Published in final edited form as:

Transl Stroke Res. 2012 June 1; 3(2): 263–265. doi:10.1007/s12975-012-0152-2.

Brain water content. A misunderstood measurement?

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Abstract

Brain edema is a major contributor to poor outcome following ischemic and hemorrhagic stroke. In animal models, edema has historically been quantified as a change in % brain water content (water content/wet weight). As described in this communication, this number can be misleading, as ‘small’ changes in % brain water content actually reflect much bigger changes in brain swelling. Using either water content, expressed as g/g dry weight, or a measure of brain swelling, better reflect the impact of edema after stroke and brain injury.

Keywords

Brain edema; swelling; water content; cerebral hemorrhage; cerebral ischemia

Cerebral edema is a major contributor to poor outcome in many neurological conditions (e.g. hemorrhagic stroke, ischemic stroke, traumatic brain injury and brain tumors). Historically, in animal disease models, edema has been quantified by comparing the water content of the affected tissue with normal brain. The water content has been expressed as % brain water, determined from the difference in wet and dry weights (i.e. the water weight) divided by the wet weight (1–3). As described below, this is unfortunate as it can lead to a misinterpretation of the impact of ‘small’ changes in % brain water.

To examine this issue, different examples of brain injury are used from the literature and three parameters are calculated by the equations.

$$\% \text{Water content} = 100 * (\text{wet weight} - \text{dry weight}) / \text{wet weight} \quad \text{Equation 1}$$

$$\text{Water content} = (\text{wet weight} - \text{dry weight}) / \text{dry weight} \quad \text{Equation 2}$$

$$\% \text{Tissue swelling} = 100 * (\text{final wet weight} - \text{initial wet weight}) / \text{initial wet weight} \quad \text{Equation 3}$$

To demonstrate these terms, data from Betz et al. (4) is used. Rats underwent 6 hours of permanent middle cerebral artery occlusion (MCAO) and then tissue was sampled from the ipsilateral (ischemic) and contralateral cortex. For a 100 mg sample of the ipsilateral cortex, the dry weight was 17.6 mg and the water weight was 82.4 mg. For the contralateral cortex, the same wet weight of sample had a dry weight of 21.4 mg and a water weight of 78.6 mg. From Equation 1, the ipsi- and contralateral cortex samples had % water contents of 82.4 and 78.6%, respectively, a difference of 3.8%. However, using Equation 2, the water content

in the ipsilateral cortex is 4.68 g water/g dry weight, while that for the contralateral cortex is 3.67 g water/g dry weight. Assuming that the dry tissue weight doesn't change during the course of 6 hours of MCAO, this means that there is a 27.5% increase in water content. Using the contralateral cortical sample water content, and the final ipsilateral dry weight, it is possible to calculate an initial wet weight for the ipsilateral sample $(3.67+1)*17.6 = 82.2$ mg and, thus, using Equation 3 the tissue swelling as 21.6%. This example shows that a fairly small change in % water content actually reflects large changes in tissue water and tissue swelling.

Table 1 gives five examples from the literature to encompass different neurological conditions. Wagner et al. (5) reported that for perihematomal white matter in the pig the % water content was 86%, compared to 73% in the contralateral hemisphere. In terms of water content (g/g dry weight), this represents a 127% change, while tissue swelling was 93%. These results show the magnitude of the changes in water content and swelling that can result from brain edema. It should also be noted that the relationship between % water content and either water content (g/g dry weight) or brain swelling is not linear. This is emphasized in Figure 1 which plots changes in % water content with the other two parameters for a hypothetical tissue, with an initial 77% water content. A change in % water content of 1% results (to 78%) in a 6 and 4.5% increase in water content (g/g dry weight) and brain swelling, respectively, but a 10% increase in % water content (to 87%) results in a 100 and 77% change in these two parameters.

Gerriets et al. made measurements of % water content (wet/dry weight method) and hemispheric swelling (using magnetic resonance imaging) in the same rats 24 hours after permanent MCAO (6). They reported % water contents of 80.08 and 75.89% in the ipsi- and contralateral hemispheres, respectively, an increase of 4.19%. This was accompanied by an 18.34% swelling of the ipsilateral hemisphere as assessed by MRI. These direct measurements also indicate that relatively 'small' changes in % water content actually reflect large change in tissue swelling.

The impact of brain edema may be local, through change in spatial relationships between cells and local blood flow, or global, due to changes intracranial pressure, blood flow and potential herniation. In this regards, Table 1 lists four rat studies, one of which is from a model of global ischemia with reperfusion (7) and the other three are from more focal injuries (MCAO, intracerebral hemorrhage and traumatic brain injury with more local tissue sampling; (4, 8, 9)). The global ischemia study reported an increase in % brain water content from 77.16 to 78.2%, a smaller increase than reported for the three focal models. It should be noted, however, that these small global increases may have a profound effect on intracranial pressure (and potential herniation). Brain swelling can initially be compensated by CSF (and blood) displacement. However, the CSF only accounts for ~15% of cranial volume (intracranial CSF volume of ~200 ml (10) and brain weight of 1350 g) and, as depicted in Figure 1, an increase in brain water content from 77 to 80% would cause 15% brain swelling, exhausting any possible displacement.

As a measurement, % brain water content has the disadvantage that edema (an increase in water) affects both the numerator and the denominator, the water mass and the wet weight. It is, unfortunately, ingrained in the scientific community. It is, therefore, important to realize that relatively small changes in % brain water content can actually reflect large changes in the absolute water content of the brain and brain swelling. These may potentially cause major local disruption of structure and/or global effects on intracranial pressure and blood flow.

Acknowledgments

This work was supported by the National Institutes of Health grants NS034709 (RFK), NS039866 (GX), NS057539 (YH) and a grant from the American Heart Association, 0840016N. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH or the AHA.

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Fig. 1.

Graph showing the relationship between % water content and either percent changes in water content (g/g dry weight) or swelling. The % water content of a hypothetical piece of brain tissue is increased in 1% increment from a baseline of 77%. For each increment, the percent change in water content (g/g dry weight) is calculated as is the degree of swelling of the tissue.

% Brain water content, water content (g/g dry weight) and % brain swelling in five studies on brain injury from the literature (see equations 1–3 for how these were calculated). Please note that the % changes in the latter two parameters with injury were 4 to 7-fold greater than that for % brain water content. ICH = Intracerebral hemorrhage, TBI = traumatic brain injury.

Table 1

Model	% Brain water content			Water content (g/g dry weight)		Brain swelling	
	Non-injured	Injured	% change	Non-injured	Injured	% change	% change
Rat global ischemia (7)	77.16%	78.2%	1.3%	3.38	3.59	6.2%	4.8%
Rat focal ischemia (4)	78.6%	82.4%	4.8%	3.67	4.68	27.5%	21.6%
Rat ICH (Reference)	78.0%	81.9%	5.0%	3.54	4.52	27.6%	21.5%
Rat TBI (8)	78.6%	84.2%	7.1%	3.67	5.33	45.1%	35.4
Pig ICH -white matter (5)	73%	86%	17.8%	2.70	6.14	127%	93%