

# Simple quantitative measurement based on DWI to objectively judge DWI-FLAIR mismatch in a canine stroke model

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## PURPOSE

Diffusion-weighted imaging (DWI) - fluid attenuated inversion recovery (FLAIR) mismatch was proven useful to time the onset of wake-up stroke; however, identifying the status of FLAIR imaging has been mostly subjective. We aimed to evaluate the value of relative DWI signal intensity (rDWI), and relative apparent diffusion coefficient (rADC) in identifying the FLAIR status in the acute period.

## METHODS

Autologous clot was used to embolize left middle cerebral artery in 20 dogs. Magnetic resonance imaging was performed 3–6 hours and 24 hours after embolization. DWI-FLAIR mismatch was defined as hyperintense signal detected on DWI, but not on FLAIR. The mean values of rDWI or rADC of FLAIR- and FLAIR+ lesions were compared and the critical cutoff values of rDWI and rADC for identifying the FLAIR status were determined.

## RESULTS

Stroke models were successfully established in all animals. DWI+ lesions were found in all 20 dogs from three hours, while FLAIR+ lesions were found in three, 11, 16, 19, and 20 dogs at five time points after embolization, respectively. The mean rDWI values were significantly different between FLAIR- and FLAIR+ lesions ( $P < 0.001$ ), but rADC values were not ( $P = 0.73$ ). Using rDWI=1.90 as the threshold value, excellent diagnostic efficacy was achieved (AUC, 0.88; sensitivity, 0.77; specificity, 0.88). However, rADC appeared not useful (AUC, 0.48; sensitivity, 0.52; specificity, 0.58) in identifying the FLAIR status.

## CONCLUSION

In our embolic canine stroke model, rDWI was useful to identify FLAIR imaging status in the acute period, while rADC was not.

**D**iffusion-weighted imaging (DWI) - fluid attenuated inversion recovery (FLAIR) mismatch refers to the situation where an ischemic lesion is detected on DWI in the absence of a corresponding lesion on FLAIR imaging. Recently, several studies indicated that DWI-FLAIR mismatch might aid to predict whether the stroke onset time is within 4.5 hours or not (1–6). Furthermore, this mismatch pattern, which is based on the detection time difference between DWI and FLAIR imaging, would help to time the stroke lesions in patients with unclear onset time. This information is important for clinicians to select the optimal treatment, because more ischemic stroke patients would benefit from thrombolytic therapy (7). However, in previous studies, assessment of FLAIR imaging has been subjective. An objective, simple, and quantitative measurement to help judge the status of FLAIR imaging is yet to be found.

DWI can detect a hyperacute ischemic lesion as soon as 30 minutes after stroke, and it is viewed as a sensitive and effective tool to detect ischemic stroke events (8, 9). Meanwhile, several studies observed that the relative signal intensity (SI) of lesions on DWI could be a reliable parameter to demonstrate the secondary pathologic process after ischemic stroke (10). Therefore, we hypothesized that, quantitative parameters derived from DWI, such as relative DWI signal intensity (rDWI) and relative ADC value (rADC), might be useful to evaluate the status of FLAIR imaging.

In this study, we aimed to determine the value of rDWI and rADC in evaluating the status of FLAIR imaging, based on our embolic canine ischemic stroke model, considering different temporal evolution of the volume of ischemic lesions demonstrated on DWI and FLAIR imaging.

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## Methods

### Stroke model establishment

Twenty adult healthy beagle dogs (weighing  $13.8 \pm 0.7$  kg) were used in our study. Animal preparation and cerebral ischemia model establishment were performed according to our previous studies by two experienced interventional neuroradiologists (11, 12). In brief, after anesthetizing the dog with intravenous pentobarbital (3 mg/kg; Chemical Reagent Company), prepared autologous clot of appropriate size was injected into the left proximal middle cerebral artery under live fluoroscopy (Axiom Artis, Siemens AG). Then, a 5F catheter (Terumo Medical Corp.) was guided 2 cm distal to the orifice of ipsilateral internal cerebral artery to block the blood flow for two hours. After successful embolization, the animals were transferred to magnetic resonance imaging (MRI) scan room. This experiment was approved by the institutional animal care and use committee of our university. Effective methods were used to reduce pain or discomfort during the entire experiment.

