Non-contrast MRI characterization of thrombus composition and susceptibility to thrombolysis in a mouse model of deep vein thrombosis.

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Introduction

Treatment of deep vein thrombosis is still under debate, mainly due to the difficulty in differentiating between red cell, fibrin and collagen rich thrombus in vivo, which is important information to better guide medical treatment. We have previously demonstrated that MTR, ADC (1), and T1 mapping sequences (2) allow assessment of collagen content, water diffusion and methemoglobin (red cells) content of thrombus, respectively. In this work we investigated the merits of these MR parameters for the identification of thrombus that is suitable for thrombolysis.

Materials and Methods:

Venous thrombosis was induced in the inferior vena cava (IVC) of 8-10wk male BALB/C mice in a surgical procedure that involved a combination of reduced blood flow and endothelial disturbance. A partial stenosis reduced blood flow by approximately 90%. Magnetization transfer (MT), diffusion weighted, T1 mapping images of *in vivo* thrombi and phase contrast images of the vena cava were acquired at days 2, 4, 7, 10, 14, 21 and 28 after thrombus induction. Eight mice were imaged at each time point, and subjected to intravascular thrombolysis therapy (10 mg/kg of tissue plasminogen activator, Actilyse, Boehringer Ingelheim, Germany) immediately after the imaging session. To evaluate the success rate of the treatment, mice were scanned again 24 hours after thrombolysis. All scans were performed on a 3T Philips Achieva Gyroscan scanner (Philips Healthcare, Best, The Netherlands) equipped with a dedicated small animal surface coil (diameter = 47 mm). Arterial and venous time-of-flight (TOF) images were used to locate the thrombus. Dynamic T1FFE 3D images were acquired without and with an on resonance MT pre-pulse. Imaging parameters were: TR=115s, TE=16ms, flip angle=18°, NEX=1, slice thickness=0.4 mm, acquired matrix=148x150, FOV=18x14x30 cm, (rec. resolution=0.1x0.1 mm), duration=6min. The MT pre-pulse was a binomial block (1:2:1, *90°x 90°-x 90°-x90°x*) pulse with a duration=1.92ms, repetition=1, and offset=0 Hz. MTR maps were generated based on the formula MTR=[(M$_o$-M$_s$)/Mo]*100 using Osirix. Two-dimensional DW spin-echo images were acquired with TR=2.8s, TE=105ms, flip angle=90°, diffusion echo time=333ms, FOV=18×30×12mm, acquired matrix=88×150, slice thickness=0.5mm, acquired resolution=0.2×0.2mm, reconstructed resolution=0.1×0.1mm, slices=24, averages=2, and duration=36 minutes. The ADC was calculated from 4 b-values of 0, 333, 667, and 1000 mm2/s. Diffusion gradients were applied parallel and perpendicular to the external magnetic field. T1 mapping of thrombus was performed using a Look-Locker based sequence. T1 maps of 20 slices were calculated using custom-made software implemented in Matlab. To evaluate the success of the thrombolytic therapy a phase contrast sequence was performed to measure blood flow in the infra-renal IVC pre and post thrombolysis.

Results & Discussion

An example of angiograms acquired before lysis, after successful and after unsuccessful thrombolytic treatment are shown in **Fig.1**. Thrombus with shorter T1 relaxation time, larger ADC values and smaller MTR values were more responsive and resulted in successful lysis (**Fig. 2**). **Table 1** shows that T1 relaxation time by itself had the best prediction of successful thrombolytic treatment. The combination of two parameters improved the prediction rate; and the combination of all three parameters further improved the prediction of lysis with a Sensitivity of 88% and a Specificity of 97%.

Conclusion

We have previously demonstrated that thrombus T1 relaxation time, MTR and ADC correlates well with thrombus composition and therefore could be used to detect thrombus amenable to successful thrombolysis.. In this work, we demonstrated that the combination of these three MRI-derived parameters significantly improved the detection of thrombus amenable for thrombolysis in a murine model of deep venous thrombosis. The non-invasive nature of this approach and the lack of the need of contrast agents make this study directly translatable in the clinical arena. Thus is may allow to improve selection of patients with DVT that may benefit from systemic thrombolytic treatment.

References: (1) Phinikaridou, Circ Cardiovasc Imaging 2013. (2) Saha, Circulation 2013.
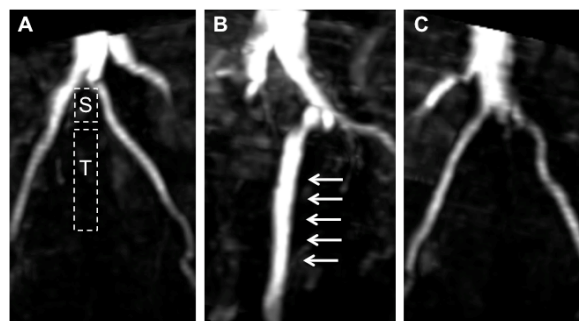
Figure 1: TOF IVC venography in a mouse with venous thrombosis (S: Suture location, T: expected location of the IVC venous thrombus) (A); mouse with successful thrombolytic treatment (B); and mouse with unsuccessful thrombolytic treatment (C) .
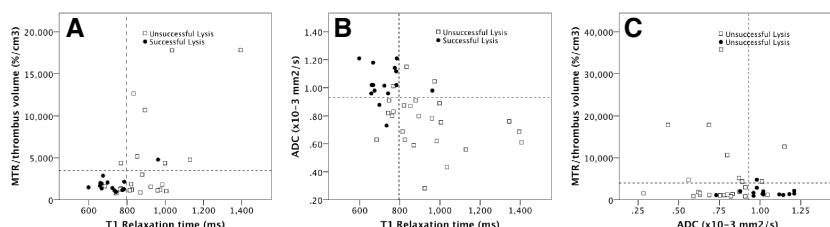
Figure 2: Successful and unsuccessful thrombolytic treatment and its relation with thrombus T1, MTR and ADC values.

T1 (ms)	MTR (%/cm^3)	ADC (x10^{-3}mm^2/s)	Sensitivity (%)	Specificity (%)
<784			87%	76%
	<2,900		45%	93%
		>0.88	87%	76%
<784		>0.93	82%	96%
<784	<2,800	>0.90	88%	97%

Table 1- Sensitivity and Specificity to predict successful thrombolysis using different criteria based in the MRI parameters: T1 relaxation time, MTR and ADC.