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Value of Diffusion-Weighted Imaging and Apparent Diffusion Coefficient in Recent Cerebral Infarctions: A Correlative Study with Contrast-Enhanced T1-Weighted Imaging

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BACKGROUND AND PURPOSE: **The clinical usefulness and the time course of diffusion-weighted imaging and apparent diffusion coefficient (ADC) in acute and subacute cerebral infarction have not yet been established, although it is known that contrast-enhanced T1-weighted spin-echo imaging can detect a subacute infarct. Our aim was to study which imaging technique is useful in detecting recent infarcts, and whether an increase in ADC or a decrease in signal intensity on diffusion-weighted images is correlated with enhancement on T1-weighted spin-echo images.**

METHODS: **Forty-one infarctions with a duration of 9 hours to 27 days were studied in 29 patients. The ADC and signal intensity on diffusion-weighted images were compared with the contrast-enhancement ratio (CER) on T1-weighted spin-echo images (CER = signal intensity after contrast injection/signal intensity before contrast injection).**

RESULTS: **ADC was linearly correlated with CER, and signal intensity on diffusion-weighted images was inversely correlated with CER. The correlation between ADC and age of the infarct in the subacute phase was weak.**

CONCLUSION: **Diffusion-weighted and contrast-enhanced T1-weighted spin-echo images complement each other in detecting subacute infarcts. Neovascularization and disruption of the blood-brain barrier in infarcts can be important in increasing ADC in subacute infarcts.**

MR imaging is widely used in the diagnosis of cerebral infarction. In clinical practice, physicians are required to detect stroke-related foci or to rule out ischemic stroke in patients with recent neurologic episodes. T1-weighted spin-echo (SE), T2-weighted SE, and fluid-attenuated inversion recovery imaging are commonly used to detect infarcts. It is, however, frequently difficult to identify stroke-related foci in patients with multiple or recurrent infarcts on conventional images.

Recently, many authors have reported that diffusion-weighted images can depict acute and subacute infarcts and that the apparent diffusion coefficient (ADC) is reduced in the acute phase and then increases gradually (1–4). Our initial experience has indicated, however, that signal intensity on diffusion-weighted images and ADC in the subacute phase in human stroke varies case by case, depending on the location in the infarct. In comparison, contrast enhancement on T1-weighted SE images is weak and rare in the acute phase and increases in the subacute phase (5, 6).

We considered whether ADC is associated with time since stroke onset, and which imaging technique is useful for detecting recent infarcts: diffusion-weighted imaging or contrast-enhanced T1-weighted SE imaging. Our aim was to determine whether an increase in ADC or a decrease in signal intensity on diffusion-weighted images is related to reperfusion or blood-brain barrier breakdown seen on contrast-enhanced T1-weighted SE images.

Methods

A total of 38 randomly selected cases of infarcts (19 thrombotic and 19 embolic) in 29 patients (age range, 55 to 90 years; mean, 69 years) in acute and subacute phases (9 hours to 27 days) were studied. Only patients in whom an infarct was eventually confirmed by MR and/or CT examination were included. Classification of embolic or thrombotic infarcts followed the final diagnosis and was determined on the basis of the time of stroke onset (abrupt or progressive), the location of the infarct (the end-arterial region or elsewhere), the echocardiographic findings (presence of a cardiogenic embolic source), and the angiographic findings (presence of arteriosclerosis or stenosis).

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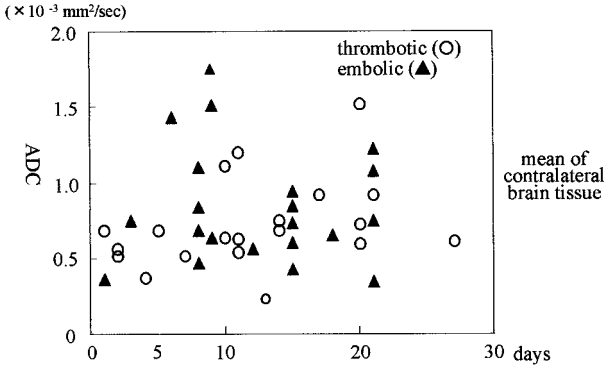

FIG 1. ADC as a function of time after stroke onset. Both embolic and thrombotic infarcts have a low ADC before 6 days, but they vary in the subacute phase (6 ≤ 27 days). An extremely high ADC is observed in three embolic infarcts in the early subacute phase (6 ≤ 10 days).

