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Serial analysis of the apparent diffusion coefficient time course in human stroke

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Abstract Acute cerebral ischemic injury can be rapidly detected on diffusion-weighted images. The apparent diffusion coefficient (ADC) depends on the stage of cytotoxic edema and water content in the infarcted parenchyma. The purpose of this study is to determine the time course of ADC during the first days of ischemic stroke. These data should make it possible to distinguish between multiple stroke and a single progressive infarction. Eight patients with clinically diagnosed acute cerebral ischemia were examined by diffusion-weighted MRI from 2 to 20 h after onset of symptoms. Daily control scans were performed for up to 10 days. ADC values were analyzed from 55 MRI studies. Furthermore, ADC was measured in the tissue which showed a hyperintense signal at the first examination and in the contralateral tissue. White and gray matter were analyzed separately. Data were expressed as the ratio ADC (rADC) of lesion to control region of interest. All patients showed a uniform reduction in rADC from the first hours of stroke and decreasing to the 3rd day. The rADC increased again from the 4th day up to the point of pseudo-normalization on day 9. The gray matter showed a slightly faster increase than the white matter. rADC shows significant changes in the first days after stroke, following a rather uniform time course. Together with T2-weighted MRI this makes it possible to differentiate between hyperacute, acute, and chronic stroke. Furthermore, the age of an ischemia can be determined and multiple strokes can be distinguished from a single progressive stroke.

Keywords Water diffusion · Stroke · ADC · Pseudo-recovery

Introduction

Acute human stroke causes a decrease in extravascular water diffusion in ischemic brain tissue. This is related to a decrease in Na^+/K^+-ATPase activity, for which energy is required to maintain ionic gradients [1]. Further, this leads to intracellular water accumulation and a reduction in the extracellular space. Tissue in which water diffusion is reduced can be rapidly detected as a hyperintense area on heavily diffusion-weighted (DW) magnetic resonance images. These signal abnormalities reflect a reduced apparent diffusion coefficient (ADC) of water in ischemic brain tissue [2], due to cytotoxic edema [3]. Both experimentally and in the clinical setting, diffusion-weighted magnetic resonance imaging (DWI) has demonstrated a high accuracy for detecting hyperacute ischemia of brain parenchyma [4].

Several groups have described different time courses in the ADC from hyperacute to chronic stroke. Welch et al. analyzed the ADC time course in human stroke compared with a rat model [5]. The rat model shows a pseudo-normalization of ADC values after 24 h [6]. However, Lutsep et al. analyzed 40 MRI examinations

in humans, conducted at different stages of stroke, and observed reduced ADC values until day 9 [7]. Schlaug et al. analyzed 157 DWI studies from 101 patients and demonstrated a pseudo-normalization around the 4th day after onset of symptoms.

In this study we investigated stroke patients daily according to a standardized MRI protocol, using diffusion-weighted sequences, and calculated the ADC in the same anatomical region every day. Based on this, we determined the time course of ADC in the stroke core which was identified on DW images of the first MRI examination.

Patients and methods

Patients

Eight patients (five men and three women) with acute ischemic stroke were investigated immediately after cranial computed tomography (CT) with a standardized MRI stroke protocol, including DW, perfusion-weighted (PW), and T2-weighted images. After informed consent was given, the patients were examined daily by DW and T2-weighted images for up to 10 days after symptom onset. ADC maps were calculated to avoid T2 shine-through effects and to differentiate the acutely infarcted tissue from old lesions.

Patients ranged in age from 45 to 82 years (mean = 60.25years). The mean lesion size on the day-2 DW image was 73.8 ml (2 ml, 12 ml, 13 ml, 34 ml, 39 ml, 145 ml, 167 ml, 178 ml). One patient terminated the examination after 4 days, two patients were examined for only 5 days, one for 6 days, one for 7 days, one for 9 days, and two patients underwent ten examinations. This amounted to 55 MRI examinations in all.

