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Evaluation of the Applicability of Resovist in DSC-MR Perfusion-Weighted Imaging of Rat Hyperacute Cerebral Infarction

Sıçan Hiperakut Serebral Enfarktüsü DSC-MR Perfüzyon Ağırlıklı Görüntülemesinde Resovist Uygulaması Değerlendirmesi

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ABSTRACT

AIM: The aim of this study was to evaluate the use of Resovist in perfusion-weighted imaging (PWI) of rat hyperacute cerebral infarction.
MATERIAL and METHODS: 30 Wistar rats were randomly divided into 2 groups. Group A was intravenously injected with 8 μmol Fe/kg body weight of Resovist, whilst Group B was injected with 0.2 mmol/kg body weight of Gd-DTPA. These dosages were chosen to provide comparable maximum signal changes in normally perfused brain. CBV, CBF and MTT parameter profiles were obtained for the core diseased region and the penumbra of brain ischemia and compared between the two groups. These results were then correlated with pathological findings and TTC staining.

RESULTS: In our rat stroke model, signal-time curves were similar between Gd-DTPA and Resovist, both in the core area with severe ischemia and in the penumbra area with moderate ischemia. The CBV, MTT, and TTP values of PWI for ischemic penumbra in Groups A and B showed no statistical disparity.

CONCLUSION: The efficacy of Resovist in MR PWI is similar to Gd-DTPA in the diagnosis of perfusion reduction in the rat stroke model.

KEYWORDS: Resovist, Hyperacute cerebral infarction, MRI, Perfusion weighted imaging, Rat

ÖZ

AMAÇ: Bu çalışmanın amacı, sıçan hiperakut serebral enfarktüsünde perfüzyon ağırlıklı görüntülemede Resovist kullanımını değerlendirmekti.

YÖNTEM ve GEREÇLER: 30 Wistar sıçanı olarak 2 gruba bölündü. Grup A'ya intravenöz olarak 8 μmol Fe/kg vücut ağırlığı Resovist intravenöz olarak enjekte edilirken Grup B'ye 0,2 mmol/kg vücut ağırlığı Gd-DTPA enjekte edildi. Bu dozlar normalde perfüze olan beyinde karşılaştırılabilir maksimum sinyal değişiklikleri oluşturmak üzere seçildi. CBV, CBF ve MTT parametre profilleri merkez hastalıklı bölge ve beyin iskemisi penumbrası için elde edilip iki grup arasında karşılaştırıldı. Bu sonuçlar sonra patolojik bulgular ve TTC boyaması ile korele edildi.

BULGULAR: Sıçan inme modelimizde sinyal zaman eğrileri hem şiddetli iskemili merkez bölge hem orta derecede iskelemili penumbra bölgesinde Gd-DTPA ve Resovist arasında benzerdi. CBV, MTT ve TTP değerleri perfüzyon ağırlıklı görüntülemede iskemik penumbra bölgesinde A ve B Grupları açısından istatistiksel fark göstermedi.

SONUÇ: Resovist'in MR perfüzyon ağırlıklı görüntülemede etkinliği sıçan inme modelinde perfüzyon azalması tanısı açısından Gd-DTPA ile benzerdir.

ANAHTAR SÖZCÜKLER: Resovist, Hiperakut serebral enfarktüs, MRG, Perfüzyon ağırlıklı görüntüleme, Sıçan

INTRODUCTION

In recent years, with the development of MRI scanning technology, there has been an increased use of MR perfusion imaging studies to observe cerebral blood flow. MR perfusion imaging using Gd-DTPA as the main contrast agent makes it possible to obtain a fast and accurate diagnosis and to acquire hemodynamic parameters and metabolic change information through imaging studies of cerebral infarction (5, 9). However, high-dose intravenous injections of Gd-DTPA inevitably bring about side effects (1) such as anaphylactic shock, blood pressure drop, skin hives, and even systemic fibrosis (NSF). Pharmacokinetic studies of Resovist have confirmed human intravenous bolus injection of Resovist to be safe (12). Resovist is one type of SPIO, which are iron oxide particles wrapped in carboxydextran that act as a negative enhancer of MRIs in clinical settings. Resovist can significantly shorten T2 reducing signal intensity of target organs, which leads a clearer appearance of lesioned parts. This characteristic makes Resovist a possible contrast agent for use in MR perfusion (3, 7, 9, 12-14).