MR imaging was performed on a 1.5-T system by using single-shot SE echo-planar imaging (EPI) with Stejskal-Tanner diffusion-encoding gradient pairs along the through-plane direction with b values of 30 (T2-weighted EPI) and 1200 (diffusion-weighted EPI) seconds per mm^2. Imaging parameters included a TE of 123, a field of view of 23 cm, a matrix of 128 × 128, a section thickness of 4 mm, and an intersection gap of 2 mm. Imaging sections were parallel to the orbitomeatal line, and 20 sections covered the whole brain. The ADC maps were generated from T2-weighted EPI and diffusion-weighted EPI on the section through the central portion of an infarct by using the following relationship:

$$S = S_0 \exp(-b \cdot ADC),$$

where S and S_0 are the signal intensities of diffusion-weighted EPI and T2-weighted EPI, respectively.

Conventional SE imaging was also performed at each examination in T2-weighted (5400/99 [TR/TE]) and T1-weighted (630/14) conditions. T1-weighted SE imaging was repeated 5 minutes after injection of 0.1 mmol/kg of contrast medium in the antecubital vein.

The ADC, the signal intensity on diffusion-weighted EPI images, and the signal intensity on T1-weighted SE images were measured using operator-defined regions of interest (ROIs) placed in the core region of each infarct. Two infarcts in two patients were imaged two times. In a broad infarct of the left middle cerebral artery, two ROIs were placed in regions with relatively high and low signal intensities on diffusion-weighted EPI. Consequently, 41 ROIs of 38 infarcts were studied. Relative signal intensity (SI) to the contralateral normal brain tissue on diffusion-weighted images was calculated as follows:

Relative SI on diffusion-weighted images
= (SI of infarct)/(SI of normal brain)

Signal enhancement with contrast medium was evaluated as a ratio of the signal intensities before and after contrast medium injection on T1-weighted SE images (CER = contrast-enhancement ratio):

CER on T1-weighted SE images
= (postcontrast SI)/(precontrast SI).

Results

The time course of ADC after stroke onset is shown in Figure 1. All acute infarcts (within 5 days) had a low ADC (mean ± SD = 0.57 ± 0.16 × 10^{-3} mm^2/s), and the mean ratio of the infarcts to normal contralateral brain tissue was 0.55 (Fig 2, right frontal infarct). In the early subacute phase (6 to 10 days), three of eight embolic infarcts had an extremely high ADC (Fig 2, left frontal infarct), and the eight embolic infarcts had an ADC of 1.06 ± 0.47 (× 10^{-3} mm^2/s), which was higher than that of the three thrombotic infarcts (0.76 ± 0.31). In the late subacute phase (11 to 27 days), the ADC had various values, and no difference was observed between thrombotic (0.78 ± 0.33) and embolic (0.75 ± 0.27) infarcts. Even in the near chronic phase (27 days after onset), a low ADC was observed (Fig 3).

Contrast enhancement on T1-weighted SE images (CER) was extremely weak within 5 days (mean ± SD = 1.09 ± 0.08), and then increased in the subacute phase (Fig 4). In the early subacute phase (6 to 10 days), three of eight embolic infarcts revealed a high CER in accordance with a high ADC (the high CER and the high ADC infarcts were the same) (Fig 2, left frontal infarct). The mean CER was 1.52 for the eight embolic infarcts and 1.12 for the three thrombotic infarcts. In the late subacute phase (10 to 27 days), no difference in the CER was observed between thrombotic (1.28 ± 0.30) and embolic (1.30 ± 0.30) infarcts. The CER and the ADC were linearly correlated with each other in both thrombotic and embolic infarcts (Fig 5).

Relative signal intensity on diffusion-weighted EPI was inversely correlated with CER on T1-weighted SE images. Almost all infarcts revealed high intensity on either diffusion-weighted images or postcontrast T1-weighted images (Fig 6). Relative signal intensity was high in all the acute infarcts (within 5 days); no significant difference was observed between thrombotic (mean, 3.3) and embolic (mean, 2.7) infarcts. Relative signal intensity in the subacute phase (6 to 27 days) was higher in thrombotic infarcts (2.65 ± 1.38) than in embolic infarcts (1.67 ± 0.62).

