Neurosurgical forum
Letters to the editor

Normal-pressure hydrocephalus and cerebral blood flow

To The Editor: We would like to make a comment on a recently published article by Chang et al. (Chang CC, Asada H, Mimura T, et al: A prospective study of cerebral blood flow and cerebrovascular reactivity to acetazolamide in 162 patients with idiopathic normal-pressure hydrocephalus. Clinical article. J Neurosurg 111:610–617, September, 2009).

One of the major conclusions of this interesting article, as described by the authors in the summary, is that “preoperative CVR [cerebrovascular reactivity] was significantly impaired . . . in responders compared with healthy controls, but not in nonresponders.”

So, they conclude: “Impaired CVR and reduced CBF [cerebral blood flow] with the development of symptoms can be proposed as diagnostic criteria for idiopathic NPH [normal-pressure hydrocephalus].”

If normal CVR after acetazolamide administration in healthy elderly volunteers is 31%,¹ according to their data, as described by the authors in the summary, is that the difference cannot be used as a preoperative criterion.

There is obviously a great difference between healthy volunteers and nonresponders with respect to CVR, and the only reason that this difference does not reach statistical significance is that the number of nonresponders included in the article is very small (15 vs 141 responders). If the number of nonresponders was, for example, the same as that of responders, there would be a statistically significant difference between healthy controls and nonresponders (t = 4.1, p < 0.01).

The authors also state that there is a significant difference between responders and nonresponders, but this is not the same conclusion as that claimed in their summary, because this difference cannot be used as a preoperative diagnostic criterion.

Relying on the existing data, unfortunately we cannot draw the conclusion that CVR can be used as a preoperative diagnostic test discriminating the patients who will respond to shunting of NPH.

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Reference


RESPONSE: We appreciate Dr. Sakellaridis and Mr. Stavropoulos for their interest in our article and the time they took to analyze our data statistically. Unfortunately, they made an important mistake in the statistical analysis of our data.

According to CT studies by Vorstrup et al., the mean CBF increases by 31% in healthy elderly volunteers after intravenous injection of 1 g of acetazolamide. However, in this study, the CVR was obtained from the response to 500 mg of acetazolamide administration and was calculated as the percentage change from the baseline mean CBF value. The dose of acetazolamide administration was 500 mg, not 1 g. The CVR value to 500 mg of acetazolamide obtained from 13 healthy age-matched controls is 14 ± 2.5%, not 31%. It is well known that increase of CBF after acetazolamide administration is dose dependent. The control value of CVR to 500 mg of acetazolamide (14 ± 2.5%) seems to be compatible with that of CVR to 1 g of acetazolamide reported by Vorstrup et al. (31%).

Differences between the 2 groups were evaluated using the Student t-test. Unpaired 2-tailed tests were used, and probability values < 0.05 were considered significant. We evaluated our data again using the computer application software StatView J-5.0 and this analysis resulted in the same conclusions. Responders had a significant lower preoperative CVR (p < 0.005) than nonresponders. Preoperative CVR was significantly reduced (p < 0.0025) in responders compared with 13 healthy age-matched controls (14 ± 2.5%), but not in nonresponders (p = 0.099). Responders with the complete triad had significantly lower preoperative CBF and CVR than those with the incomplete triad (p < 0.01 and p = 0.04, respectively).

Both CBF and CVR decrease with the development of NPH, suggesting that hemodynamic ischemia may be responsible for manifestation of the symptoms. Progressive symptoms of NPH, along with impaired CBF and reduced CVR, can be proposed as diagnostic criteria of idiopathic NPH.

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Traumatic brain injury and metabolism

To The Editor: We read with great interest the article by Ho et al. (Ho CL, Wang CM, Lee KK, et al: Cerebral oxygenation, vascular reactivity, and neurochemistry following decompressive craniectomy for severe traumatic brain injury. J Neurosurg 108:943–949, May, 2008). Uncontrollably high intracranial pressure (ICP) due to posttraumatic brain swelling may be considered not as a...
single clinical and pathophysiological entity, but as a condition with several subsets in which variable responses to surgical measures can be expected. Therefore, a range of patient outcomes is possible: from death to satisfactory neurological recovery. Investigations on the role of surgical decompression in the pathophysiology of malignant posttraumatic brain swelling must be encouraged since there is still a paucity of scientific evidence concerning the effectiveness of this surgical technique in improving outcome. Our recent publications\(^1,2\) on cerebral hemodynamic changes gauged by transcranial Doppler ultrasonography in patients with traumatic brain injury (TBI) who underwent surgical decompression revealed that decompressive craniectomy leads to a significant elevation in cerebral blood flow (CBF) velocity and, consequently, CBF in most patients. This finding could explain the significant increase in cerebral oxygenation noted by Ho et al. after surgery: a majority of their patients (85%, regardless of outcome) presented with acceptable postoperative brain tissue PO\(_2\) (> 10 mm Hg). Given that adequate brain oxygenation is an important prerequisite for morphofunctional recovery of the brain as well as for restoration of aerobic cell metabolism, an interesting question arises: why, in their study, did some patients progress to unfavorable outcomes whereas others progressed to unfavorable outcomes when both groups had acceptable postoperative brain tissue PO\(_2\)? An in-depth analysis of the data reported by Ho et al. on pre- and postoperative cerebral oxygenation and biochemistry reveals that patients with unfavorable outcomes appear to have lost the ability to metabolize brain tissue O\(_2\), shifting from aerobic to anaerobic metabolism, possibly as a consequence of mitochondrial dysfunction. This hypothesis is supported by the following findings.