Imaging parameters

MRI studies were performed using a whole-body, 1.5-T system capable of echo planar imaging (EPI) (Edge, Marconi, Cleveland, Ohio, USA). The patient's head movement was comfortably restricted and earplugs were used to control noise discomfort. First, we performed T2-weighted, fast-spin-echo sequences [repetition time (TR) = 10,180 ms, echo time (TE) = 90 ms, number of averages (NA) = 1, slice thickness (Thk) = 6 mm, field of view (FOV) = 22 × 22 cm^2, number of slices (slices) = 19, and matrix size (matrix) = 192 × 256]. For DWI we used an isotropically diffusion-weighted spin-echo EPI sequence (TR = 1,983 ms, TE = 106 ms, NA = 1, Thk = 6 mm, FOV = 17 × 31 cm^2, slices = 10, matrix = 119 × 116, b values: 0, 333, 666, 1,000 s/mm^2). The diffusion scans on day 1 were used to detect the new ischemic region and to calculate parameter maps of the ADC using standard software on a workstation (Vistar, Marconi, Cleveland).

Data analysis

In all patients the stroke core was identified on the heavily DW images (b = 1,000 s/mm^2) from the examination on day 1. After ADC maps had been calculated, ADC values from white and gray matter in the stroke core were measured separately. We used a voxel size of 5 × 5 × 6 mm^3 to measure comparable areas in the acute infarcted tissue and in the corresponding healthy tissue of the opposite hemisphere. In the follow-up MRI studies the voxel of measurement was always placed at exactly the same site as in the initial MRI. This procedure gave four ADC values from each patient for every MR examination. Relative ADC values were calculated by the quotient of the infarcted tissue to the normal one ($rADC = ADC_{ischemia}/ADC_{healthy}$).

Results

The mean delay between symptom onset and first MRI examination was 4.6 h (range: 2–20 h). DWI demarcated the hyperintense ischemic areas with concomitantly reduced ADC values relative to the surrounding brain tissue and the contralateral normal brain tissue in all patients. In the ischemic core, rADC values were always below 1.0 in the first days after symptom onset. We never observed that early recovery of impaired diffusion resulted in a normalization of the rADC (Figs. 1 and 2). The hyperacutely infarcted tissue never demonstrated an increased signal on T2-weighted images within the first 8 h after symptom onset. Old lesions were identified on T2-weighted images in three patients but demonstrated no signal increase on DW images (b = 1,000 s/mm^2).

Mean ADC of control regions in healthy tissue was 943 × 10^{-6} mm^2/s for the white matter and 980 × 10^{-6} mm^2/s for the gray matter. Mean ADC was 468 × 10^{-6} mm^2/s on the first MRI for gray matter lesions and 527 × 10^{-6} mm^2/s for the white matter. The mean rADC for gray matter decreased from 0.546 on day 1 to 0.439 on day 3 after symptom onset. From day 4 onwards the rADC increased continuously to 0.957 at day 9. In the two patients who accepted ten examinations, the mean rADC increased to 1.1 for gray matter (Fig. 1).

The time course for white-matter rADC was similar to that of gray-matter rADC but the gradient of recovery was lower (Fig. 2). The mean ADC decreased to 362 × 10^{-6} mm^2/s on day 3 with a mean rADC of 0.376. On day 10 after symptom onset the mean rADC increased to 1 for the white matter. Thus, around day 10

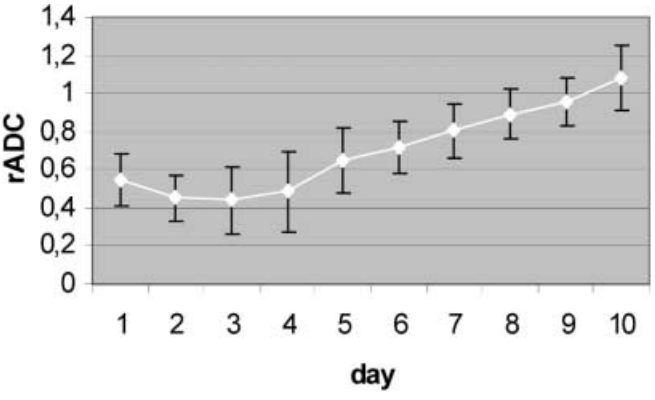

Fig. 1. Time course of rADC in gray matter according to the data from 55 examinations