All infarcts revealed a higher intensity than surrounding brain tissue on T2-weighted EPI, except an overt hemorrhagic region in an embolic infarct that was eliminated from the evaluation (Fig 2).

Discussion

In this study, both embolic and thrombotic infarctions were included. The reperfusion process can be significantly different between the two types of infarctions. In addition, time of onset of infarction was somewhat unclear if a patient had a progressive symptom and/or recurrent episodes. These findings may be a cause of the weak correlation between signal intensity on diffusion-weighted images and time, and between the ADC and time after stroke. Even though we used a set of infarcts with various clinical conditions, the correlation between ADC and contrast enhancement on T1-weighted SE images was high.

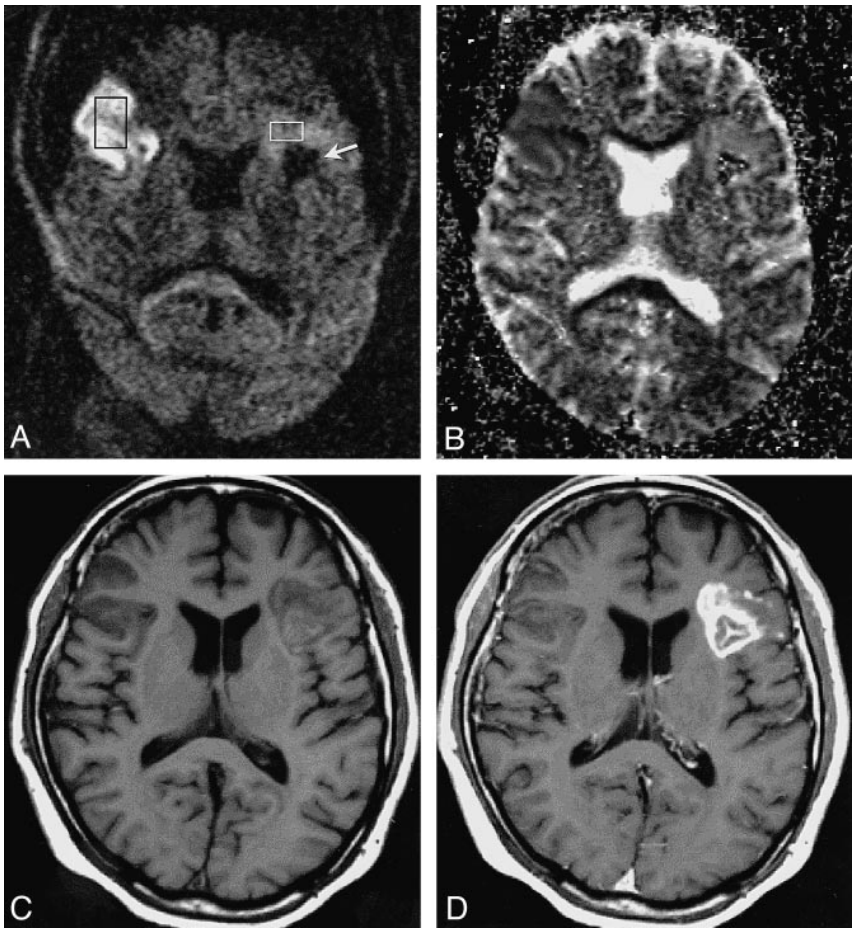

FIG 2. *A–D*, Embolic infarcts at 3 days (right frontal) and 6 days (left frontal) after stroke onset. Right frontal infarct reveals marked high intensity on the diffusion-weighted image (*A*), and a low ADC (*B*) and little enhancement (*C*, before contrast; *D*, after contrast) on the T1-weighted SE images. *Black rectangle* indicates the ROI placed in the core region (*A*). Anterior portion of left frontal infarct reveals a mild high-intensity signal on the diffusion-weighted image (*A*) and a moderately high ADC (*B*) and marked enhancement (*C* and *D*) on the T1-weighted SE images. The posterior portion has extremely low intensity on the diffusion-weighted image because of hemorrhage (*arrow* in *A*). *White rectangle* (*A*) indicates the ROI placed in the anterior portion.