### Magnetic resonance imaging

All animals underwent MRI on a 3.0 T MRI device (Trio, Siemens Medical Solutions) with transmit-receive extremity coil. All animals were fixed and placed in the magnet in the supine position. The same anesthetic medication and doses were used to maintain the immobility of animals during the scan. Imaging acquisitions were performed serially at 3, 4, 5, 6, and 24 hours after model establishment, respectively. DWI and FLAIR imaging were performed as two important sections of all image sequences. DWI was performed with an echo-planar spin-echo sequence with 22 coronal sections acquired at  $b=50$  s/mm<sup>2</sup> and  $b=800$  s/mm<sup>2</sup>. Other imaging parameters were: TR 5500 ms, TE

96 ms, section thickness 2 mm, no gap, matrix 192×192, field of view 20 cm. FLAIR was performed using a turbo spin-echo sequence. The parameters for FLAIR were: TR 8000 ms, TE 97 ms, section thickness 2 mm, no gap, matrix 320×320, field of view 20 cm. After sequential MRI scans, the animals were recovered and kept in the animal facility for other stroke-related studies.

### Imaging process

DWI positive (DWI+) or FLAIR positive (FLAIR+) lesions were defined as new hyperintense signals detected on DWI or FLAIR imaging. The imaging assessments were performed as follows:

First, for temporal evolution of the rDWI and rADC value of the whole ischemic lesions, three regions of interest (ROIs) were placed on initial DWI (at 3 h) that showed the most obvious lesions. After ROIs were determined on initial DWI, the same ROIs were reproducibly placed at the same location on the ADC map and on subsequent DWI scans. ROIs were manually positioned in the ischemic cerebral hemisphere, and control values were obtained from mirrored normal regions in the contralateral hemisphere. The average size of ROIs was  $6.6 \pm 0.3$  mm<sup>2</sup>. The rDWI and rADC were calculated as follows:  $rDWI = SI_{\text{lesion}} / SI_{\text{contralateral}}$ ,  $rADC = ADC_{\text{lesion}} / ADC_{\text{contralateral}}$ . This step of imaging assessment was finished by two radiologists and the mean value of their measurements was used in the statistical analysis.

Second, one radiologist and one interventional neuroradiologist experienced in stroke-related imaging and intervention research judged the status of FLAIR imaging as positive or negative. In case of discrepancy between the judgements, the senior observer made the final decision.

Third, the area of the FLAIR lesions was delineated by all three observers in consensus and copied on DWI for further imaging segmentation. The imaging segmentation process was performed according to the methods previously proposed by Madai et al. (13). After this process, there were three possible scenarios: a) FLAIR imaging is negative; b) FLAIR imaging is positive, but the volume of FLAIR+ lesion appears smaller than that of DWI+ lesion; c) FLAIR imaging is positive and the volume of FLAIR+ lesion is almost equivalent of that of DWI+ lesion (Fig. 1). In case of smaller FLAIR lesion, we subdivided the volume of DWI+ lesion by the volume of FLAIR+ lesion. The mismatch area between

DWI+ and FLAIR+ lesions was viewed as FLAIR negative (FLAIR-).

Fourth, to separately measure the rDWI or rADC of FLAIR+ and FLAIR- lesions, three ROIs were placed on 1–3 slices which showed the most obvious lesions and covered the FLAIR+ or FLAIR- lesions. Control SI values were also obtained from mirrored ROIs in the contralateral normal hemisphere. The rDWI and rADC value were calculated using the formula mentioned above. Measurement of rDWI and rADC for FLAIR+ and FLAIR- lesions were performed by two radiologists, and the mean value of their measurements was used in the statistical analysis.

### Statistical analysis

Repeated-measure test was used to assess the temporal changes of mean rDWI and rADC values of the whole ischemic lesions at five different time points. Interobserver agreement for quantitative measurements of rDWI and rADC was assessed with Pearson correlation coefficient. Interobserver agreement for the judgment of FLAIR imaging status was assessed with Kappa test. The mean rDWI and rADC values of FLAIR- and FLAIR+ lesions were compared with paired t test. Furthermore, a receiver operating characteristic (ROC) curve was drawn to analyze the rDWI or rADC cutoff value to predict the status of FLAIR imaging with optimal sensitivity and specificity. A significant difference was considered if the two-tailed *P* value was less than 0.05. All statistical analyses were performed using SPSS 17.0 (SPSS Inc.).