In previous studies on MR perfusion-weighted imaging (PWI) (19), we found that differences in both the magnetic

susceptibility of the contrast agent and the dosage affect the results. Therefore, the appropriate selection of contrast agent dosage was very important. When replicating or comparing tests performed on different individuals, the comparability of the administered doses should be a point of attention. Therefore, for an accurate and objective analysis, the dosage choice for two different types of contrast agent was based on obtaining the same maximum signal intensity changes in MR PWI of normal brain tissue. Our previous findings (19) showed that similar signal attenuation values could be obtained using 0.2 mmol/kg body weight (BW) Gd-DTPA and 8 umol Fe/kg BW Resovist in MR PWI of normal rabbit brain. The purpose of this study is to evaluate applicability of Resovist in MR PWI of artery embolization ischemia in a rat brain model by comparing it with Gd-DTPA.

MATERIAL and METHODS

Animals

30 male Wistar rats (BW 350 – 400 g) were provided by Sun Yat-sen University Animal Experimental Breeding Center. The rats were given free access to food and water and subjected to a 12 h circadian rhythm feeding. This study was carried out in strict accordance with the recommendations in the *Guide for the Care and Use of Laboratory Animals* of the National Institute of Health. The animal use protocol was reviewed and approved by the Institutional Animal Care and Use Committee (IACUC) of Guangdong General Hospital. Rats were randomly divided into 2 groups (n = 15 per group): Group A was given Resovist and Group B was given Gd-DTPA. After occluding the left middle cerebral artery with thread for 1 hr in all rats, two dynamic MR perfusion imaging series were acquired after intravenous injections of Resovist or Gd-DTPA,.

Preparation of Line Embolism

Line embolism was prepared with imported nylon line 0.2 mm in diameter and 40 mm in length. Under the microscope, quick-drying lacquer was applied on 5 mm of one end of the nylon line, forming a round and smooth head end with a diameter of 0.26 - 0.28 mm. The line was dried and placed in a solution of 1% heparin for further use after UV disinfection.

Establishing the Hyperacute Cerebral Infarction Model

The hyperacute cerebral infarction model was established using the line embolism method, where a line is used to occlude the brain artery. Rats were anesthetized with an intraperitoneal injection of 10% chloral hydrate, 0.03 mg/100 g BW, fixed, disinfected, and towel-spread. The thigh was cut along the left side and the femoral artery and vein were separated. The distal end of the femoral vein was ligated and after the proximal end was occluded by micro-aneurysm clips, the femoral vein was cut 5 mm away from the distal end of the ligation. A 24th pediatric venous catheter needle was inserted into the femoral vein and fixed. The clip was then removed for injection of the MRI contrast agents. The gaster-neck was slit along the middle line, separated from the left common carotid artery, the left external carotid artery, and internal carotid artery. The external carotid artery was ligated both at the carotid bifurcation and 15 mm away from the bifurcation, and then cut at 5 mm away from the bifurcation with a microsurgical scissor. The line embolism was inserted with the 0.26 - 0.28 mm head end into the carotid artery and gently ligated to fix in place. The ligature at the bifurcation was unlocked, the external artery was sheared at 10 mm away from the bifurcation and lightly stretched until it was aligned with the internal carotid artery. The line embolism was then extended into the internal carotid artery and pushed along about 23 - 25 mm to occlude the middle cerebral artery, with strong ligation of the external carotid artery to avoid line slipping. All operations were carried out under the microscope. During surgery, rat body temperature was continuously monitored by anal probe and maintained at 37°C with a heated pad during MRI scans. Arterial blood pressure was continuously monitored with the femoral artery cannula.

Dosage Selection of Contrast Agents

To facilitate comparison between our two contrast agents, we selected their dosage based on the dosage required to obtain the same maximum signal changes of MR PWI in normal brain tissue. According to these criteria, we selected 8 umol Fe/kg BW Resovist for Group A and 0.2 mmol/kg BW Gd-DTPA for Group B. The bolus injection method was the same as described above. Five ml saline in a high-pressure syringe was injected at a rate of 2 ml/s to bolus inject the contrast agent via the extension tube into the femoral vein.