The mean brain tissue PO\(_2\) level in the poor-outcome group was extremely low (3 ± 2 mm Hg), suggesting reduced brain O\(_2\) consumption. By contrast, the preoperative mean brain tissue PO\(_2\) level in the good-outcome group was extremely low (3 ± 2 mm Hg) probably due to preserved O\(_2\) utilization associated with reduced CBF caused by intracranial hypertension. This theory is corroborated by the fact that most patients from the poor-outcome group had acceptable brain tissue PO\(_2\) prior to surgery (> 10 mm Hg in 78% of patients), whereas all patients from the favorable-outcome group suffered from brain hypoxia before surgery (brain tissue PO\(_2\) < 10 mm Hg).

After surgical decompression, brain tissue PO\(_2\) values increased significantly in both groups. However, the mean brain tissue PO\(_2\) level in the poor-outcome group remained higher than the values in the good-outcome group (20 ± 3 and 17 ± 4 mm Hg, respectively), reinforcing the idea of lower brain O\(_2\) consumption in the former group.

Brain lactate concentration remained high following surgery in the poor-outcome group (6 ± 2 and 5 ± 2 mmol/L, pre- and postoperatively, respectively), which suggests the maintenance of a high anaerobic metabolic rate in the brain after surgical decompression, whereas a significant reduction in lactate concentration was detected in the good-outcome group (7 ± 4 and 3 ± 2 mmol/L, pre- and postoperatively, respectively). Moreover, abnormal levels of lactate (> 3.8 mmol/L) were found in most of the patients with unfavorable outcomes (66% of individuals), before and after operation, whereas in the group with favorable outcomes, this percentage decreased from 100% to 48%. Elevated lactate levels in brain tissue have been assumed to indicate a shift from aerobic to anaerobic metabolism due to brain hypoxia and/or impairment of brain O\(_2\) consumption.\(^3\)

The mean lactate/pyruvate ratio remained high after surgery in the unfavorable-outcome group despite decreasing by 27% (54 ± 10 and 39 ± 5, pre- and postoperatively, respectively), which may reflect maintenance of anaerobic metabolism, even in the presence of acceptable pre- and postoperative brain tissue PO\(_2\) levels. Conversely, the mean lactate/pyruvate ratio decreased by 71% after brain decompression in the good-outcome group despite the fact that postoperative values remained high (from 137 ± 85 to 40 ± 12). An elevated lactate/pyruvate ratio in brain tissue combined with low levels of glucose may be interpreted as the result of a shift from aerobic to anaerobic metabolism; the lactate/pyruvate ratio reflects the intracellular redox state and can be considered a reliable marker of ischemia.\(^4\)

The mean glucose concentration remained unchanged after decompressive craniectomy in the poor-outcome group (2 ± 0.5 and 2 ± 0.4 mmol/L, pre- and postoperatively, respectively), whereas a significant increase in glucose concentration was noted in the good-outcome group (0.6 ± 2 and 1 ± 1 mmol/L, pre- and postoperatively, respectively). Furthermore, the percentage of poor-outcome patients with abnormal levels of glucose (< 0.5 mmol/L) did not change after decompressive craniectomy (21% and 23%, pre- and postoperatively, respectively), while in the favorable outcome group this parameter decreased significantly from 50% to 34%. These data are indicative of an increased glucose supply to the brain resulting from postoperative CBF augmentation and/or lower glucose consumption due to the restoration of aerobic metabolism (aerobic metabolism utilizes less glucose to produce the same quantity of adenosine triphosphate compared with anaerobic metabolism). A low glucose concentration can occur in hyperglycolysis and impairment of oxidative phosphorylation in mitochondria.\(^3,4\)

The glutamate concentration remained high during the postoperative period in the unfavorable-outcome group (13 ± 6 and 13 ± 3 mmol/L, pre- and postoperatively, respectively), suggesting persistent ischemia in the brain after surgical decompression, whereas a significant decrease in glutamate concentration was seen in the good-outcome group (36 ± 54 and 3 ± 1 mmol/L, pre- and postoperatively, respectively). In fact, the percentage of poor-outcome patients with abnormal levels of glutamate (> 10 mmol/L) did not change after decompressive craniectomy (48%), despite increased brain tissue PO\(_2\) levels, while in the group of favorable outcome this figure decreased from 100% to 2%. As noted by Ho et al., extracellular glutamate, an excitotoxic amino acid released into the extracellular fluid, has been considered an early marker of cerebral ischemia.

Verweij et al.,\(^3\) using tissue fractionation procedures,