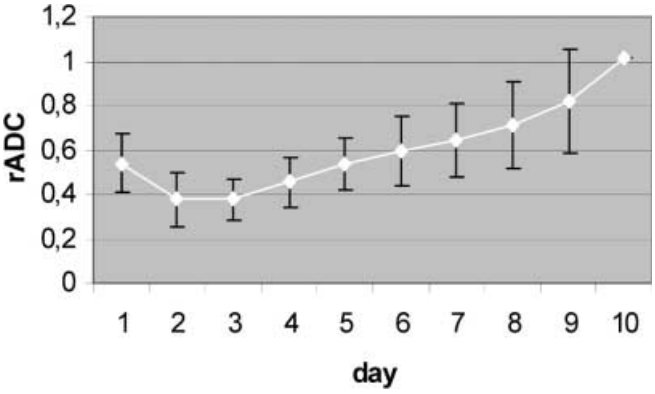

Fig. 2. Time course of rADC in white matter according to the data from 55 examinations

both gray and white matter showed a pseudo-recovery, with rADC values of around 1.0 (Fig. 3).

Discussion and conclusion

The sensitivity of DWI to detect ischemia in hyperacute stroke patients has been demonstrated by several groups in recent papers [4, 8, 9]. Warach and co-authors analyzed the potential of ADC maps in stroke and described the pitfalls of DWI. ADC maps provide more information about water diffusion in brain tissue than DWI [10]. They eliminate the T2 shine-through phenomenon and show diffusion changes in different stages of stroke [11].

Benveniste et al. showed a decrease in the ADC values of 33% in ischemic rat brain tissue 3 h after vessel occlusion [12]. Knight et al. measured ADC changes in the rat brain in serial experiments [6]. They observed a recovery of ADC values in the stroke core after 48 h. At that time the rADC was 1.0 in the infarcted tissue. Based on these findings, Welch et al. analyzed ADC maps from eight patients and correlated the ADC changes in humans to the ADC time course in rats [5]. They analyzed different ADC and T2 patterns and compared those signal changes with the ADC time course of rats. Based on their rat model they identified ischemic tissue with signal changes on DWI which showed no progression of the infarction. They postulated a T2/ADC pattern which can be histopathologically correlated in human brain and suggested that a large clinical study be conducted to prove this. However, they also postulated a pseudo-normalization of the rADC in humans on day 2 after stroke.

Lutsep and colleagues described a different time course in their patients after ischemic stroke [7]. They examined the DWI results of 40 patients which were obtained within the first hours and days after symptom onset. They also calculated the rADCs between ischemic and contralateral healthy tissue. Within the first 8 h

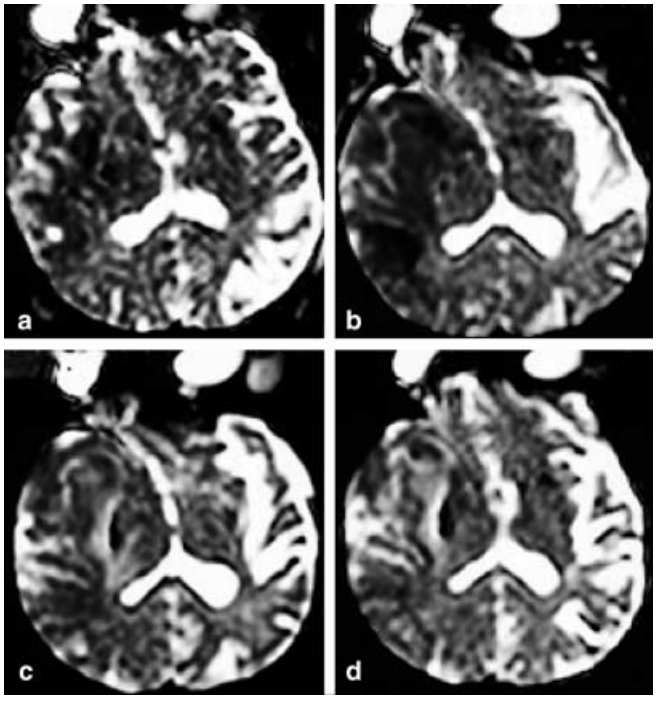

Fig. 3a–d. Examination images from a patient with right-sided occlusion of the middle cerebral artery: **a** day 1; **b** day 3; **c** day 6; **d** day 10

($n = 8$) they observed the lowest rADC. Between 8 and 24 h after stroke, ADC values increased slightly and decreased again until day 4. All their patients showed reduced rADC from the first examinations onwards until day 9. In contrast to the ischemic rat model [6], they never observed an rADC recovery before day 9. From day 10 onwards they observed increasing rADC of up to 3.