Magnetic Resonance Imaging

GE Signa Infinity Twin Speed 1.5T superconducting MR imaging equipment was used and a 7.6 cm (3 in) annular surface coil was used as the receiving coil. The rats were laid supine with their head in the center of the coil and normal breathing was permitted. All the animals were given coronary-status scanning, with a thickness of 2 mm and with the optic chiasm as the center. The order and sequence of MRI examination were as follows: FSE T2WI: TR 3000 ms, TE 95 ms, Matrix 256 × 192, NEX = 2; SE T1WI: TR 400 ms, TE 14 ms, Matrix 256 × 192, NEX = 3; PWI: T2*GE-EPI sequence, 2 mm thick, axial scan of 4 consecutive layers, field view 14 × 14 cm. Fifty phases were collected in total, and the scan parameters were TR = 800 ms, TE = 40 ms and NEX = 1. Contrast agents were injected after collection of the first seven phase images.

Pathological Examination

Three rats from each group (randomly selected from Groups A and B) underwent pathological examination. After MRI examination, the rats were decapitated under anesthesia, the brains were removed and the level of brain corresponding to MRI imaging was cut into a 2 mm sheet. Basal ganglia and adjacent slices were taken, placed in 2% TTC solution at 37°C water bath for 30 min, and the remaining brain tissue was fixed with 10% formalin for immunohistochemistry and HE staining.

Image Processing and Data Analysis

Original images from MR PWI were transferred to an AW4.2 workstation for post-processing. Four regions of interest (ROI) of the same size were selected for analysis: one was in the central area of the lesion, one was at the edge of the lesion (i.e., half dark band in the image), and the two others were located at the corresponding anatomical positions in the contralateral brain hemispheres. The selected ROIs were expressed as ROI_1, ROI_2, ROI_3, ROI_4, respectively. The corresponding negative enhancement signal intensity-time curve was obtained for each ROI, and the data obtained were entered into the appropriate software program to calculate the cerebral blood volume (CBV), cerebral blood flow (CBF), and mean transition time (MTT) values. The formulas used are as follows:

$\Delta R_2^* = -\ln(SI_t/SI_0)/TE$

$rCBV = \int \Delta R_2^*(t)dt$

$rCBF = Cmax$

$rMTT = rCBV/ rCBF = \int \Delta R_2^*(t)dt/Cmax$ (5, 10, 18)

In the above formulas, ΔR_2^* represents the change in T_2^* relaxation rate (i.e., change rate of $1/T_2^*$), SI_t indicates the signal strength in the ROI at any time point during the contrast agent's first passing, and TE is the echo time of PWI. The regional CBV (rCBV) was calculated using the area under the concentration-time curve, regional CBF (rCBF) was represented by the maximum height of the curve (i.e., the maximum concentration, Cmax), and the regional mean transition time (rMTT) was calculated. In addition, the time to peak (TTP) concentration was obtained from the signal intensity-time curve.

Statistical Analysis

All data were analyzed with SPSS11.5 statistical package, a paired-samples *t* test and an independent-samples *t* test.

RESULTS

General Data

During the scan period, the rats were in a stable physiological state. Rats in Group A had arterial blood pressure of 131 ± 14 mmHg and rectal temperature of 36.8 ± 0.2°C, prior to Resovist injection. Rats in Group B had blood pressure and temperature values of 132 ± 13 mmHg and 36.7 ± 0.3°C, respectively, before injection of Gd-DTPA. After injection of the contrast agents, the rats in both groups all experienced a small and transient increase in blood pressure, but none of the rats developed hypertension.

Four ROI signal intensity-time curves are shown in Figure 1 (A,B) along with the cerebral ischemia function of the rats. The signal intensity-time curves of ROI_1, ROI_2, ROI_3, ROI_4 were almost identical between Groups A and B. The curves of the central area of the lesion ((ROI_{a1} and ROI_{b1}) did not show an obvious peak, but showed the formation of perfusion defects. The curves of the edge area of the lesion (ROI_{a2} and ROI_{b2}) indicated a delayed peak and a prolonged steady state recovery time, while the curves corresponding to the contralateral normal hemispheres (ROI_{a3}, ROI_{b3} and ROI_{a4}, ROI_{b4}) all showed normal morphology.

The rCBV, rMTT and TTP values of Groups A and B were calculated and are shown in Table I.

The rCBV, rCBF, and rMTT values between ROI_1 and ROI_3, as well as the values between ROI_2 and ROI_4 in Groups A and B were significantly different when analyzed by the paired samples t-test ($p < 0.01$), while the rCBV, rCBF, and rMTT values between ROI_1 and ROI_2 were significantly different ($p < 0.01$) by paired samples t-test ($p < 0.05$).