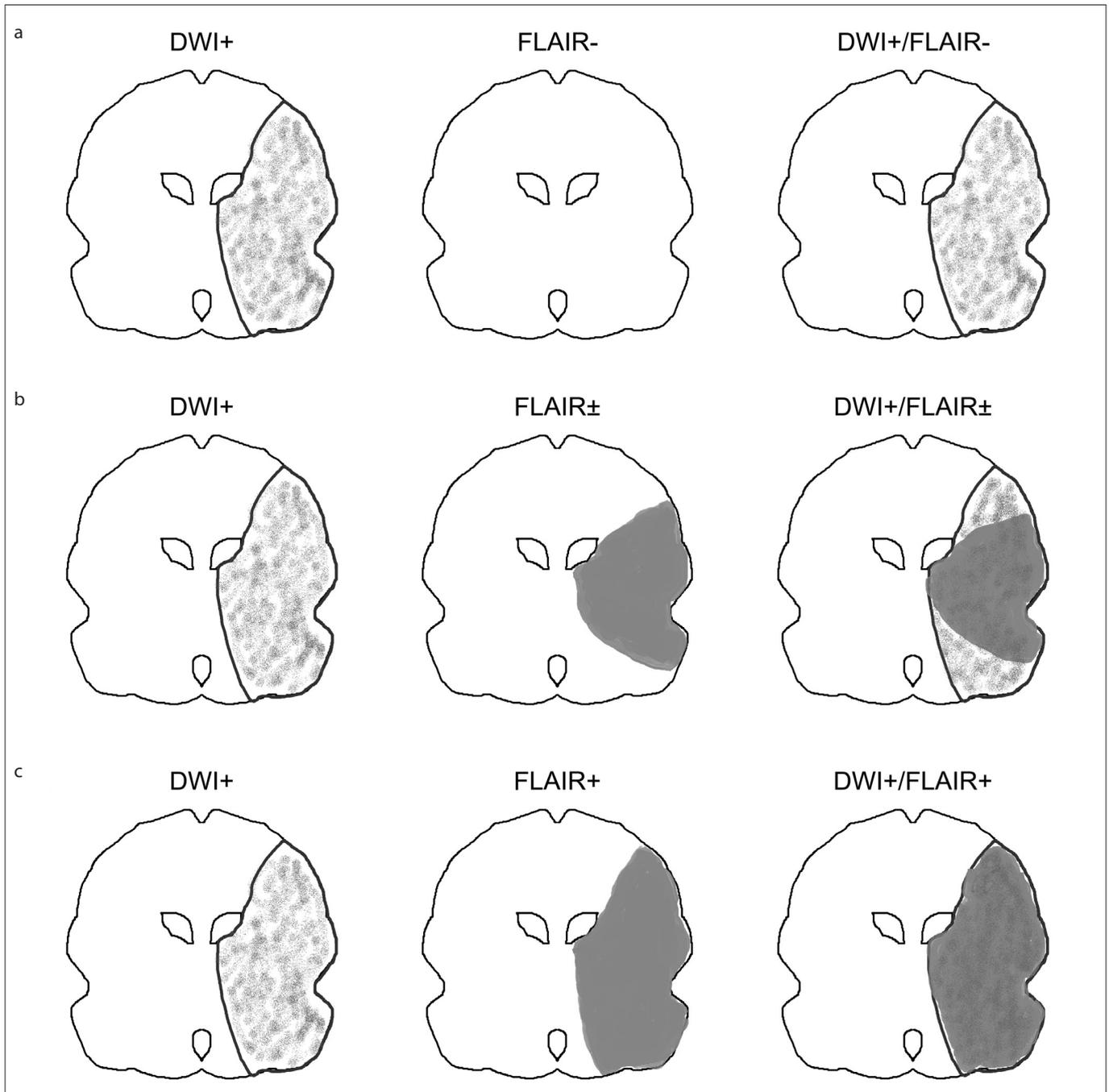
## Results

Ischemic models were established successfully in 20 beagle dogs without any procedure-related complications or casualties. DWI showed ischemic lesions located on the ipsilateral caudate nucleus and the cortical area of the temporal lobe. In general, ischemic lesions were primarily detected at the caudate nucleus, and then gradually appeared in the cortical area of the temporal lobe.

Interobserver agreement was 0.84 ( $\kappa=0.79$ ; 95% confidence interval [CI], 0.77–0.89) for rDWI quantification and 0.85 ( $\kappa=0.80$ ; 95% CI, 0.77–0.90) for rADC quantification. At 3, 4, 5, 6, and 24 hours after embolization, rDWI values were measured as  $1.57 \pm 0.53$ ,  $1.86 \pm 0.41$ ,  $2.13 \pm 0.57$ ,  $2.36 \pm 0.40$ , and  $2.56 \pm 0.81$ , meanwhile, rADC values were measured as  $0.56 \pm 0.08$ ,  $0.55 \pm 0.06$ ,

### Main points

- The relative diffusion-weighted imaging signal intensity (rDWI) of ischemic lesions might be helpful to identify the status of fluid attenuated inversion recovery (FLAIR) imaging in acute ischemic stroke.
- The relative apparent diffusion coefficient (rADC) value appears not useful to identify the status of FLAIR imaging in the acute period.
- Based on our embolic canine model, rDWI increased gradually in the acute period, while the rADC kept stable, which might explain why rDWI is helpful to identify the status of FLAIR imaging, while rADC is not.



