Influence of Tangential Plasma Flow on Fibrinolysis of Non-occlusive Thrombi: Study by MR Microscopy

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Introduction
Lysis of occlusive thrombi initially proceeds via penetrating channels that recanalize the occluded vessel, but does not result in a complete dissolution of the clot. When the first reperfusion channel pierces the clot, blood starts flowing through the channel and further blood lysis proceeds from the borders of the channel into the direction of the remaining clot [1-3]. It has not been known whether tangential flow of blood plasma along the clot causes exchange of the serum inside the clot by diffusion alone or also by convective exchange when the tangential flow is turbulent [4,5]. Our aim was to test by high-resolution magnetic resonance imaging on an in vitro model system how non-occlusive whole blood clots were dissolved by tangential flow of plasma that contained either fibrin-specific tissue plasminogen activator (t-PA), or fibrin nonspecific streptokinase.

Materials and Methods
Concentrations of t-PA at 2 µg/ml and streptokinase at 250 IU/ml were chosen to represent the average therapeutic concentrations during thrombolytic treatment of myocardial infarction. Cylindrical clots with a diameter of 3 mm and length of 3 cm were formed in glass tubes and pierced lengthwise by a needle with a diameter of 0.7 mm. The nonocclusive clots were connected to a perfusion system. The velocity of plasma flowing through the preformed channel in the clot was initially 426 ± 13 cm/s and fell to 86 ± 3 cm/s (n = 5) after complete clot dissolution. Magnetic resonance imaging of transverse clot sections was used for measuring the transport of plasma, containing the contrast agent Gd-DTPA, from the flow channel into the clot. Simultaneously, the clot dissolution was measured. MR images were acquired on a 100 MHz Bruker Biospec system equipped with micro-imaging accessories. In each experiment, 20 consecutive T1 weighted magnetic resonance images (TE/TR = 12.5/400 ms) at the field of view 2 cm and the slice thickness 2 mm were acquired in 2 min intervals. The image resolution was 80 µm per pixel.

Results
Penetration of contrast agent-containing plasma into clots did not depend on the choice of a thrombolytic agent (Fig. 1).

Fig. 1: Penetration of contrast agent containing plasma into the clot. Gd-DTPA containing area S, divided by the initial clot area S0 is plotted as a function of time.

At 6 min Gd-DTPA-containing areas were found at a distance 1.78 ± 0.49 mm (n = 4) from the border of the channel in clots dissolved with streptokinase, and at a distance of 2.22 ± 0.25 mm (n = 4) in clots dissolved with t-PA (p = 0.11). However, the dissolution of blood clots was significantly faster when t-PA was in comparison with streptokinase (Fig. 2).

Fig. 2: Micro MR images of two blood clots in transverse cross-section acquired 2, 10 and 40 minutes after the beginning of clot lysis with thrombolytic agent: t-PA (upper row) and streptokinase (lower row).

After 12 min of clot lysis the cross section of clots, exposed to t-PA was reduced to 0.49 ± 0.25 (n = 4) of their initial size, whereas clots exposed to streptokinase were reduced to only 0.79 ± 0.16 (n = 4) of their initial size (p = 0.029). The differences in clot size remained significant through 40 min.

Fig. 3: Clot lysis. Relative clot sizes S(t)/S0 calculated from MR images (Fig. 2) are plotted as a function of dissolving time.

The concentration of plasminogen did not change substantially in plasma containing t-PA, but was reduced to about one third of its initial value when streptokinase was used.

Discussion
Rapid, turbulent flow of plasma through a channel in the clot caused rapid exchange of the serum inside the clot with outer plasma. The rate of plasma-serum exchange was much more rapid than transport caused by diffusion alone. Using fibrin-specific t-PA that did not deplete the plasma of its plasminogen favorably affected the rate of blood clot lysis in comparison with non fibrin-specific streptokinase that depleted the plasma of two thirds of its plasminogen content.

References