Lysability of arterial thrombi assessed by magnetic resonance imaging

M. Kozak¹, U. Mikac², A. Blinc¹ and I. Serša²

Summary

Background: Intravascular thrombi change in time due to retraction and organization, which is reflected in the appearance of magnetic resonance images of clots. We have hypothesized that MRI has the potential to improve patient selection for thrombolytic treatment. The aim of our study was to analyze occlusive arterial thrombi with MRI, and to correlate the MRI parameters with the therapeutic outcome in patients with occlusive atherothrombotic disease of the superficial femoral artery who were treated with catheter-directed thrombolysis by streptokinase.

Patients and methods: We included 13 patients with subacute (2 weeks to 3 months old) occlusive arterial thrombi and 4 patients with chronic (more than 6 months old) arterial occlusions. We measured the MRI signal intensity on gradient echo images of 98 axial slices of the subacute occlusive thrombi and in 45 slices of 4 chronic thrombi. Following MRI, the patients with subacute history were treated with catheter-directed thrombolysis.

Results: Thrombolysis was successful in 11/13 patients. The normalized MRI signal intensity was significantly higher in the unsuccessfully treated thrombi than in the successfully treated thrombi (1.10 ± 0.08 vs. 0.72 ± 0.17, p < 0.003), but the subacute and chronic thrombi did not differ in signal intensity.

Conclusions: High signal intensity of arterial thrombi on gradient echo MRI might predict resistance to thrombolytic therapy.

Key words
arterial thrombi, magnetic resonance imaging, thrombolysis, streptokinase

Zusammenfassung

Auflosbarkeit von arteriellen Thromben bewertet mit MRT

Hintergrund: Die intravasculären Thromben verändern sich mit der Zeit aufgrund von Retraction und Organisation, was sich im Erscheinungsbild der Thromben in MRT Bildern niederschlägt. Unsere Hypothese war es, dass das MRT ein Potential bietet, um die Auswahl von Patienten für die thrombolytische Therapie zu optimieren. Das Ziel der Studie war das Analysieren von okkludierenden arteriellen Thromben mittels MRT und die Korreletion der MRT Parameter mit den therapeutischen Ergebnissen derjenigen Patienten mit okklusiver atherothrombotischer Krankheit der Arteria femoralis superficialis, die mittels Kathetergeleiteter Thrombolysen mit Streptokinase behandelt wurden.


Ergebnisse: Die Thrombolysen war in 11 von 13 Fällen erfolgreich. Die normalisierte Intensität des MRT Signals war wesentlich höher bei den erfolgreich behandelten Thromben als bei den erfolgreich behandelten Thromben (1.10 ± 0.08 vs. 0.72 ± 0.17, p < 0.003), jedoch gab es hinsichtlich der Intensitäten der Signale keinen Unterschied zwischen subakuten und chronischen Thromben.

Schlussfolgerungen: Signale mit hoher Intensität der arteriellen Thromben auf den Gradientenbildern könnten die Erfolglosigkeit der thrombolytischen Therapie voraussagen.
Introduction

Peripheral arterial thrombosis can be successfully treated by catheter-directed infusion of thrombolytic drugs. Adequate thrombolysis can be achieved in about 40–80% of treated patients [2]. It has been widely accepted, that patients with occlusions of iliac arteries not older than one year and patients with occlusions of superficial femoral artery not older than six months can be treated with local thrombolysis [14]. Recently, this time window has been shortened to roughly one month [17]. However, there are no firm data for such a decision. In addition, it is often difficult to estimate the exact time of arterial occlusion based only on the patient's history.

Intravascular thrombi change in time due to retraction and organization, which is reflected in the appearance of magnetic resonance images of clots [1, 3, 8, 10]. We have hypothesized that MRI has the potential to improve patient selection for thrombolysis treatment. The aim of our study was to analyze occlusive arterial thrombi with MRI, and to correlate the MRI parameters with the therapeutic outcome in patients with occlusive atherothrombotic disease of the superficial femoral artery who were treated with catheter-directed thrombolysis by streptokinase.

Patients and methods

Patients and the protocol of the study

Seventeen patients (3 women, 14 men), aged 43–79 (mean 64) years with angiographically documented occlusive disease of a superficial femoral artery were studied after giving their informed consent. In 13 patients (subacute group) symptoms of peripheral arterial occlusion lasted from two weeks to three months, and in 4 patients (chronic group) the symptoms lasted for more than 6 months. In all patients MRI of the occluded artery was performed and MR images of thrombi were analyzed. Patients in the subacute group were treated with catheter-directed local thrombolysis started one day after MRI. Patients in the chronic group did not undergo thrombolysis. The study was approved by the Ethical Committee for Biomedical Research of the Republic of Slovenia.

MRI

Gradient echo MR images (repetition time TR = 300 milliseconds, interecho time TE = 12 milliseconds, flip angle = 75°, field of view FOV = 17 cm, matrix 256 x 256) were acquired on a whole body 1.5 Tesla MR scanner (Magnetom, Siemens 1.5 T) with a surface coil for the thigh. The area of interest was located on the coronal plane and subsequently axial images were acquired. The number of analyzed slices per thrombus varied from 7–12. We selected consecutive, 4 mm thick axial slices of the starting at the proximal end of the arterial occlusion.