**Figure 1.** a–c. Schematic illustration of three different patterns of diffusion-weighted imaging (DWI) - fluid attenuated inversion recovery (FLAIR) mismatch. In panel (a), ischemic lesions are detected on DWI but not on FLAIR. In panel (b), ischemic lesions are detected on both DWI and FLAIR, but  $V_{FLAIR} < V_{DWI}$ . In panel (c), ischemic lesions are detected on both DWI and FLAIR, and  $V_{FLAIR} = V_{DWI}$ .

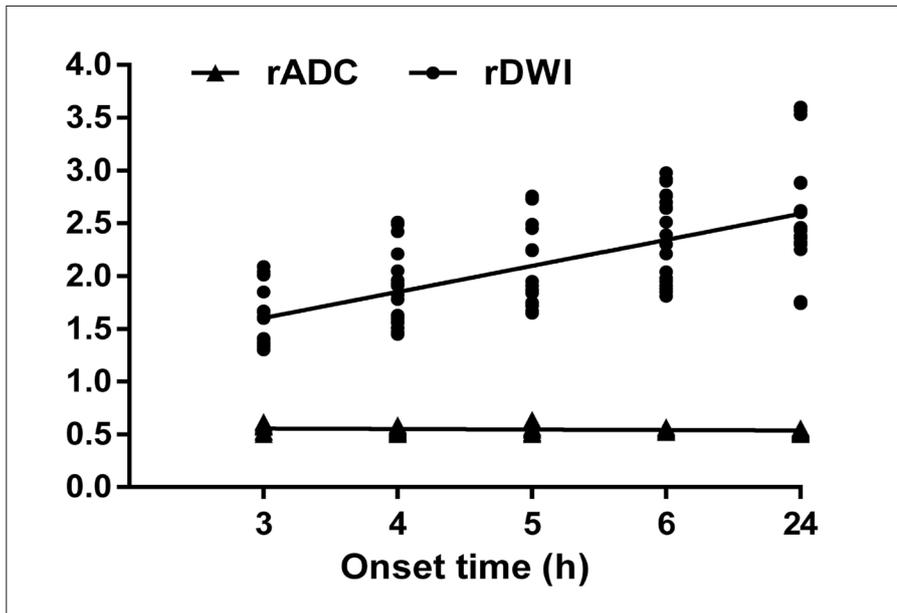
0.54±0.01, 0.54±0.04, and 0.54±0.02, respectively. All values were linearly correlated with onset time until 24 hours after embolization (rADC,  $P = 0.02$ ; rDWI,  $P < 0.001$ ). The mean rDWI value increased significantly until five hours after embolization (4 h vs. 3 h,  $P = 0.03$ ; 5 h vs. 4 h,  $P = 0.04$ ), with no significant difference in rDWI measured at 6 and 24 hours ( $P > 0.05$ ). No significant difference was seen in rADC values measured at

any two time points ( $P > 0.05$ ). Time course of mean rDWI and rADC values after model establishment is shown in Fig. 2.

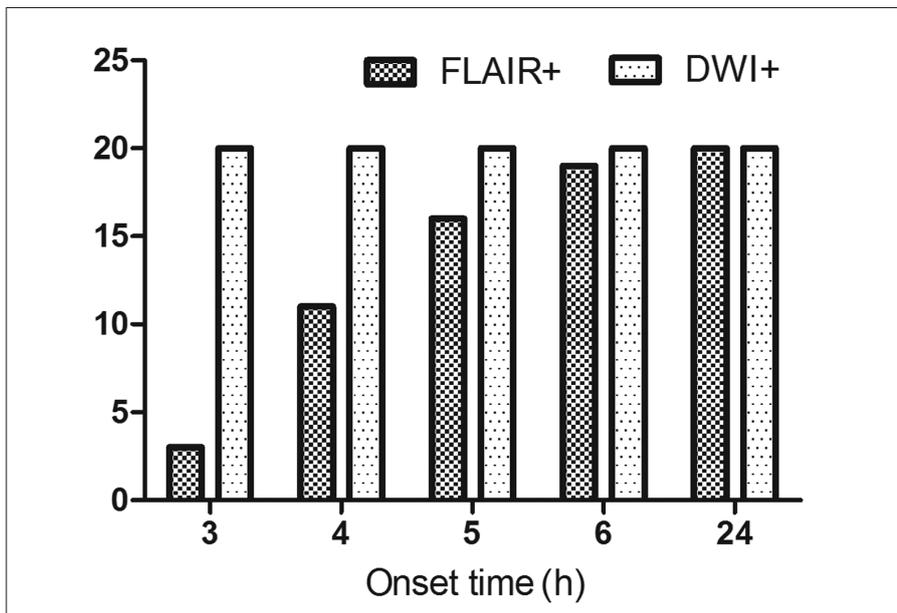
The interobserver agreement for qualitative judgement of FLAIR status was 0.60, 0.80, 0.80, 0.90, and 1.00 at 3, 4, 5, 6, and 24 hours after model establishment, respectively. DWI was rated as positive beginning at three hours after embolization in all 20 beagle dogs. FLAIR was rated as positive in three

