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REPLY FROM AUTHORS: ATTEMPTING TO SOLVE THE PUZZLE—HOW TO UNVEIL THE TRUTH ABOUT THE ORIGIN OF STROKE IN POSTCARDIOTOMY EXTRACORPOREAL LIFE SUPPORT?

Reply to the Editor:

In our series of patients on postcardiotomy extracorporeal life support (ECLS), we described predominantly right hemispheric strokes in patients cannulated via the axillary artery. In accordance with our results, Grunfeld and colleagues shared their experience and stress the role of primary procedure in the likelihood of developing ECLS-related stroke. Furthermore, they described a case of innominate artery occlusion in a patient with axillary artery ECLS cannulation recovering cardiac function, shifting interest on the flow phenomena in the watershed zone during weaning, and possible relation to stroke.

Because patients on postcardiotomy ECLS are an especially complex subset of cardiac surgical patients, there are various possible sources for stroke. Mechanisms can be divided into 3 possibilities: (1) Strokes taking place during the primary procedure. These strokes may be diagnosed during ECLS but are not attributable to ECLS. (2) Stroke related to embolism from an intracardiac source occurring during ECLS—with varying likelihood for intracardiac thrombus formation depending on primary procedure, and potentially cannulation site-related flow patterns. (3) Thromboembolism from the circuit and/or cannulation site—it remains difficult to clearly distinguish the origin of stroke; whereas in certain cases it may seem rather clear, in others it might not.

Ohira and colleagues report an increased incidence of stroke associated with mitral valve replacement. We agree that the likelihood of intracardiac thrombus formation on ECLS is likely dependent on the primary procedure, and we included the primary procedure of all patients with stroke in our cohort in Table 1. It would be of interest whether, in the study by Ohira colleagues, ECLS was prolonged in patients undergoing mitral valve replacement or whether the greater stroke rate was independent of longer support durations, and whether ECLS duration was included in the multivariable analysis. As there is obviously more time for intracardiac thrombus formation to occur with increasing ECLS duration, this may support that these patients should be weaned off ECLS as soon as possible.

A considerable issue in axillary cannulation seems to be right hemispheric stroke diagnosed shortly after ECLS explantation, suggesting thromboembolism from the cannulation site at the time of decannulation as the most likely mechanism. This is a mutual finding in our study and the study of Ohira and colleagues, who report 5 cases of stroke to right middle cerebral artery territory after decannulation in patients with axillary arterial cannulation. In our experience, in some patients, even thrombotic appositions in the circuit or even device stop were described in advance of catastrophic neurologic events. This leads to the conclusion that great care must be taken at the time of decannulation, especially after a long run duration, as thrombus formation at the site of cannulation may have occurred.

We further hypothesize that in cases of hemorrhagic stroke, small subclinical embolic lesions in the brain, caused by embolism from the ECLS circuit or cannulation site, in combination with ECLS-related flow alterations might be a mechanism of hemorrhagic stroke.

We feel this topic deserves further attention, and investigations of flow characteristics in the cerebral circulation depending on cannulation sites and flow rates and possible influence of cannulation site location on likelihood of stroke from an intracardiac origin are warranted.

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TABLE 1. Characterization of all strokes (n = 48) with timing and clinical indication for CCT, preceding ECLS-related events, and possible causes, now including the type of initial surgery and preoperative left ventricular function

| Cannulation site group | Patient # | Timing of CCT                  | Indication for CCT | Hemorrhagic/Ischemic | mRS score at discharge | Likely cause of stroke | Primary procedure | Preoperative LVEF |
|-----------------------|-----------|--------------------------------|--------------------|----------------------|------------------------|------------------------|------------------|------------------|
| Axillary artery       | 1         | Respiratory weaning/after explant | Reduced vigilance  | Hemorrhagic          | 1                      | Unknown                | HTX              | Preoperative LVAD |
|                       | 2         | Respiratory weaning/after explant | Left-sided hemiplegia | Ischemic            | 4                      | ECLS                  | AVR + annular reconstruction (endocarditis) | 45               |
|                       | 3         | Respiratory weaning/after explant | Left-sided hemiparesis | Ischemic           | 4                      | ECLS                  | Ascending aortic aneurysm repair + CABG | 15               |
|                       | 4         | Respiratory weaning/after explant | coma                | Hemorrhagic          | 6                      | ECLS                  | AVR + MV repair      | 15               |
|                       | 5         | Directly after explant           | Sudden-onset fixed dilated pupils | Hemorrhagic      | 6                      | ECLS explant           | Bentall procedure   | 15               |
|                       | 6         | 2 days after explant             | Left-sided hemiplegia, decrease of right-sided near-infrared spectroscopy to 29% directly after ECLS explant | Ischemic          | 4                      | ECLS explant           | AVR + CABG + aortic arch repair | 60               |
|                       | 7         | Respiratory weaning/after explant | Reduced vigilance  | Ischemic            | 2                      | ECLS                  | AVR              | 25               |
|                       | 8         | Respiratory weaning/after explant | coma                | Ischemic            | 4                      | ECLS                  | AVR + MV repair + CABG | 25               |
|                       | 9         | After extubation                 | Paresis of right arm | Ischemic          | 2                      | ECLS or surgery related (type A aortic dissection) | Aortic dissection repair (aortic arch replacement) | 45               |
|                       | 10        | 2 weeks after ECLS explant, on regular ward before discharge | Visual field loss | Ischemic            | 1                      | Unknown/patient also had type A dissection | Aortic dissection repair (aortic reconstruction with patch + CABG) | 60               |
|                       | 11        | during ECLS run (day 6)          | Sudden onset fixed dilated pupils on day 6 during ECLS run | Hemorrhagic      | 6                      | ECLS                  | HTX              | Preoperative LVAD |
|                       | 12        | Respiratory weaning/after explant | Reduced vigilance  | Ischemic            | 1                      | Unknown, patient also underwent perioperative CPR | HTX              | Preoperative LVAD |
|                       | 13        | Respiratory weaning/after explant | Left-sided hemiplegia | Ischemic          | 4                      | Patient also had mechanical mitral valve thrombosis | MV replacement (thrombosed mechanical mitral valve) | 40               |
|                       | 14        | During ECLS run (day 3)          | Sudden onset anisocoria at day 3 of ECLS | Ischemic          | 6                      | ECLS                  | AVR + MV – replacement + tricuspid valve repair + maze | 30               |
|                       | 15        |                                 |                     |                      |                        |                       | AVR + CABG          | 50               |

