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Ventricular Lactate in Normal Pressure Hydrocephalus: From Where Has It Come to Where Does It Go?

I read with interest the article "Proton Chemical Shift Imaging in Normal Pressure Hydrocephalus" by Kizu et al (1), but I wish to point out some alternative interpretations to those offered by the authors of this article and the associated editorial (2). The findings presented show elevated lactate levels in the lateral ventricles of the patients with normal pressure hydrocephalus (NPH) but no lactate in the adjacent subependymal white matter. This result would seem to suggest that the concentration of lactate in the ventricles is higher than that in the subependyma, that is, an osmotic gradient exists from the ventricle to the subependyma. The presence of bulk flow of water from the ventricle to the subependyma in NPH is well established, and the absorption of this fluid by the periventricular veins (2, 3) indicates that the hydrostatic pressure gradient is also present from the ventricle to the subependyma. Given the gradients, the lactate seems unlikely to have originated in the subependyma, as the authors suggest (1). Most likely, given the osmotic and hydrostatic gradients, lactate is being resorbed by the subependyma.

Lactate, as Kizu et al described (1), is an end-product of anaerobic glycolysis, and the site of formation of lactate would be expected to closely follow the derangement of glucose metabolism. PET with 2-[fluorine 18]-fluoro-2-deoxy-D-glucose (FDG) is performed to directly measure glucose metabolism and has shown reduced glucose metabolism in all cortical gray matter and subcortical white matter regions in NPH (4). These regions are drained by the superficial venous system, and ischemia of parts of the brain drained by the superficial system has been previously described (3). It is untenable that anaerobic conditions could be restricted to the immediate periventricular brain as stated (1), because no lactate was found in this region and the normal *N*-acetylaspartate concentrations found in the same region suggest no neuronal loss. High concentrations of lactate in the brain interstitial fluid most likely occur in the other forms of dementia investigated in this study as well, but no ventricular lactate was seen in these cases (1). In the absence of a fluid-absorption abnormality in these conditions, lactate would pass rapidly into the venous system because of the osmotic gradient. In NPH, the only way that lactate could avoid absorption into the venous system at its point of origin is if a significant hydrostatic pressure in the superficial venous system opposed this osmotic pressure. Thus, lactate is more likely to be forming throughout the cortex and the central white matter rather than in the periventricular white matter, and because of a higher hydrostatic pressure in the superficial venous system (3), it would pass directly from the cortex into the subarachnoid space through the pia or perivascular spaces. In NPH, nuclear cisternography shows that any molecules in the CSF eventually enter the ventricles by means of reflux through the aqueduct from where they are subsequently resorbed by the subependymal white matter, because the deep venous system is at a lower pressure (3) and not a higher pressure as stated (1).

The editor correctly states that interstitial fluid moves into the venules under a combined pressure and osmotic gradient (2), but then an association between arteriolar obstruction with subsequent capillary and venular collapse is used to explain the reduction in fluid resorption in NPH. Collapsed veins, on the basis of low flow, have low hydrostatic pressure, and if as suggested, bulk fluid flow away from the capillary bed to the ventricles were to occur, then the osmotic pressure in the draining veins would be high. Both of these latter outcomes would increase interstitial fluid resorption into the veins rather than reduce it.

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Reply: We thank Dr Bateman for his interest and comments regarding our article (1). We are also grateful for these comments that highlight an area of potential confusion. Dr Bateman is correct in saying that bulk flow of water is present and that the lactate may originate in the subependyma (2). That was, however, not what we were trying to address. The main issue of the article was intraventricular lactate in normal pressure hydrocephalus (NPH), as observed with proton chemical shift imaging (^{1}H-CSI), and not in other dementias. Intraventricular lactate seems to be a specific finding for NPH, and its presence may assist in differentiating NPH from other dementias. We agree that bulk flow of water occurs from ventricle to subependyma in NPH and that this fluid is absorbed into the periventricular veins (2, 3). On the other hand, an osmotic gradient from the ventricle to the subependyma may not clearly exist, although we reported that no lactate was present in voxels from periventricular regions. We actually observed a lactate peak in voxels from the ventricular wall, more proximal to the lateral ventricles than the periven-

tricular voxels. Because the nominal in-plane resolution was 10–11 mm and because an *N*-acetylaspartate peak was observed in the intraventricular voxels, whether lactate was present in the subependyma or whether the lactate was due to a contamination signal from cerebrospinal fluid is difficult to say. For these reasons, we did not discuss lactate in voxels from the ventricular wall. Therefore, conclusively determining the origin of lactate from our findings is difficult because of the limited number of cases and the spatial resolution of ^{1}H-CSI.

As Dr Bradley suggested, our study has opened a new window of investigation into the diagnosis and etiologic factors of NPH (3). We would like to emphasis that the clinical importance of our study is not affected by the source of lactate.

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