The time course of the ADC in human stroke is controversial. Welch et al reported that three of eight cases revealed an increased ADC within 4 days after onset (7). Chien et al reported that two of four infarcts studied at 3 to 4 days revealed an extremely high ADC (8). The number of patients in these studies, however, was small. Warach et al studied 40 patients from 3 hours to over 3 months after infarction and found that the transition from a reduced to an elevated ADC occurred at approximately 9 to 10 days after stroke onset (2). The results of this study coincided with the results of Warach et al, with the ADC being lower than normal tissue before 6 days. After 6 days, however, our study indicated a discrepancy with their report, with the ADC increase being variable from case to case.

The differences in the results among these studies are probably attributable to the use of different patient populations, as well as to technical issues. Calculating the exact average of an ADC for the entire region of an infarct that is seen in multiple sections is not easy. Warach et al visually identified high-intensity lesions on diffusion-weighted images and computed the average ADC in that region. In our study, a single ROI in a single section was placed in the core region of the infarct; iso- or low-intensity lesions on diffusion-weighted images with high enhancement were also included, as well as high-intensity lesions. Although our results may not necessarily establish the exact time course of the ADC after stroke onset, they emphasize the close relationship between the ADC and contrast enhancement.

The mechanism of the increase of the ADC in the subacute phase may be complex, reflecting various pathologic events, including cell death, membrane disruption, and the development of so-called vasogenic edema. The latter event would preferentially increase extracellular volume and, thereby, increase the ADC, but the precise mechanism for this has not yet been established. In comparison, parenchymal contrast enhancement in the subacute stage is considered to be caused by neovascularization and breakdown of the blood-brain barrier (5, 9). The findings of our study have established that the processes that increase parenchymal enhancement might be related to, or are in accordance with, extracellular fluid collection and cell membrane disruption, which can increase ADC.

The recanalization of embolic infarcts in the acute phase does not necessarily cause an immediate increase in ADC. In one of our patients, who had cardiogenic embolic infarction of the right middle cerebral, the infarct recanalized 14 hours after stroke onset, and ADC was low 18 hours after recanalization. The results of both our study and previous studies of enhanced MR imaging in isch-

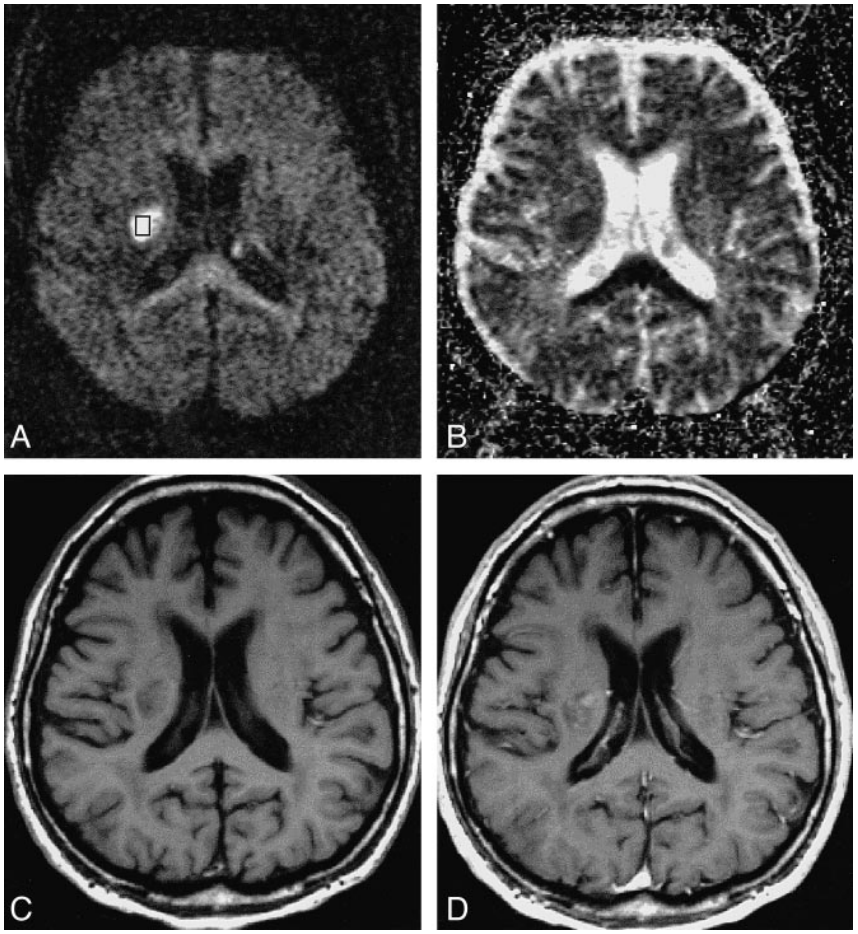

FIG 3. Thrombotic infarct of the right corona radiata (27 days after stroke onset) has marked high intensity on the diffusion-weighted image (*A*) and a low ADC (*B*) and little enhancement (*C* and *D*) on the T1-weighted SE images. *Black rectangle* shows the ROI placed in the core region (*A*).