The rCBV of ROI_1 and ROI_2 were not significantly different ($p > 0.05$) when analyzed using the independent sample *t*-test, while the rMTT and TTP of Group B were both slightly greater than those of Group A, but showed no significant difference ($p > 0.05$). The rCBV, rMTT and TTP values of ROI_3 and ROI_4 from Groups A and B were not significantly different ($p > 0.05$). The rrCBV of Group A were 0.36 ± 0.08 and 0.61 ± 0.10, respectively, and those of Group B were 0.39 ± 0.08 and 0.63 ± 0.12, respectively. There was no significant difference ($p > 0.05$) between the corresponding values of the two groups by independent sample *t*-test, as well as the rMTT and rTTP.

Pathological Examination

In both groups the brain tissue from the middle cerebral artery area with TTC embolism appeared with no staining. Changes due to infarction were observed under light microscopy (Figure 1), and we observed under the electron microscope that the swelling part of the nerve cells in the central area of the lesions had partially disintegrated, the number of organelles was reduced, the nucleus was shriveled and the nucleoli were no longer visible, the mitochondria swelled markedly, the Golgi showed expansion with vacuolation, the perivascular space expanded, and the internal membranes were damaged. The TTC around lesions was mildly stained in pink, and while we observed no obvious brain tissue abnormalities under light microscopy, nerve cells were swollen under electron microscopy, the nuclei were slightly deformed, while the mitochondrial cristae, rough endoplasmic reticulum and Golgi were enlarged.

DISCUSSION

Villringer (17) derived the following formulas: $\Delta R_2^* = k \cdot C_v$, $SI_t = SI_0 e^{-TE(\Delta R2^*(t))}$, and $C_v = -\ln(SI_t/SI_0)/ k \cdot TE$, in which ΔR_2^* is the change rate of $1/T_2^*$, C_v is the concentration of the contrast agent within the tissue, SI_t is the signal intensity at t time point, and SI_0 is the signal intensity of baseline level. Therefore, in studying MR PWI, the dosage of contrast agent can affect the results and influence the comparative study of different contrast agents. In order to compare two different contrast agents, we selected our dosage based on generating the same maximum signal changes of MR PWI in normal brain tissue. Our previous findings (7) showed that using the same scan sequence and parameters, the rate of signal decrease in