dogs at three hours, 11 dogs at four hours, 16 dogs at five hours, 19 dogs at six hours, and all 20 dogs at 24 hours after embolization, respectively. The numbers of DWI+ and FLAIR+ dogs are shown in Fig. 3. Pattern of DWI-FLAIR mismatch is shown in Fig. 4 using the DWI and FLAIR images acquired six hours after model establishment in Dog 11.

After the imaging segmentation, the mean rDWI and rADC values for FLAIR+



**Figure 2.** Time course of relative DWI signal intensity (rDWI) and relative apparent diffusion coefficient (rADC) is shown at five time points after model establishment.



**Figure 3.** Number of FLAIR+ dogs at each time point is presented in a bar graph. All 20 dogs were DWI+ at all time points.

and FLAIR- lesions were measured. Interobserver agreement was 87% ( $\kappa=0.78$ ; 95% CI, 0.77–0.96) for quantitative measurement of rDWI and 86% ( $\kappa=0.80$ ; 95% CI, 0.78–0.97) for quantitative measurement of rADC.

The mean rADC values of FLAIR- and FLAIR+ lesions were  $0.54\pm0.02$  and  $0.54\pm0.04$ , with no significant difference between them ( $P = 0.73$ ) (Fig. 5a). The critical rADC cutoff value to predict positive FLAIR imaging was determined as 0.54, yielding 0.52 optimal sensitivity, 0.58 specificity, and 0.48 AUC (Fig. 5b).

The mean rDWI values of FLAIR- and FLAIR+ lesions were significantly different ( $1.67\pm0.39$  vs.  $2.29\pm1.53$ ,  $P < 0.001$ ) (Fig. 6a). The critical rDWI cutoff value to predict positive FLAIR imaging was determined as 1.90, yielding 0.77 optimal sensitivity, 0.88 specificity, and 0.88 AUC (Fig. 6b).