Image analysis

For image analysis and calculations we used the computer programs Imagetools (UTHSCA, USA). On each image the intraarterial thrombus was identified and delineated by an expert observer. All pixels corresponding to the thrombus in a given slice were analyzed for image intensity. Subcutaneous fat from each image was taken as the internal reference and all MRI signal intensities were normalized, i.e., divided by the mean signal intensity of the fat. For each slice of the thrombus the mean and standard deviation (SD) of the normalized MRI signal intensity were calculated. The inhomogeneity of MR signal intensity of thrombi was quantified by two parameters: the coefficient of variation (SD/mean x 100) of signal intensity and the shift in the center of "mass" (defined as the relative distance between the center of the thrombus area and the center of the thrombus "mass", where each pixel in the thrombus area was weighted by its MRI signal intensity). The coefficient of variation is spatially independent, i.e.; the same result is obtained for a checkerboard, interspersed structure or a distinctly bimodal structure where one entire half of the sample is hyperintense and the other hypointense. On the other hand, the shift in the center of "mass" depends on the symmetry of the sample.

Statistical analysis

The MRI signal intensities and the measures of variation were compared between different groups by the t-test for independent samples. In all cases the Bonferroni's correction was used for multiple comparisons.

Catheter-directed thrombolysis

Catheter-directed thrombolysis was performed with streptokinase (Streptase, Boehringer, Germany) infused at 5000 IU/h. Heparin (Heparin, Krka, Slovenia) was infused at 450 U/h through a coaxial channel of the same intraarterial catheter. The effect of thrombolytic treatment was monitored angiographically every 12–24 hours. If partial lysis was confirmed, the tip of the catheter was repositioned into or close to the rest of the thrombus. Treatment lasted until full lysis was achieved or for a maximum of 48 hours. Lysis was regarded as successful, when the thrombosed part of the artery, previously evaluated by MRI, was rechannelized.

Results

In 11 patients (83 thrombus slices) in the subacute group the treatment was successful, whereas in 2 patients (15 thrombus slices) thrombolysis was unsuccessful. Typical images of a successfully lysed clot, an unsuccessfully lysed clot and a chronic clot are shown in Figure 1.

In the subacute group the mean-normalized MR signal intensity was 0.80 ± 0.22 (n = 98) which was not significantly different from 0.75 ± 0.16 (n = 45) in the chronic
Discussion

We found significantly higher normalised MR signal intensity in the unsuccessfully lysed thrombi than in either the successfully lysed or chronic thrombi. This indicates that thrombus structure is a predictor of success of thrombolytic therapy in addition to procedural variables such as positioning of the catheter port, passage of the guide wire through the occlusion and clinical variables such as presence of diabetes diabetic status and the number and lengths of arterial segments involved [12].

The MRI signal intensity depends on the MRI technique [6, 16] and on thrombus structure, especially on the content, distribution and oxygenation of hemoglobin, the most abundant protein in red blood cells that is paramagnetic and strongly determines the magnetic resonance relaxation times T1 and T2 [3, 16]. It is also influenced by clot organisation [8]. We have chosen the gradient echo MRI technique for our study because it gave the best resolution of blood vessels in our preliminary experiments where we compared gradient echo images with T1 and T2-weighted spin-echo images, and because gradient echo MRI has proven optimal for studying venous clots [9]. Francis and Totterman [16] used gradient echo MRI in venous clots subjected to thrombolysis by streptokinase and found better lysis in thrombus segments with darker, lower-intensity MRI signal than in segments with brighter, higher-intensity MRI signal. Our results concur with theirs, although venous and arterial thrombi can not be directly compared.

The differences in structure between successfully lysed and unsuccessfully lysed clots remain speculative, since none of our patients had undergone amputation and we therefore did not have histological data for correlation with the MRI images. Clot retraction strongly changes the MRI appearance of clots [3, 7, 13] and decreases their lysability by thrombolytic agents [5, 15]. However, retraction occurs in the first hours after clot formation and was therefore unlikely to influence the structure of thrombi that were at least 2 weeks old. Other factors that influence the MR characteristics of thrombi are the proportion of oxy- and deoxy-haemoglobin [7], haemolysis which facilitates the
interact with haemoglobin with water and thus further shorten T1 and T2\(^*\) [11], whereas the characteristics of the fibrin network in the clot play a minor role, since fibrin represents a very small proportion of the clot mass [4, 7]. Images acquired with gradient echo MRI depend on T2\(^*\) that is determined by the local inhomogeneity of the magnetic field and magnetic susceptibility of the sample. However, we did not find significant differences in the coefficient of variation of MRI signal intensity or in the shift of the centre of “mass” between the successfully lysed and unsuccessfully treated clots. Clot organisation, i.e., growth of endothelial cells, smooth muscle cells, and fibroblasts into the fibrin scaffold is a slower process that has been studied in a porcine carotid model where a plateau of MRI signal intensity was found after 6 weeks [8]. Replacement of red blood cells containing paramagnetic haemoglobin with ingrowing cells containing only non-paramagnetic proteins would be expected to prolong T1, T2, and T2\(^*\) which could result in brighter MRI signal intensity on gradient echo images if the ratio TR/T1 decreased less than the ratio TE/T2\(^*\).

Our study was limited by the small number of patients, especially in the subgroup of unsuccessfully lysed thrombi. As the thrombolytic agent we have used streptokinase, which is somewhat less effective than the fibrin-specific tissue plasminogen activator. Another limitation is that thrombolysis was not attempted in the chronic group with MR signal intensities comparable to successfully treated patients. It is possible that if thrombolysis were performed, the chronic group would also break down into a successfully treated subgroup and an unsuccessfully treated one. In conclusion, arterial thrombi in the superficial femoral artery that were successfully lysed had significantly lower signal intensity on gradient-echo MRI than the unsuccessfully lysed thrombi. Larger studies will be needed to validate our findings. The other main finding of our study is that there were no significant differences in signal intensity between arterial thrombi aged 2 weeks to 3 months and thrombi older than 6 months. A study might be warranted whether gradient echo MRI can select those patients with chronic peripheral arterial occlusions who are not candidates for surgical treatment or angioplasty alone who might still benefit from thrombolytic treatment.

References