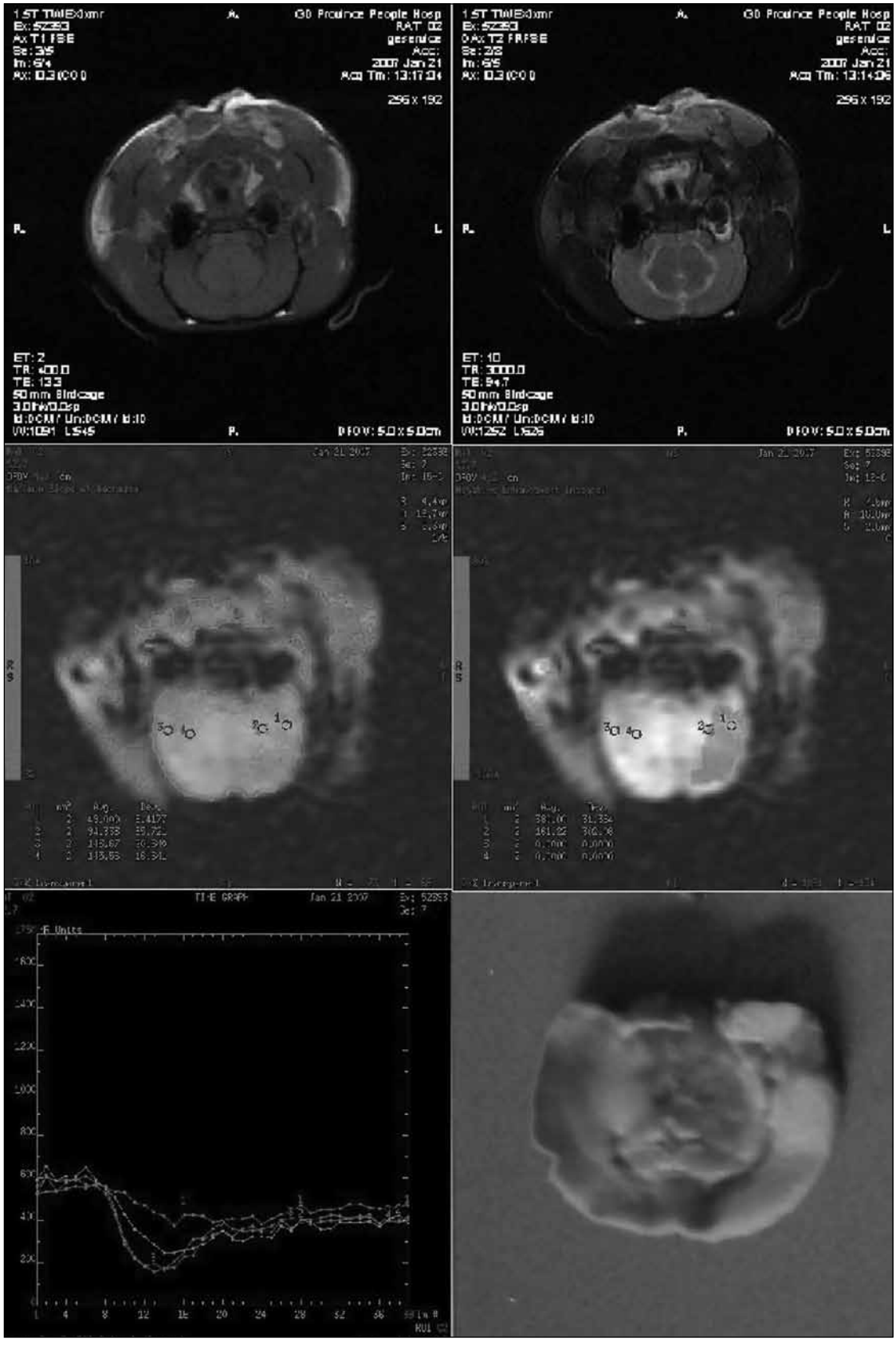

Figure 1: T1WI, T2WI, functional diagram a, functional diagram b, STC figure and TTC staining of ROI (from left to right and from top to bottom).

Table I: rCBV, rMTT, TTP Values and the Corresponding Ratios (n = 15)

		Group A (Resovist)	Group B (Gd-DTPA)	t-value	p-value
ROI_1	rCBV (ml·kg^{-1})	22.97±3.55	23.44±3.51	0.362	0.720
	rMTT (s)	15.69±2.30	15.91±2.38	0.257	0.799
	TTP (s)	8.15±1.34	8.27±1.35	0.239	0.813
ROI_2	rCBV (ml·kg^{-1})	54.51±7.20	52.10±6.16	0.989	0.331
	rMTT (s)	11.10±1.79	11.59±1.50	0.801	0.430
	TTP (s)	6.76±0.59	7.04±0.91	1.002	0.325
ROI_3	rCBV (ml·kg^{-1})	65.52±9.80	61.61±8.27	1.182	0.247
	rMTT (s)	6.76±0.45	7.14±0.74	1.706	0.099
	TTP (s)	3.97±0.57	4.28±0.66	1.382	0.178
ROI_4	rCBV (ml·kg^{-1})	89.93±11.02	84.34±8.48	1.556	1.131
	RMTT (s)	6.84±0.56	7.31±0.79	1.874	0071
	TTP (s)	3.88±0.56	4.12±0.51	1.244	0.224
ROI_1/ ROI_3	RrCBV (%)	0.36±0.08	0.39±0.08	0.938	0.356
	RrMTT (%)	2.33±0.37	2.26±0.46	0.479	0.636
	TTP ratio (%)	2.09±0.44	2.00±0.58	0.499	0.621
ROI_2/ ROI_4	RrCBV (%)	0.61±0.10	0.63±0.12	0.323	0.749
	RrMTT (%)	1.63±0.30	1.61±0.31	0.208	0.836
	TTP ratio (%)	1.77±0.24	1.73±0.32	0.345	0.733

normal rabbit gray and white matter was comparable when 0.2 mmol/kg body weight of Gd-DTPA or 8 umol Fe/kg of Resovist were used. The rates of decrease as a percentage of the maximum signal were also very similar. Meanwhile, using the same scanning conditions, results from preliminary experiments performed in normal rats using the same doses were comparable to those obtained in rabbits. As a result, we used the above doses of the two contrast agents to be compared for our current study.

