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. The authors observed a decrease in the apparent diffusion coefficient (ADC) in diffusion-weighted MR imaging and a corresponding decrease in CT density in 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, i.e., with net water content 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 intravascular 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 viscose intracellular space were also published such as (1) loss of cytoplasmic streaming and/or the increased intracellular viscosity result in the ADC drop2–4; (2) space were also published such as (1) loss of cytoplasmic streaming and/or the increased intracellular viscosity result in the ADC drop2–4; (2) the transition of water from sol to gel state.8


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.12 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 tetrodotoxin3 and osmotic manipulations,5,6 which can reverse or even inverse ADC decrease.5,9 In fact, the main reason for diffusion restriction may be the reduction of the extracellular volume9–12 and increasing the overall tortuosity of the sample.11 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.11 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.\(^1,16\) For the
diffusion component to signal intensity at low b values\(^1,15\); however, the
nature of the fast and slow components awaits further investigation.

ADC decrease due to association of water protons to macromolecules
is unlikely, since the net water uptake results in an increase of free water.
This can be shown by an increase in the spin-spin relaxation time T2
which correlates linearly with the ADC decrease (unpublished results).

This can be shown by an increase in the spin-spin relaxation time T2
affected brain tissue within the time window of aggressive treatment,\(^1,18\)
which is much more valuable in daily practice than any discussion of the
ultrastructural basis of ADC decrease so far.

Quantitative T2 image of the patient shown in our original article (Figure 1).
Pixel values were calculated by SI(t) = SI0e\(^{-t/T2}\) with TE=15, 75
and 135 ms. The ROI of decreased ADC has been superimposed on
the patient shown in our article, mean T2 increased from 99\(^\pm\)8 ms (control
region) to 105\(^\pm\)7 ms (Figure).

Even such basic phenomena like spin-spin relaxation are confounded
by net water increase, diffusion restriction and T2* effects form
deoxymyoglobin. The term “apparent” diffusion coefficient, originally
introduced for physical reasons, reminds us that there are a lot of
uncertainties concerning the nature of the ADC decrease in acute stroke.
Despite this, diffusion-weighted imaging is not a tool of uncertain
value,\(^1,7\) since the physician can rely on the visualization of severely
affected brain tissue within the time window of aggressive treatment,\(^1,18\)
which is much more valuable in daily practice than any discussion of the
ultrastructural basis of ADC decrease so far.

Thomas Kucinski, MD
Ole Vaterlein
Jens Fiehler, MD
Bernd Eckert, MD
Hermann Zeumer, MD
Department of Neuroradiology
University-Hospital Hamburg Eppendorf
Eppendorf, Germany

Volkmar Glauche, MS
Joachim Röther, MD
Department of Neurology
University-Hospital Hamburg Eppendorf

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T. Dócsi and A. Schwarcz

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