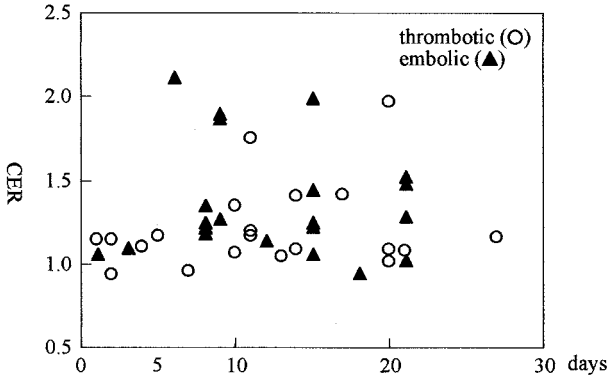

FIG 4. CER on T1-weighted SE images is low in the acute phase (<6 days), but varies in the subacute phase (6 to 27 days). An extremely high CER is observed in three embolic infarcts in the early subacute phase (6 to 10 days).

emic stroke have indicated that parenchymal enhancement on T1-weighted SE images is unusual before 6 days (5, 6, 9). These results agree with the finding that ADC was low before 6 days.

Because of the anisotropy of diffusion in brain tissue, a trace (sum of diagonal elements) of the diffusion tensor and mean diffusion-weighted images may be preferable to an evaluation of ADC and signal intensity on diffusion-weighted images (3, 10, 11). We used diffusion-encoding gradient pairs in the through-plane direction, which may be a cause of the variation in ADC. Diffusion anisotropy in an infarct would be reduced if the cells were lysed; therefore, the use of a relative ADC in the contralateral brain tissue that is anisotropic would not necessarily result in a better correlation between CER and time after stroke onset than would the use of an absolute ADC. We have confirmed in another patient group that diffusion anisotropy is maintained in acute infarcts and decreases in subacute infarcts by using three directions of diffusion-encoding gradient pairs (unpublished data).

High signal intensity on diffusion-weighted images relative to the contralateral normal brain tissue (high relative signal intensity) is useful for detecting recent infarcts. Quantitative evaluation of the relative signal intensity has, however, a few limitations. First, relative signal intensity depends on the b value used for diffusion-weighted images, as well as on the signal intensity on T2-weighted EPI and the ADC. A radically different b value (eg, several hundred seconds per mm^2) may produce a qualitatively different result on the relative signal intensity-CER relationship from that in our study. Second, relative signal intensity on diffusion-weighted images with a diffusion-encoding gradient in a single direction depends on diffusion

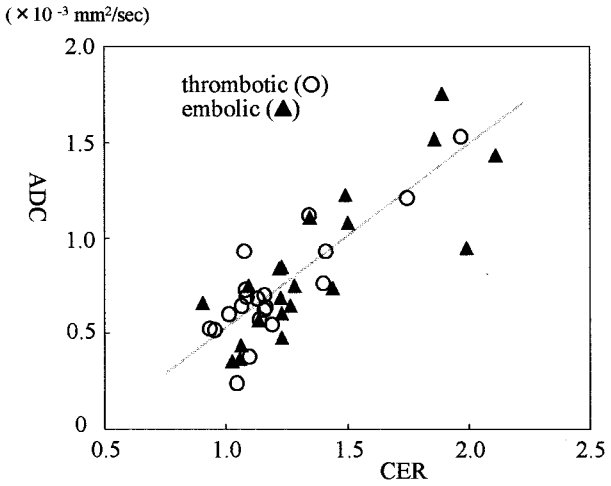

FIG 5. ADC is linearly correlated with contrast enhancement on T1-weighted SE images (CER) in both thrombotic and embolic infarcts. Correlation coefficients are 0.85 for thrombotic and 0.82 for embolic infarcts.