Under normal circumstances, there is a difference in perfusion related to the area of the brain tissue under study (gray matter, white matter, basal ganglia area) (15). After the onset of ischemia, the capillary perfusion pressure of the ischemic area decreases, MTT becomes prolonged, while normal compensatory mechanisms of the body allow cerebral vasodilation and rCBV to increase in order to maintain normal rCBF. When capillary perfusion pressure continues to decline and reaches the compensatory limit, rCBV cannot increase and instead decreases while rCBF also begins to decline. For these reasons, MTT is the most sensitive and accurate indicator of ischemia, and it can be used to determine the range of change of ischemia that results in pathological change (8, 20). The rCBV can change in the initial stages of ischemia, with high accuracy and specificity.

Our experimental results identified the feasibility of conducting functional MRI of focal acute cerebral infarction and re-perfusion by using Resorvist as negative enhancer of MR images in our rat model. Abnormal signal changes were observed in all experimental rats after the middle cerebral artery was occluded with line embolism for 1 h. The original image of MR PWI showed relatively hyperintense and constant range of abnormal signal. The signal intensity-time curves corresponding to ROI_1, ROI_2, ROI_3, ROI_4 of Groups A and B were almost identical, whereas the curves of the central area of the lesion did not show an obvious peak, indicating the formation of perfusion defects because of reduced perfusion of contrast agent. The curves of the edge area of the lesion indicated the peak was delayed and the time of recovery to a steady state was prolonged, while the curves corresponding to the contralateral normal hemispheres of ROI_3 and ROI_4 all maintained normal morphology. Our data show that not only is the rat model used in this study a successful model of focal cerebral ischemia, but that the signal strength-time curves of Resovist in acute cerebral ischemia are stable and reliable. The rCBV of ROI_2 of Groups A and B were 54.51 ± 7.20 and 51.10 ± 6.16, which were significantly smaller than the rCBV of ROI_4, which was 89.93 ± 11.02 and 84.34 ± 8.48 for Groups A and B, respectively. This observation further indicates that similar results can be obtained using a comparable dose of Resovist and Gd-DTPA for MR brain perfusion in the diagnosis of cerebral ischemic penumbra. There was no obvious difference in rrCBV (i.e., the ratio between the affected side and uninjured side), consistent with the ischemic region shown by TTC staining.

These results show that Resovist is very useful in MR PWI of acute cerebral ischemia and there is no significant difference in diagnostic sensitivity compared with a comparable dose of Gd-DTPA. For ROI_2, the rMTT and TTP values of Group B were both slightly greater than the values of Group A, but without a statistically significant difference.

Similarly, there was no significant difference between the two sets of rrMTT and rTTP, which further confirms the feasibility of using Resovist. At the same time, the negative enhancement functions and the measurement methods of the parameter values generally used in MR PWI were equally applicable to Resovist in MR of brain perfusion samples. In addition, rCBV, rMTT and TTP values of ROI_3 and ROI_4 were not significantly different between Groups A and B, which further supports our conclusions.

When Resovist is used in MR PWI, another potential issue is its side effects. Previously, AMI-25 and Feridex could only be used for slow intravenous infusion because of significant toxicity caused by rapid injection. As a kind of early SPIO, it was found that rapid intravenous injection of AMI-25 can cause significant toxicity and side effects in the cardiovascular system, as well as shoulder and back pain, dizziness and other symptoms in clinical trials (16). During clinical use, 10 to 15% of patients experience various degrees of side effects when AMI-25 is administered by intravenous infusion. These side effects include facial flushing, rash, dyspnea and lower back pain (2). Resovist can be administrated by intravenous bolus injection due to its small particle size, good solubility in water, and stability conferred by the carboxyldextran coating. In our studies, after all experimental animals were injected with contrast agent, only a slight and transient rise in blood pressure was observed and not in one instance was there any obvious hypertensive response. Phase II clinical trials of Resovist also showed that no adverse reactions were caused by rapid intravenous injection of 4 umol Fe/kg, 8 umol Fe/kg and 16 umol Fe/kg (11). Another study confirmed these results with intravenous bolus injections of Resovist (12). Therefore, Resovist is a good candidate for use in brain perfusion and functional MRI.

This study demonstrates that rapid intravenous bolus injection of Resovist is safe and that more histological and hemodynamic information that cannot be obtained in conventional MR can be provided in clinical diagnosis and follow-up of acute cerebral infarction by its use in perfusion MR imaging. In this study of the applicability of MR PWI in acute cerebral infarction, Resovist and Gd-DTPA proved to be equally effective. However, because Resovist requires a smaller dose and does not cause renal toxicity, it has a broader application potential in brain perfusion analyses.

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