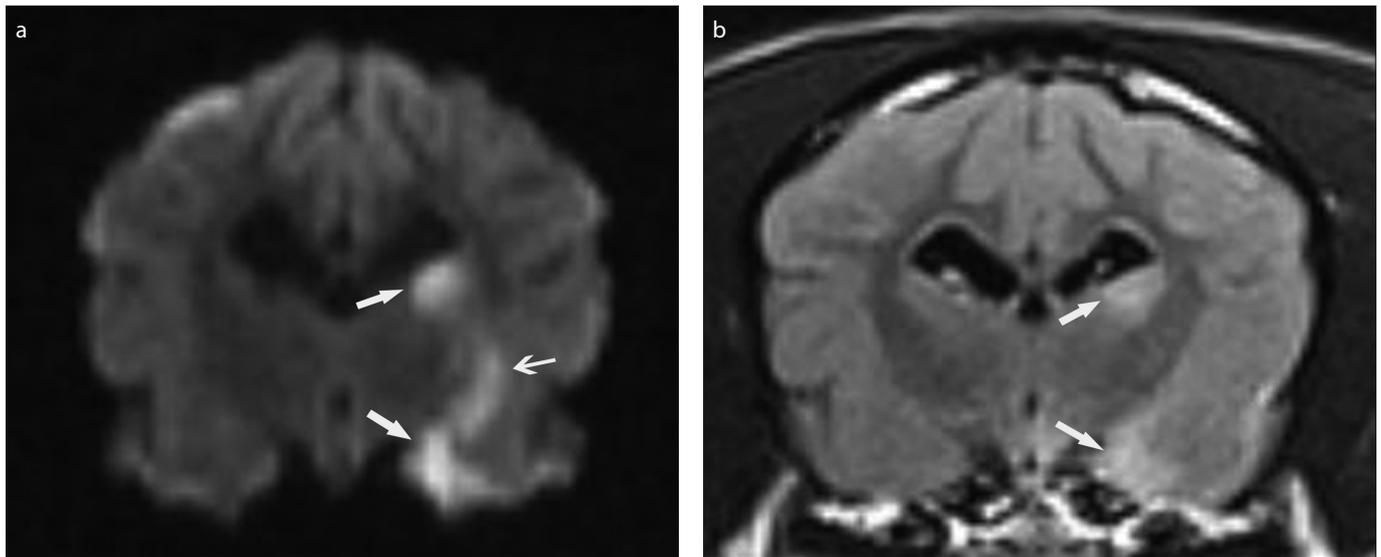
## Discussion

Our study demonstrates several major findings. First and most importantly, the

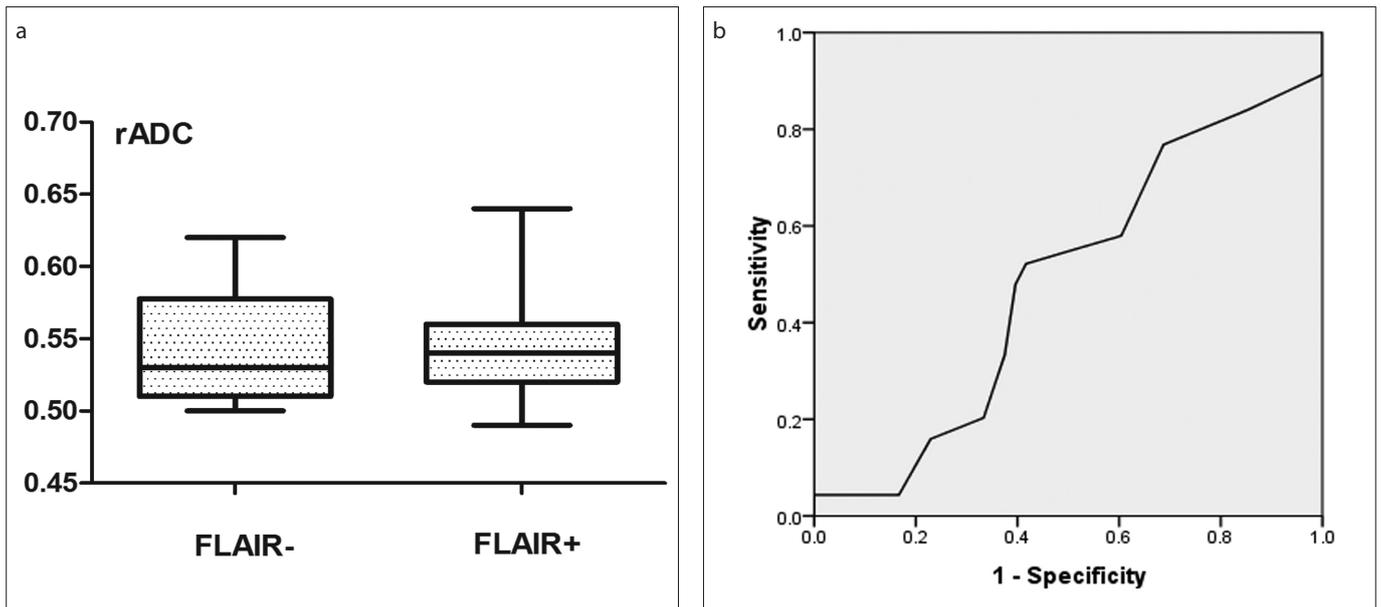
rDWI may help identify whether the FLAIR imaging was positive or not in the acute period. Second, as expected, the sensitivity of DWI for detecting hyperacute ischemic lesions was higher than that of FLAIR imaging, which is the theoretical basis of the concept of “DWI-FLAIR mismatch”. Third, the rADC kept stable and the rDWI increased significantly in the acute period based on our embolic canine model, which might be the reason why rDWI, and not rADC, may be helpful to identify the status of FLAIR imaging.