(Continued)
| Cannulation site group | Patient # | Timing of CCT | Indication for CCT | Hemorrhagic/ischemic mRS score at discharge | Likely cause of stroke | Primary procedure | Preoperative LVEF |
|-----------------------|-----------|---------------|-------------------|---------------------------------|------------------------|------------------|-----------------|
| Respiratory weaning/ after explant | 16 | Respiratory weaning/ after explant | Coma, left-sided hemiplegia, embolectomy of right brachial artery after ECLS explant | Ischemic | 5 | ECLS related: CCT at beginning of ECLS normal, embolectomy right brachial artery after explant | MV repair + tricuspid valve repair | 25 |
| Respiratory weaning/ after explant | 17 | Respiratory weaning/ after explant | Tetraplegia and coma | Ischemic | 6 | Known left atrial thrombus and systemic embolism, also to left leg | AVR + MV replacement + CABG + MAZE | >50 |
| Respiratory weaning/ after explant | 18 | Respiratory weaning/ after explant | Unknown | Ischemic | 3 | Unknown | HTX | 15 |
| Before hospital discharge | 19 | Before hospital discharge | Visual field loss | Ischemic | 1 | Unknown, patient underwent concomitant right-sided carotid endarterectomy | AVR + CABG + carotid endarterectomy | 73 |
| During ECLS run (day 3) | 20 | During ECLS run (day 3) | Sudden onset fixed dilated pupils at day 3 of ECLS | Hemorrhagic | 6 | On ECLS | MV repair + TV repair | 60 |
| Respiratory weaning/ after explant | 21 | Respiratory weaning/ after explant | Hemiplegia | Ischemic | 4 | ECLS | AV + myectomy + annular augmentation | 60 |
| During ECLS run (day 4) | 22 | During ECLS run (day 4) | Sudden onset anisocoria on day 4 of ECLS | Hemorrhagic | 6 | On ECLS | Aortic dissection repair (Bentall procedure + aortic arch replacement) | 55 |
| Respiratory weaning/ after explant | 23 | Respiratory weaning/ after explant | NCSE | Ischemic | 5 | Unknown, also underwent CPR | MV replacement + CABG | Unknown |
| Respiratory weaning/ after explant | 24 | Respiratory weaning/ after explant | Aphasia, left-sided Hemiparesis | Ischemic | 3 | ECLS explanted because of device thrombosis despite adequate anticoagulation | Aortic dissection repair (ascending aortic replacement + CABG) | Unknown |
| Respiratory weaning/ after explant | 25 | Respiratory weaning/ after explant | Hemiplegia | Ischemic | 4 | ECLS, arterial cannula was changed due to thrombus formation | MV repair + CABG | 25 |
| During ECLS run | 26 | During ECLS run | Seizure | Ischemic | 2 | ECLS | AVR+ TV replacement + myectomy + LAA closure | 60 |

