Correlation of Apparent Diffusion Coefficient and Computed Tomography Density in Acute Ischemic Stroke

To the Editor:

We read with interest the recent article by Kucinski et al.1 The authors observed a decrease in the apparent diffusion coefficient (ADC) in diffusion-weighted MR imaging and a corresponding decrease in CT density from patients suffering from acute ischemic stroke of the anterior cerebral circulation. CT measurements showed a continuous linear decrease of 0.4 Hounsfield U/h, whereas the decrease in ADC was almost complete after 1.5 hours. Thus, a different time course was found between the 2 phenomena. A correlation between the decrease in ADC and that of CT density was found. They concluded that the severity of diffusion restriction correlated with net water uptake in acute ischemic stroke.

However, as the authors stated, the underlying pathophysiology and different time courses indicated a common reason rather than a direct causality for both phenomena. The underlying pathophysiology was explained as follows: Changes in CT density are known to correlate linearly with the specific gravity of the nervous tissue, ie, with net water changes in ischemic brain tissue, thus describing the course of water uptake after ischemia. The decrease in ADC in acute ischemia correlates with the reduction in extracellular space caused by a shift of extracellular water into intracellular compartments with consecutive restriction of molecular water diffusion. This water shift results from ion pump failure caused by a severe decrease in oxygen and glucose supply. The different time courses of ADC and CT values do not support a direct causality between diffusion restriction (brought about by intracellular volume expansion and extracellular volume restriction) and water uptake. This is consistent with previous results showing sudden ADC drop within minutes after induction of ischemia.

The authors propose a common underlying reason for both phenomena: the severity of regional cerebral blood flow reduction. The water increase is suggested to be a consequence of an evolving osmotic gradient between the intravasal and extracellular compartment evoked by the water shift into the intracellular space. Thus, the early ischemic edema is suggested to be a passive “net water uptake” delayed to the steep, initially occurring decrease in ADC. It occurs before the blood-brain barrier breaks down (vasogenic edema).

Although it is generally believed that the ADC changes measured by diffusion-weighted MRI (DWI) in brain pathologies are related to the alterations of the water compartments, the authors should also consider that despite the widespread use of the DWI, the underlying mechanisms that cause the ADC changes are still unclear. Theories independent of water shift from the extracellular space to the more viscous intracellular space were also published such as (1) loss of cytoplasmic streaming and/or the increased intracellular viscosity result in the ADC drop; (2) extracellular space becomes more tortuous during the aforementioned water shift; and (3) the transition of water from sol to gel state.

Although van Zijl et al provided evidence that complete separation of the intracellular and extracellular space was feasible also by diffusion weighted spectroscopy in cell culture, the work of Niendorf et al carried out on rat brain outlines that, in vivo, the correspondence between the water populations determined by localized diffusion weighted spectroscopy and extra-, intracellular compartments is not straightforward. In recent years it became apparent that a sufficiently high b value water diffusion characteristics during progressive ischemia and terminal anoxia in the spinal cord of the rat. J Cereb Blood Flow Metab. 1994;14:301–311.


Response

We appreciate Dr. Dóczi’s and Dr. Schwarz’s interest in our study on the correlation of the decrease of the apparent diffusion coefficient (ADC) and the decrease of computed tomography (CT) density. In this work, we described the quantity and time course of CT hypodensity evolution in ADC lesions, to our best knowledge, for the first time in human acute ischemic stroke. It was not our final goal to clarify the nature of ADC decrease in ischemia. The ADC decrease has originally been attributed to a shift of extracellular water molecules into the intracellular space.1,2 This mechanism appears quite attractive due to the well-known observation of early cell swelling in ischemic brain1 which correlates with ADC decrease.4,5 The water shift theory is further supported by findings of ADC decrease following anoxic depolarization, which can be delayed by the sodium channel blocker tetrodotoxin1,2 and osmotic manipulations,2,6,7 which can reverse or even inverse ADC decrease.6,9 In fact, the main reason for diffusion restriction may be the reduction of the extracellular volume10–12 and increasing the overall tortuosity of the sample. This is exactly what we have stated in the sentence “The decrease in ADC in acute ischemia correlates with the reduction in extracellular space…” and is not disproven by a recently assumed equal diffusibility of small molecules in the extra- and intracellular space.13 Actually, the increase of intracellular water in the early ischemic edema may increase the intracellular ADC in isolated cells,14 while the total ADC still can be decreased due to extracellular narrowing in brain tissue.15 Second, for b values up to 2000 s/mm2 a mono-exponential approach seems sufficient due to the relative low contribution of the slow
In case of macromolecular binding, T2 should decrease. For the nature of the fast and slow components awaits further investigation. This can be shown by an increase in the spin-spin relaxation time T2 that correlates linearly with the ADC decrease (unpublished results).

Despite this, diffusion-weighted imaging is not a tool of uncertain value, reminds us that there are a lot of uncertainties concerning the nature of the ADC decrease in acute stroke. Even such basic phenomena like spin-spin relaxation are confounded by net water increase, diffusion restriction and T2* effects form apparent diffusion coefficient, originally introduced for physical reasons, which is much more valuable in daily practice than any discussion of the ultrastructural basis of ADC decrease so far.

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