Approximately 25% of ischemic strokes happen during sleep with no clear onset time (5). This situation would preclude the patients from thrombolytic therapy, due to insufficient evidence of safety and efficacy. As a result, strategies to identify patients who can potentially benefit from thrombolytic therapy have always been the major focus in stroke-related studies. At present, based on multiparametric MRI, a characteristic pattern, known as DWI and FLAIR mismatch, has attracted widespread attention (4–6). DWI can detect ischemic lesions as soon as 30 minutes after onset time, while FLAIR imaging can detect ischemic lesions at a later time (14, 15). Previous studies suggested that the time gap of detection between DWI and FLAIR imaging, can allocate patients to the current thrombolysis treatment time window (within 4.5 hours), with high specificity and positive predictive value (4–6). Assessment of FLAIR imaging status is a key factor, if DWI-FLAIR mismatch is to be used in the clinical setting. However, assessment of FLAIR status was mostly subjective in previous studies and depended on the clinical experience of the neuroradiologist, sometimes leading to a relatively low interobserver agreement. Therefore, a simple and objective method is urgently needed to identify whether FLAIR imaging is positive or not.

Currently DWI is a routine and essential imaging sequence during stroke-related imaging studies. Based on DWI, relative signal intensity and ADC value are the most common and simple quantitative parameters. Meanwhile, previous studies indicated that rDWI might be a useful parameter to reflect the pathophysiologic processes following an ischemic stroke (10, 16). Thus, we hypothesized that DWI might be helpful to assess FLAIR imaging and that we may be able to establish a DWI-based diagnostic model to predict the status of FLAIR imaging. Moreover, our previous studies indicated that the



**Figure 4.** a, b. Coronal DWI (a) and FLAIR (b) images of Dog 11 acquired six hours after model establishment show increased signal intensity (arrows). Volume of DWI lesion is larger than that of FLAIR lesion (thin arrow, a), indicating apparent  $V_{\text{DWI}} - V_{\text{FLAIR}}$  mismatch.



**Figure 5.** a, b. Mean rADC values were not significantly different between the FLAIR- and FLAIR+ lesions ( $P = 0.73$ , a). ROC analysis (b) determined the cutoff value of rADC as 0.54 (AUC, 0.48; sensitivity, 0.52; specificity, 0.58) for judging positive FLAIR.

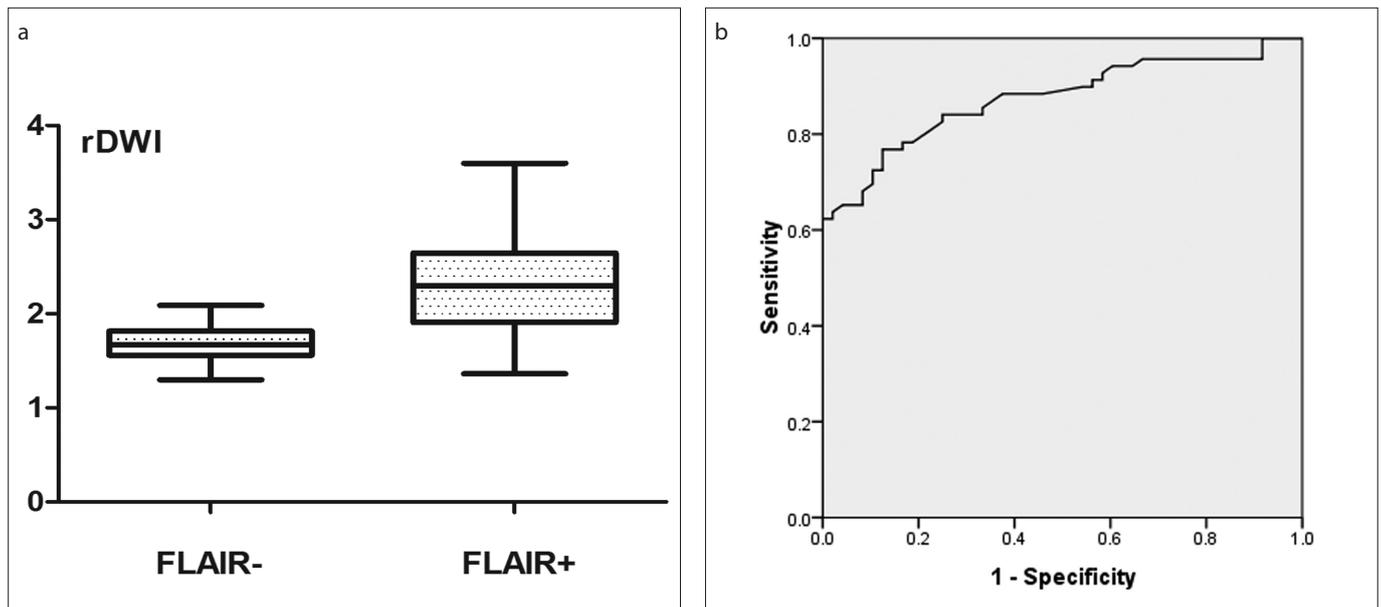
volume of DWI and FLAIR lesions evolved independently. The volume of DWI lesions commonly appeared bigger than that of FLAIR lesions, yielding a mismatch pattern (2). Thus, in this study, we performed an imaging segmentation based on the volume of DWI and FLAIR lesions when we observed the mismatch between DWI and FLAIR lesions. We believed that the imaging segmentation, which took full account of the independent evolution of the volume of DWI and FLAIR lesions, could effectively decrease the impact of the heterogeneous signal intensity of DWI.