(Continued)
| Cannulation site group | Patient # | Timing of CCT | Indication for CCT | Hemorrhagic/ ischemic | mRS score at discharge | Likely cause of stroke | Primary procedure | Preoperative LVEF |
|-----------------------|-----------|---------------|--------------------|-----------------------|------------------------|-----------------------|-------------------|-----------------|
| 27 Respiratory weaning/ after explant | Reduced vigilance | Ischemic | 1 | Unknown | AVR + aortic root replacement (Freestyle) + CABG | 60 |
| 28 Respiratory weaning/ after explant | Left-sided hemiplegia and dysphagia | Ischemic | 4 | Patient had normal CCT 2 days before ECLS explant, large right sided ischemic stroke in CCT 3 days after ECLS explant | MV repair + CABG | 45 |
| 29 After arterial cannula change (same day) | Sudden onset anisocoria after cannula exchange | Hemorrhagic | 6 | Normal CCT 2 days before explant, onset of anisocoria after arterial cannula change due to thrombus formation | Bentall procedure | 45 |
| 30 Respiratory weaning/ after explant | Myoclonia | Ischemic | 5 | Unknown, potentially ECLS related | AVR+MV repair | 65 |
| 31 Respiratory weaning/ after explant | Reduced vigilance, positive Babinski right side | Ischemic | 4 | ECLS | MV repair + TV repair + LAA closure | 65 |
| 32 Directly after explant | fixed dilated pupils after explant, thrombus in arterial cannula | Ischemic | 6 | 2 days after explant, occlusion of the right internal carotid artery was diagnosed and patient underwent thrombectomy; however, patient developed a fatal stroke. Thrombotic material in the arterial cannula was noted at the time of explant | MV replacement + TV repair | 60 |
| 33 On ECLS (day 3) | Sudden onset fixed dilated pupils | Hemorrhagic | 6 | ECLS | AVR+CABG | 45 |
| 34 Respiratory weaning/ after explant | Coma | Ischemic | 6 | Unknown, 30 min CPR | MV repair + TV repair + CABG + LAA closure + maze | 60 |
| 35 During ECLS (day 5) | Seizure | Ischemic | 1 | ECLS | PV-replacement | 60 |
| 36 On ECLS (day 3), after revision for mediastinal bleeding | Sudden onset fixed dilated pupils | Hemorrhagic | 6 | Hypertensive phase during revision for bleeding; fixed unresponsive pupils after revision → CCT | HTX | Preoperative LVAD |

(Continued)
## TABLE 1. Continued

| Cannulation site group | Patient # | Timing of CCT | Indication for CCT | Hemorrhagic/ischemic | mRS score at discharge | Likely cause of stroke | Primary procedure | Preoperative LVEF |
|------------------------|-----------|---------------|--------------------|----------------------|------------------------|-----------------------|------------------|-----------------|
| 37 Respiratory weaning/after explant | Reduced vigilance and seizure | Ischemic | 3 | Unknown | HTX | Preoperative LVAD |
| 38 During ECLS run (day 24) | unknown | Ischemic | 6 | ECLS | Ventricular rupture repair | unknown |
| 39 Respiratory weaning/after explant | Hemiparesis and aphasia after extubation | Ischemic | 4 | ECLS | MV repair + TV repair + LAA closure + maze | 60 |
| 40 During ECLS (day 17) | Seizures, dilated pupils | Hemorrhagic | 6 | ECLS | MV repair + CABG | 15 |
| 41 Respiratory weaning/after explant | Unknown | Ischemic | 1 | Unknown, also had aortic dissection | Aortic dissection repair (Bentall + aortic arch repair) | 31-50 |

| Femoral artery | 1 Respiratory weaning/after explant | Reduced vigilance | Ischemic | 1 | ECLS | AVR+CABG | 25 |
| 2 Respiratory weaning/after explant | Reduced vigilance | Ischemic | 4 | Embolic? Patient also underwent CPR before implant | MV repair + CABG | 55 |
| 3 Respiratory weaning/after explant | Unknown | Ischemic | 1 | Watershed infarct, CPR before implant | Chronic type a dissection repair (ascending aortic replacement) | 60 |
| 4 During ECLS run (day 6) | Anisocoria | Ischemic | 6 | On ECLS, cannulation site was changed from femoral to axillary artery 4 days before the event | CABG | 55 |
| 5 Respiratory weaning/after explant | Hemiparesis | Ischemic | 3 | Unknown, perioperative CPR | CABG | 16-30 |
| 6 On ECLS (day 8) | Anisocoria during ECLS run | Ischemic | 6 | ECLS, cannulation site was changed from femoral to axillary artery on day 4 after implant | Bentall procedure | 31-50 |
| 7 On ECLS (day 7) | Evaluation for durable left ventricular assist device implantation | Ischemic | 6 | Mechanical mitral valve thrombosis | AVR+MV replacement | 49 |

Table adopted from Table E6 of the original manuscript. CCT, Cerebral computed tomography; ECLS, extracorporeal life support; mRS, modified Rankin Scale; LVEF, left ventricular ejection fraction; HTX, heart transplantation; LVAD, left ventricular assist device; AVR, aortic valve replacement; CABG, coronary artery bypass grafting; MV, mitral valve; CPR, cardiopulmonary resuscitation; TV, tricuspid valve; NCSE, nonconvulsive status epilepticus; PV, pulmonary valve; LAA, left atrial appendage.
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