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LETTER TO THE EDITOR

Reply to Letter to the Editor "Neuroimaging of Intracranial Perfusion and the Clinical Diagnosis of Brain Death: Setting the Gold Standard in Humans"

M. Sawicki[1] · J. Sołek-Pastuszka[2] · K. Chamier-Ciemińska[1] · A. Walecka[1] · J. Walecki[3] · R. Bohatyrewicz[2]

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Addressing the concerns expressed in the Letter to the Editor entitled "Neuroimaging of intracranial perfusion and the clinical diagnosis of brain death: Setting the gold standard in humans" relating to our study "Computed Tomography Perfusion is a Useful Adjunct to Computed Tomography Angiography in the Diagnosis of Brain Death" [1] we would like to formulate the following statements.

Measurements of cerebral blood flow (CBF) in experimental animals subjected to cerebral ischemia have demonstrated the existence of two separate thresholds for ischemic neuronal damage. Electrocerebral activity diminishes at flows below 20 ml/100 g/min, whereas membrane failure and cell death occur when CBF falls below 10 ml/100 g/min [2–5]. These thresholds were confirmed in many human studies using different techniques, e. g. computed tomography perfusion (CTP), perfusion magnetic resonance imaging (MRI) and positron emission tomography (PET) and established as gold standards [6–11]. All of these studies have employed acute reductions in CBF lasting from minutes to a few hours.

Although, the degree to which the human brain can tolerate more gradual development of ischemia or more prolonged duration of milder degrees of ischemia is still not reliably investigated it is evident that the response of cerebral neurons to ischemia is too complex to be described by simple threshold concepts. The degree of irreversible neuronal damage depends not only on the magnitude and duration of the CBF reduction, but also on the selective vulnerability of specific neuronal populations, and a wide variety of other factors, including antecedent cerebral glucose stores [2–4, 12–15]; however, to the best of our knowledge, there are no reports in the literature about preservation of viable tissue with CBF below 10 ml/100 g/min maintained for more than 4–5 min in normothermia.

Considering this, CBF values revealed in our study should be regarded as compatible with the presence of non-viable tissue (NVT) and cannot be interpreted as global ischemic penumbra. We do not negate the possible occurrence of global penumbra in non-functioning brain at some stage but it was not revealed at the moment of performing CTP in our study participants.

Our results cannot be exactly referred to the neuropathologic findings reported by Wijdicks and Pfeifer [16] because of two key factors. Firstly, in the study by Wijdicks and Pfeifer the time from initial injury to brain death (BD) diagnosis was below 24 h in 27 out of 41 (66%) patients. In our population this time was usually much longer (48 h or more). These data are incomplete and therefore were not analyzed in our study; however, during this time, further progression of neuronal membrane failure and cell death could occur. Secondly, the causes of brain injury were to a large extent differently distributed in both studied populations. In the study by Wijdicks and Pfeifer it was trauma in 33 out of 41 (80%) cases. In contrast, in our population trauma was the cause of BD in only 5 (10%), cerebrovascular accidents in 36 (72%), and ischemic anoxia in 9 (18%) patients.

The authors of the letter suggested that the examination of the brain structures at autopsy should be adopted as the reference standard to validate neuroimaging modalities threshold in detection of CBF reduction to confirm irreversible ischemia and necrosis in BD. In common situations, as in the report of Wijdicks and Pfeifer, the autopsies may be performed from 0–36 h after cerebral circu-

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✉ J. Sołek-Pastuszka
joanna.pastuszka@pum.edu.pl

[1] Dept. of Diagnostic Imaging and Interventional Radiology, Pomeranian Medical University, Szczecin, Poland

[2] Clinic of Anesthesiology and Intensive Care, Clinical Hospital No1, Pomeranian Medical University, Szczecin, Poland

[3] The Centre of Postgraduate Medical Education, Warsaw, Poland

latory arrest and organ procurement or withdrawal of life support. Brains are obviously not perfused during this period. Additional 10–20 h of at least hypoperfusion should be added as a time interval between appearance of clinical BD symptoms and BD declaration. And after this relatively long time, moderate to severe neuronal ischemic changes were found only in 34–68% of samples taken from different cerebral regions [16]. This clearly demonstrates that currently used neuropathologic examination methods have limited value to confirm CBF absence in time period of about 50 h.

Profound cellular disintegration appears much later in a form of "respirator brain" described in the distant past [17]. But we should not forget that in this distant past, BD diagnosis was usually completed much longer after the onset of BD symptoms than in the present time, when the physicians are more familiar with BD diagnostic procedures and organ procurement is organized shortly afterwards. Therefore, the time for disintegration of cells is obviously shorter nowadays. Prolonged supportive therapy of brain-dead patients such as described by Shewmon [18] is extremely rare with exception of pregnant women where it may be up to few months long. By the way, it would be interesting whether autopsy findings in those cases (if they were performed) were compatible with "respirator brain" or those reported by Wijdicks and Pfeifer.

Finally, it should be emphasized that our study was not focused on finding global neuronal death with CTP in suspected brain-dead patients but on investigating the sensitivities of whole brain CTP and CT angiography in the diagnosis of BD using clinical criteria as the reference.

Conflict of interest M. Sawicki, J. Sołek-Pastuszka, K. Chamier-Ciemińska, A. Walecka, J. Walecki and R. Bohatyrewicz declare that they have no competing interests.

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