In our study, rADC did not qualify as a

significant parameter for timing the stroke event, as the largest AUC was only 0.484. The mean rADC value of the whole ischemic lesion kept stable (0.56–0.54) from three to six hours after the onset of stroke. No significant difference was found between the rADC values at any two time points, similar to the findings of previous studies (17). Hence, we can conclude that the rADC appeared stable in the hyperacute period of the ischemic event. Therefore, despite more ischemic lesions being detected on FLAIR images from three to six hours, the rADC did not change significantly between

FLAIR+ and FLAIR- lesions, and did not display significant value in predicting positive or negative FLAIR imaging.

On the contrary, rDWI (cutoff value, 1.90; AUC, 0.88) appeared to be an effective index to identify the status of FLAIR imaging. The difference between rDWI and rADC parameters in predicting the status of FLAIR imaging might be related to the intrinsic quality of DWI and ADC. DWI combines diffusion-weighted and T2-weighted imaging, while ADC value is just a quantitative parameter reflecting the diffusion condition alone (13). The critical rDWI



**Figure 6.** a, b. Mean rDWI values were significantly different between FLAIR- and FLAIR+ lesions ( $P < 0.001$ , a). ROC analysis (b) determined the cutoff value of rDWI as 1.90 (AUC, 0.88; sensitivity, 0.77; specificity, 0.88) for judging positive FLAIR.

threshold value in our study was 1.90, which is slightly higher than 1.60 acquired in a previous study (13). The higher rDWI threshold value established in our study might be due to our method of stroke model establishment. We embolized middle cerebral artery followed by blockage of internal cerebral artery; thus, our model resembled the human stroke with tandem occlusion of middle and internal cerebral arteries at the same time. In our model, collateral flow was severely impaired and vessel recanalization did not happen at once, hence the rDWI of the ischemic lesions increased steeply during the MRI scan interval of one hour. The rDWI could effectively predict the status of FLAIR imaging, which essentially coincides with a previous viewpoint suggesting that, rDWI changes in a time-dependent manner and it might be associated with tissue clock and tissue fate (10, 13, 18).

Our results show that the ADC value of the ischemic lesions decreased, and remained stable at almost 50% of that of the contralateral normal hemisphere 3–24 hours after model establishment. Meanwhile, our previous study found that the T2 value of ischemic lesions also increased slightly in the corresponding period (10). Therefore, we considered that the increase of rDWI in the acute period was influenced by both diffusibility (ADC) and T2 shine through effects and especially by the ADC value, which is consistent with the study of Eastwood et al. (19). They expanded their

study to the subacute and chronic period and indicated that from three to 10 days after stroke onset, the contribution from T2 shine through effect becomes greater than that from ADC, although both of them still have a positive effect on rDWI. In the follow-up period, the ADC of the infarction lesion becomes “pseudonormal” and then increases gradually. The increase of ADC has a negative effect on rDWI. At first, the positive contribution from T2 shine through effect can compensate the negative effect from ADC, and the net effect of both contributions is still slightly positive on rDWI. Then, the ADC of infarction lesion increases even more. T2 shine through effect is still present, but it is not enough to compensate the negative effect from ADC. ADC becomes the major factor again, and the elevated ADC value leads to the decreased signal intensity on DWI.

Several limitations in our study should be discussed. First, our ischemic model resembled the tandem occlusion in humans. Our method of model establishment seriously destroyed collateral circulation and caused severe perfusion impairment. This mechanism could only imitate the cause of partial stroke event. Second, the imaging segmentation was performed manually. Further work using voxel based imaging segmentation might be more precise. Finally, the limited number of animals used in our study might affect the accuracy of the statistical results.

In conclusion, based on our embolic ischemic model, rDWI might be helpful to deter-

mine positive or negative FLAIR imaging in the acute period, while rADC appears not useful.

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#### Conflict of interest disclosure

The author declared no conflicts of interest.

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