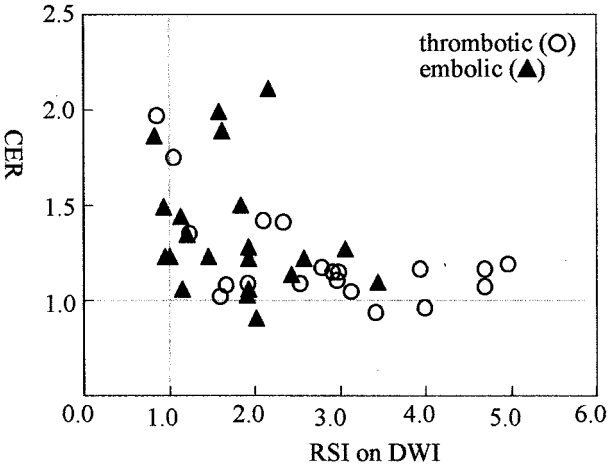

FIG 6. Contrast enhancement on T1-weighted SE images (CER) is inversely correlated with relative signal intensity (RSI) on diffusion-weighted images. All the infarcts reveal higher values than normal brain tissue with either the CER or relative signal intensity.

anisotropy. A higher relative signal intensity in subacute thrombotic infarcts than in embolic infarcts may be largely attributed to diffusion anisotropy. Twelve of 20 ROIs of thrombotic infarcts were located in the centrum semiovale, the corona radiata, the internal capsule, the pons, and the medulla oblongata; where the neuronal fibers had a tendency to run suprainferiorly, they were nearly parallel to the orientation of diffusion-encoding gradient pairs, resulting in a high ADC and a low signal intensity on diffusion-weighted images in the contralateral brain tissue. Meanwhile, only four of 21 ROIs of embolic infarcts were placed in these regions. The relative ADC of subacute thrombotic infarcts to the contralateral normal brain tissue (0.77 ± 0.35 mm^2/s) was significantly lower than that of subacute embolic infarcts (1.16 ± 0.47). All four thrombotic infarcts with an extremely high signal intensity ratio on diffusion-weighted images (relative signal intensity ≥ 4) were in the corona radiata ($n = 2$) and the pons ($n = 2$) (Fig 6). We believe that the diffusion anisotropy in contralateral normal brain tissue and the loss of anisotropy in infarcts resulted in a higher relative signal intensity of thrombotic infarcts relative to embolic infarcts in the subacute phase.

After the findings of Le Bihan et al showing that diffusion-weighted images and ADCs are available in the human brain (12, 13), Moseley et al first detected ischemic injury of the brain by diffusion-weighted images less than 1 hour after onset of ischemia in animals (14, 15). Thereafter, many authors considered that this technique might predict the outcome of acute ischemia in animal models (16–21) and in clinical studies (1–4, 22, 23). In clinical practice, however, the majority of stroke patients are admitted to the hospital several hours or more after stroke onset. The purpose of an MR examination in patients with suspected cerebral infarction is mainly to confirm or detect lesions related to recent episodes.

Our findings have established that either diffusion-weighted or contrast-enhanced T1-weighted images can depict almost all acute and subacute infarcts. We propose that if a recent infarction is suspected, diffusion-weighted imaging should be performed in addition to conventional imaging, because EPI-based diffusion-weighted images can be obtained instantaneously. Subsequently, if diffusion-weighted images do not show the stroke-related lesions, contrast-enhanced T1-weighted SE imaging is recommended. We have had many experiences to indicate that contrast-enhanced T1-weighted SE imaging was useful for depicting small cortical embolic infarcts in the subacute phase.

All five acute infarcts had a low ADC. A high ADC and a high CER in the early subacute phase suggest an embolic infarct. A lower ADC than is found in brain tissue may be specific to a recent infarct, since no other lesion is known to have a low ADC except hematoma and abscess. In general, however, the ADC itself is not vital in clinical practice. The linear relationship between ADC and CER indicates that well-enhanced lesions have low signal intensity on diffusion-weighted images, and vice versa.

Conclusion

Our findings have established that ADC is linearly correlated with CER on T1-weighted SE images and can indicate reperfusion and blood-brain barrier breakdown, and that diffusion-weighted images and postcontrast T1-weighted SE images complement each other in depicting recent infarcts.

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