflex and right coronary arteries, which were successfully stented. VA-ECMO was removed on day 2. After sedation withdrawal on day 3, patient was alert and weaned from mechanical ventilation. He displayed a sensorimotor impairment of the lower limbs. Spinal cord MRI (Fig. 1e, f) showed a T2-signal abnormality confined to anterior horns extending from T10 to the conus medullaris consistent with anterior spinal artery infarction. One-year follow-up showed no neurologic recovery.

Case 4

A 62-year-old man with medical history of ischemic dilated cardiomyopathy was admitted to ICU for cardiogenic shock. Despite optimal medical therapy, his condition worsened and he underwent heart transplantation few days later. Due to primary heart graft dysfunction and inability to wean off cardiopulmonary bypass during surgery, VA-ECMO was inserted. The patient received sedatives and the first neurological assessment was performed on day 11. He was alert but suffered from ICU acquired weakness. Patient’s cardiac condition progressively improved, and VA-ECMO was removed on day 47. One week later, he started to regain motor function, but only within the upper limbs, with lower limbs proprioceptive deficit. Spinal cord MRI (Fig. 1g, h) was performed 8 days after VA-ECMO withdrawal, showing a longitudinally extensive posterior intramedullary high T2-weighted signal extending from T6 to the conus medullaris. Ten days after VA-ECMO withdrawal, the patient suffered from a new Ventilator-associated pneumonia with septic shock, and died of refractory multiorgan failure.

Case 5

A 43-year-old man presented with acute myocardial infarction. Coronary angiography showed proximal left anterior descending artery occlusion, that was successfully stented. Because of refractory cardiogenic shock, VA-ECMO and IABP were inserted. Cardiac condition improved on day 3, and both VA-ECMO/IABP were removed on day 4. After sedation withdrawal on day 6, he was alert and weaned from mechanical ventilation. Neurological examination revealed weakness of the lower limbs. Spinal cord MRI (Fig. 1i, j) showed a longitudinally extensive anterior hyper T2-weighted signal within the conus medullaris. At 1-year follow-up, patient was moving in wheelchair.

Case 6

A 62-year-old man with medical history of ischemic dilated cardiomyopathy was admitted to the ICU for cardiogenic shock. Despite medical therapy, his condition worsened and VA-ECMO was inserted with concomitant IABP. Patient was scheduled for heart transplantation. Seven days after
VA-ECMO/IABP start, he had pain in the lower limb, with sensory abnormalities during neurological examination, but without any motor weakness. He underwent heart transplantation on day 16 after VA-ECMO/IABP initiation, but due to primary graft dysfunction and the inability to wean off cardiopulmonary bypass, VA-ECMO was left in place. On day 1 post heart transplantation, IABP was removed and mechanical ventilation was weaned. VA-ECMO was removed on day 19 (3 days after heart transplantation). Thirty-seven days after VA-ECMO withdrawal, since no neurological change was observed regarding the lower limbs sensory abnormalities, and a spinal cord MRI was performed (Fig. 1k, l). It showed a longitudinally extensive posterior T2-weighted signal abnormality extending from T12 to the conus medullaris. At 3-month follow-up, patient still had pain in the lower limbs.

Discussion

We described here the largest case series of VA-ECMO-related SCI patients. Medullary infarction is a rarely described complication of VA-ECMO support [8, 9], with only four cases in the literature. However, VA-ECMO was not the only risk factor for ischemic events in our patients; coronary angiography, IABP use and low cardiac output consecutive to heart failure/cardiac arrest may also be responsible for SCI. Thus, it is difficult to assess the respective impact of underlying disease(s) and VA-ECMO itself. However, ECMO might play a role, regarding the high rate of systemic thromboembolic events in this population [10].

SCI is usually suspected on clinical examination. As shown in four of our six cases, late awakening and severe critical illness polyneuropathy may delay its diagnosis. Because only awake patients with clinical symptoms who were explanted of their VA-ECMO underwent spine MRI, we perhaps may have missed some events in other patients. Indeed, as it is difficult to neurologically assess patients with severe disability after cardiac arrest-related brain injury, simultaneous SCI could have potentially remained unidentified in this population. Moreover, patients who died under VA-ECMO and remained sedated during their ICU stay might have been undiagnosed. Lastly, as shown with patient 6, atypical presentation with isolated sensory deficit can delay SCI diagnosis.

The pathogenesis of SCI following VA-ECMO remains unclear. Prolonged hypoperfusion can cause spinal cord ischemia [11]. Another mechanism described in autopsy reports is small arterioles occlusion by cholesterol or atheromatous emboli [4, 12, 13], that could results from aortic atheroma disruption and fragmentation during VA-ECMO/IABP implantation or coronary angiography, but also during withdrawal of the former, with subsequent occlusion of small vessels. As a matter of fact, this mechanism has been previously described in patients with IABP alone [13–16]. In our patients, SCI could have been consecutive to multiple injuries or different injury from one patient to another, such as mechanical trauma and/or arterial embolism of a spinal artery caused by the ECMO itself, coronary angiography or IABP, prolonged hypoperfusion and/or vasopressor use being precipitating, aggravating or triggering factors.

To the best of our knowledge, no large study evaluating SCI treatment has been published to date. However, prevention of secondary neurologic damage (i.e., hypotension, fever, etc.), antiplatelet therapy and steroids are usually given [17, 18]. Removal of the potential cause of SCI (VA-ECMO and/or IAPB), when possible, could be part of the treatment, as one case of neurological medullary improvement after IABP removal have been reported [19]. Finally, the most important issue is the rehabilitation program; for patient education, bladder management, and occupational therapy.

VA-ECMO-related SCI is a rare but catastrophic complication, with high rate of long-term neurological disabilities. Even if neurological examination is difficult in sedated patients or in patients with critical illness polyneuropathy, regular neurologic examinations of lower limbs should be performed for prompt SCI diagnosis and prevent secondary spine insults of systemic origin.

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Compliance with ethical standards

Conflict of interest The other authors have no conflicts of interest to declare in relationship with this manuscript.

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