Schlaug et al. performed 157 MRI examinations in 101 stroke patients [13]. They observed an rADC of 1 in one patient 5 h after symptom onset. Other patients showed rADC values of 1.0 around the 4th day.

Warach et al. described the lowest ADC values 12 to 24 h after symptom onset [10]. In contrast to other groups, they observed ADC values of 1.15×10^{-3} mm^2/s in the infarcted tissue and 2.19×10^{-3} mm^2/s in healthy tissue. Between the 4th and the 12th day the rADC was 0.77, which increased to 1.41 after 4 months. In contrast to all the other groups, they described much higher ADC values in healthy and infarcted tissue, which probably can be explained by the software and algorithms which they used in their study.

Schwamm et al. reported on the first serial ADC examinations in stroke patients [14]. Four patients were examined during the first 13 h after stroke and follow-up examinations were conducted after 8, 24, 36, and 48 h, 7 days, and 42 days. In all patients, rADC decreased until day 3. Full rADC recovery was first observed after 42 days.

All these recently published studies have described different time courses of the ADC in the ischemic tissue. These differences cannot be explained only by different sequences and mapping techniques. While most of the studies fail to describe the intra-individual time courses of the ADC in acute and subacute ischemic stroke, we examined our patients daily until day 10 according to a standardized DWI protocol. In contrast to other groups, we measured only rADC in the ischemic core. White and gray matter were analyzed separately to exclude characteristics of the tissue architecture of the two kinds of brain tissue. ADC changes were compared with the corresponding region in the healthy hemisphere to control individual differences in temperature or serum sodium concentration, and rADCs were calculated. Even in the first examination the rADC values had already decreased to 0.54 (SD = 0.13). In all infarcts the lowest rADC values were seen on day 3. Gray matter showed a slightly faster recovery of rADC than white matter, with a value of 1 at day 9.

Our findings are comparable with the findings of Lutsep et al. [7]. They observed in 40 cases rADC values between 0.2 and 0.7 within the first days after stroke. Around day 9 rADC values were 1.0 in their cohort. In contrast to the rat model [6] rADC recovery after 48 h has never been found in human brains. The difference in ADC values and time courses between human ischemic stroke and the rat model could be explained by a different cell diameter and structure and different water content in the rat brain.

We never observed a fast ADC recovery in our patients or a T2/DWI pattern indicating a transient signal change with full functional recovery. Tissue with increased signal on DWI and decreased ADC value seems to show mainly the infarct core.

Li and co-authors described a transient recovery of ADC changes in a rat model after 30 min of occlusion of the middle cerebral artery [15]. They observed decreased ADC values during vessel occlusion. Despite a normalization of ADC between 60 and 90 min after reperfusion, ADC secondarily decreased at 12 h after reperfusion. The tissue infarcted and the ADC remained unchanged. This phenomenon has now also been observed in very early recanalized cases of human stroke [16]. However, in these six patients too, initially defined DWI lesions resulted in infarction in three cases. Another case with a prolonged reversible deficit and reversible DWI changes was described by Neuman-Häfelin and co-authors [17]. They observed a slight hyperintensity in DW images 2 h after a patient had woken up with symptoms. Follow-up at 1 week showed only a small lesion on the FLAIR images at the center of the initial DW image hyperintensity.

In routine clinical examinations, ADC changes indicate both an infarction and its age. This could be helpful in distinguishing old infarctions from new ones. Additionally, a single progressive stroke and multiple strokes show different patterns of signal changes, which may be clinically significant.

We analyzed the rADC of ischemic brain tissue with daily examinations from the 1st to the 10th day after stroke. In contrast to the rat stroke model, we observed a decrease in rADC up to 3 days after stroke. From the 3rd to the 10th day we observed an increase in rADC of up to 1.0. The rADC increased slightly faster in gray matter than in white matter. Our results demonstrate the potential of rADC to differentiate hyperacute stroke from acute stroke. This coefficient can identify different stages of stroke and distinguish multiple stroke from a single, progressive stroke.

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