Determining Brain Death After Therapeutic Hypothermia on Nonpulsatile Continuous-Flow Mechanical Circulatory Support Devices

To the Editor:

Goswami et al\(^1\) described 2 cases of determining brain death (BD) after therapeutic hypothermia (TH) in patients supported on nonpulsatile continuous-flow (NPCF) systemic circulation and extracorporeal membrane oxygenation. We comment on TH, sedatives, and NPCF as confounders for reversible inhibition of the central nervous system (CNS) and BD findings.

Goswami et al\(^1\) performed BD examination at 24 to 48 hours after discontinuing TH and sedatives. TH has unpredictable effects on the pharmacokinetics and pharmacodynamics of drugs acting on the central \(\gamma\)-aminobutyric acid (GABA) receptors (eg, benzodiazepines, barbiturates, propofol, and baclofen). These drugs potentiate the GABA inhibitory effects on neurotransmission and depress the CNS-producing reversible neurologic findings. Reversible BD findings have been reported several days after discontinuing TH and sedatives.\(^2,4\) Brainstem reflexes returned 96 hours after discontinuing propofol, which could not be predicted from the kinetics of drug clearance.\(^4\) Baclofen induced a brain-death-like syndrome that was reversed after 5 to 7 days, which exceeded the recommended waiting time of 5 times the drug’s half-life.\(^5\) Plasma clearance of the drug might not exclude persistent inhibitory GABA action on the CNS because the drug concentration in brain tissue is not routinely measured.

Goswami et al\(^1\) performed 2 BD examinations at a 6-hour interval.\(^1\) The optimal timing of the second BD examination after TH is unknown. Joffe et al\(^2\) reviewed 12 cases of adult and pediatric cases with BD findings that reversed between 12 hours to several days after the first BD examination.\(^2\) Confounding factors were not recognized before the first BD examination (eg, sedatives and TH) and could explain reversible brain death findings in these cases.\(^2,4,6\) Delaying the second BD examination for several days could eliminate the residual pharmacologic CNS inhibition and reversibility of neurologic findings.\(^2,4\)

Goswami et al\(^1\) reduced the sweep gas flow on extracorporeal membrane oxygenation raising acutely the arterial carbon dioxide concentration.\(^1\) Inducing acute arterial hypercapnia can have detrimental effects on cerebral perfusion and worsen pre-existing acute neurologic injuries.\(^8,9\) Performing the apnea test soon after rewarming to normothermia can result in a false-positive test and abolish any favorable neurologic outcome of TH. Furthermore, the hypercapnic hypoxic apnea test does not verify irreversible cessation of the medullary respiratory rhythm centers.\(^8\)

Goswami et al\(^1\) determined BD according to the 2010 American Academy of Neurology (AAN) guideline.\(^1\) The authors claimed that BD determination complied with the Uniform Determination of Death Act of “irreversible cessation of all functions of the whole brain and the brainstem.”\(^11\) However, the AAN assigned the evidence level “U” (ie, insufficient or conflicting data) to several critical elements in BD determination.\(^10\) Wijdicks et al (reply from authors)\(^11\) have argued that not all neurologic functions have ceased when determining BD with the AAN guideline because “the gold standard is not the UDDA.” A normal or minimally injured brainstem was reported at autopsy in 60% of donors who clinically had absent brainstem reflexes.\(^12\) The predictive accuracy of absent brainstem reflexes in confirming irreversible brainstem injury is unknown.

Several studies recommended against making irreversible life-ending decisions based on the 72-hour neurologic examination after TH because of potential errors in neuroprognostication.\(^13,15\) Confounding factors for reversible neurologic findings including brain death have not been characterized fully in the medical literature.\(^6,7\) This knowledge gap complicates the ability of predicting with clinical certainty the short-term and long-term neurologic disability.

Goswami et al\(^1\) did not comment on whether NPCF could have altered cerebral perfusion, which, if so, would constitute an additional confounding factor in determining BD. Vascular reactivity to systemic pulsatility of arterial pressure is important in autoregulating cerebral blood flow.\(^16\) The loss of systemic arterial pulsatility can influence the CNS autoregulatory response to acute neurologic injury. It has been shown that NPCF mechanical circulatory support devices can alter cerebral hemodynamics by lowering peak systolic pressures and augmenting diastolic pressures in the carotid and vertebral arteries.\(^17\) TH lowers intracranial pressure and cerebral blood volume in pulsatile systemic circulation.\(^18\) The cerebral vascular response to abnormal patterns of arterial pressure and flow can influence the brain perfusion pattern on rewarming from TH in NPCF circulation. The neurologic findings related to abnormal perfusion induced by mechanical circulatory devices may be reversible. There is limited literature on the neurologic consequences of these mechanical circulatory devices on rewarming from TH.

Determining BD or neuroprognosis with clinical certainty after TH on NPCF mechanical circulatory devices is challenging. We urge clinicians to exercise caution when making life-ending decisions by (1) allowing an appropriate time for neurologic recovery after therapeutic interventions (eg, TH), (2) eliminating confounding factors depressing CNS functions, and (3) using confirmatory tests to increase clinical certainty about the irreversibility of neurologic findings.

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