studies of novel therapeutic agents that manipulate NO, HIF-1, or both.

Is HIF-1 a bridge between altered plasma NO consumption and adverse outcomes, as speculated by Ruan et al? We do not know, but we look forward to the translational investigations necessary to answer this question.

Pulmonary and Critical Care Medicine Unit, University of Rochester Medical Center, New York, NY.

The authors have disclosed that they do not have any potential conflicts of interest.

REFERENCES

1. Ruan H, Li S-s, Ran X: Hypoxia-Inducible Factor-1: A Bridge Between Plasma Nitric Oxide and Adverse Outcomes in Critically Ill Patients. *Crit Care Med* 2024; 52:e211–e212
2. Berchner-Pfannschmidt U, Tug S, Kirsch M, et al: Oxygen-sensing under the influence of nitric oxide. *Cell Signal* 2010; 22:349–356
3. Brüne B, Zhou J, Zhou J: Nitric oxide and superoxide: Interference with hypoxic signaling. *Cardiovasc Res* 2007; 75:275–282
4. Ruan H, Li YZ, Zhang Q, et al: Identification and clinical validation of hypoxia-inducible factor 1α protein as the potential biomarker in patients with sepsis. *Shock* 2023; 59:855–863
5. Dony CA, Illipparambil LC, Maeda T, et al: Plasma nitric oxide consumption is elevated and associated with adverse outcomes in critically ill patients. *Crit Care Med* 2023; 51: 1706–1715
6. Abraham E: New definitions for sepsis and septic shock: Continuing evolution but with much still to be done. *JAMA* 2016; 315:757–759
7. Wilson JG, Calfee CS: ARDS subphenotypes: Understanding a heterogeneous syndrome. *Crit Care* 2020; 24:102

The Relationship Between Manifestation of Diabetes Insipidus and Estimated Glomerular Filtration Rate in Brain Death: Implications Require Clarification

KEYWORDS: brain death; diabetes insipidus; glomerular filtration rate; kidney function

Ari R. Joffe, MD, FRCPC[1]
Michael Nair-Collins, PhD[2]

To the Editor:

In a single-center retrospective study in *Critical Care Medicine*, Varelas et al (1) described a relationship between renal dysfunction and the frequency of diabetes insipidus (DI) in adults with brain death (BD). We believe that some clarifications are needed.

First, severe renal dysfunction is a known confounder to the assessment of hypothalamic osmoregulation, as very-low glomerular filtration rate will reduce urine output. Nevertheless, in those with normal renal function, DI did not occur in 22.8% of patients diagnosed with BD (1). According to the Uniform Determination of Death Act, which requires the irreversible loss of all functions of the entire brain, these patients were not dead (2).

Second, the authors seemed to counter this failure of accepted medical standards to meet the legal definition of death by suggesting that the lack of DI was due to mere brain "cell activity" (1). This is disingenuous because osmoregulation is clearly a brain "function" as defined by the World Brain Death Project—osmoregulation is an essential brain function that involves the delivery of "a stimulus to provoke central processing and an efferent response" (3). This is achieved by tightly regulated release of vasopressin, in response

DOI: 10.1097/CCM.0000000000006169

to plasma osmotic changes as small as 1% (and with a half-life of 15–18 min). Vasopressin is released from magnocellular neurons that originate in the supraoptic and paraventricular nuclei of the hypothalamus, with additive glutamatergic input from circumventricular basal forebrain areas, and functions to maintain the intercellular environment necessary for all homeostasis in the organism (2). These areas of the brain are not supplied by the inferior hypophyseal artery, and so not potentially protected from high intracranial pressure (2).

Third, the authors suggest that the lack of DI may be due to "leak" of vasopressin that may "mimic osmoregulation," and that "as longer time elapses after BD declaration, a higher number of DI observations may occur" presumably because the leak from necrotic cells ceases (1). These assertions were based on evidence from two referenced studies that, if anything, support the opposite claim (4, 5). Sujimoto et al found that the hypothalamus—in three of four examined pathologically "almost completely necrotic and [with] no vasopressin positive granules" - "seems to cease its function immediately after the occurrence of BD, since the secretion of ADH [vasopressin] falls rapidly to a very low level after BD in spite of the preservation of cellular structure in the [pituitary] posterior lobe [in 11 of 12 specimens "the number of vasopressin positive granules was maintained even 20 days after BD"]" (4). This was based on $n = 7$ patients who had vasopressin measured after BD, all of whom had DI, therefore, indicating that any passive leak of detectable vasopressin was insufficient for osmoregulation (4). Ujihira et al (5) did not report any pathology for the posterior pituitary lobe nor the hypothalamus. These data clarify that osmoregulation in BD cases indicates ongoing hypothalamic and basal forebrain (i.e., brain) function.

1 Department of Pediatrics, and John Dossetor Health Ethics Center, University of Alberta, Edmonton, AB, Canada.

2 Department of Behavioral Sciences and Social Medicine, Florida State University College of Medicine, Tallahassee, FL.

The authors have disclosed that they do not have any potential conflicts of interest.

REFERENCES

1. Varelas PN, Kananeh M, Brady P, et al: The relationship between manifestation of diabetes insipidus and estimated glomerular filtration rate in brain death. *Crit Care Med* 2024; 52:e58–e66
2. Nair-Collins M, Joffe AR: Frequent preservation of neurologic function in brain death and brainstem death entails false-positive misdiagnosis and cerebral perfusion. *AJOB Neuroscience* 2023; 14:255–268
3. Greer DM, Shemie SD, Lewis A, et al: Determination of brain death/death by neurologic criteria The world brain death project. *JAMA* 2020; 324:1078, Supplement 5:20
4. Sugimoto T, Sakano T, Kinoshita Y, et al: Morphological and functional alterations of the hypothalamic-pituitary system in brain death with long term bodily living. *Acta Neurochir (Wien)* 1992; 115:31–36
5. Ujihira N, Hashizume Y, Takahashi A: A clinico-neuropathological study on brain death. *Nagoya J Med Sci* 1993; 56:89–99

The authors reply:

We appreciate Drs. Joffe and Nair-Collins' thoughtful comments (1) on our article (2). We disagree that these patients were not dead. Although there is a possibility that these patients without diabetes insipidus (DI) had circulating vasopressin/antidiuretic hormone (ADH) for the anatomical reasons we explained in our article, there are many reasons to believe that this is inconsequential to the diagnosis of brain death. First, the 2019 *American Academy of Neurology* (AAN) position article (3), the World Brain Death Project (4) and the recently published Pediatric and Adult Brain Death/Death by Neurologic Criteria Consensus Guideline (5), supported by the AAN Guidelines subcommittee and four other Societies, confirm that persistent neuroendocrine function does not exclude evaluation and determination of BD. Second, there is widespread confusion between cellular activity and function, and how function is confirmed "according to medical standards." Since the Harvard criteria and through all published Guidelines, accepted medical standards do not include all of the infinitesimal functions

Panayiotis Varelas, MD, PhD, FNCS, FAAN[1]

David Greer, MD, FAAN, FNCS[2]

DOI: 10.1097/CCM.0000000000006208