# LOCAL THROMBOSIS PREVENTION IN THE DOG'S CAROTID ARTERY BY MAGNETIC TARGETING OF ASPIRIN-LOADING ERYTHROCYTES

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Conservative treatment of postoperative thrombosis could become much more effective and harmless if a drug could be supplied directly to the zone with increased risk of thrombus formation. The authors showed recently that injection of magnetic carriers (and in particular, erythrocytes) containing colloidal magnetite into the blood stream could be followed by concentration of these carriers in a particular part of the arterial bed if a miniature magnet was placed outside the artery [1].

In the present investigation aspirin-loaded magnetic erythrocytes were used in an attempt to prevent thrombus formation locally in the carotid artery of a dog.

## EXPERIMENTAL METHOD

Experiments were carried out on male dogs (beagles) weighing 14-17 kg. The day before the experiment blood was taken from the animals and the erythrocytes were loaded with a ferromagnetic colloid and aspirin. The erythrocyte residue contained 7-8 mg of aspirin (Sigma, USA) in 1 ml, and this amount could be released spontaneously from the erythrocytes with a half-elimination time of 30-40 min. Thrombus formation in the dog's carotid artery was induced by invaginating a trapezoidal fragment of the vessel wall into the lumen [2]. A magnet made of $SmCo_5$ measuring 3 × 5 × 15 mm [1] was fixed in the tissues outside the vessel in the zone of thrombus formation. Magnetic erythrocytes loaded with aspirin were injected into a vein of the dog's hind limb in three equal portions at intervals of 1 h, starting from the end of the operation. The total dose of aspirin injected was 20 mg. The blood flow was monitored by means of a "Gould Statham SP 2201" electromagnetic flowmeter (USA). At the end of the experiment the dog's carotid arteries were excised and fixed for 24 h at 4°C in 4% formaldehyde, dissolved in phosphate-buffered physiological saline, pH 7.4 Frontal sections were cut on a "Reichert-Jung model 2700 Frigocut" freezing microtome (Austria) and stained for collagen and elastic tissue by the Verhoeff–Van Gieson method.

## EXPERIMENTAL RESULTS

Immediately after the operation the blood flow in both carotid arteries (one fitted with the magnet, the other the control) was sharply reduced to 40% of its initial value (Fig. 1). This was the result of spasm due to the operation. After injection of the magnetic erythrocytes, loaded with aspirin, the blood flow in the control artery (without a magnet) continued

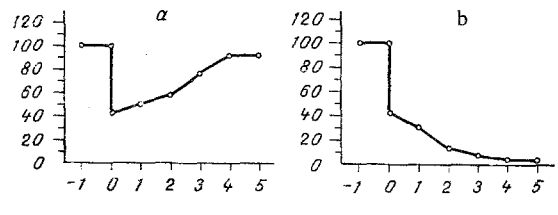


Fig. 1. Blood flow in the dog's carotid arteries. Abscissa: time after operation (in h); ordinate: blood flow (in %, blood flow in vessel before operation taken as 100%). a) Artery fitted with magnet; b) artery without magnet (control).

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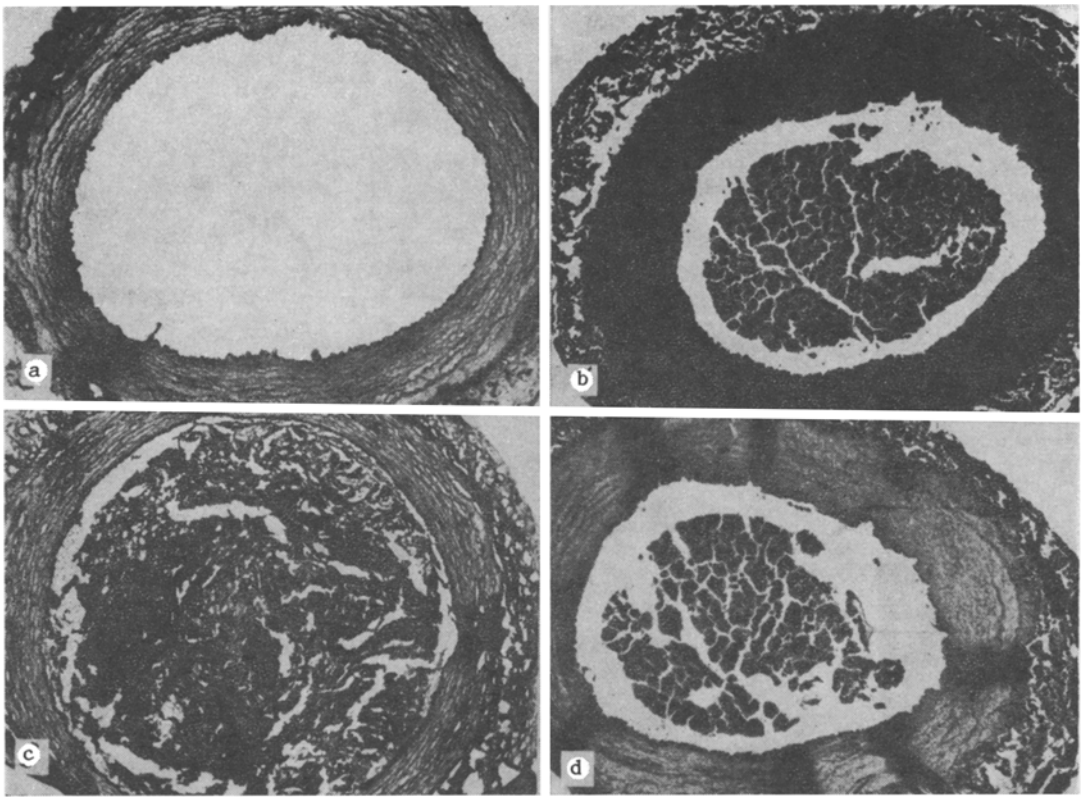


Fig. 2. Frontal sections through carotid arteries excised at end of experiment. a, b) Arteries fitted with a magnet; c, d) arteries without magnet (control). a, c) Injection of aspirin-loaded erythrocytes (it will be noted that a thrombus completely occluding the vessel is present in the control artery, but no thrombus is present in the artery fitted with the magnet); b, d) injection of erythrocytes without aspirin. The dog's carotid arteries were excised 5 h after the operation. Stained by Verhoeff—Van Gieson method. 50 ×.

to fall, and reached zero 4 h after the operation. Meanwhile the blood flow in the artery fitted with the magnet fell sharply at first to 40%, but then gradually recovered, so that after 4 h it was restored almost to its original value (Fig. 1). Histological analysis of arteries excised 5 h after the operation revealed a red thrombus, completely occluding the lumen of the vessel, in the control artery. No such thrombus was present in the artery fitted with the magnet (Fig. 2a, c).

Magnetic erythrocytes not loaded with aspirin were used in the control experiments. In this case a red thrombus occluding the lumen was formed in both of the dog's carotid arteries (with and without the magnet) 4 h after the operation (Fig. 2b, d).

The main advantage of targeted drug administration is that the dose given can be greatly reduced, so that the very harmful systemic action of many preparations can be avoided. The dose of aspirin which we injected into a dog was an order of magnitude less than the average therapeutic dose used in the conservative treatment of patients with the risk of thrombosis. This dose did not prevent the blood from clotting in the control artery of the dog, but it was sufficiently effective in the case of local administration by magnetic targeting of carriers loaded with the drug.

The approach adopted in this investigation can be used in thrombolytic as well as disaggregating therapy. In particular, it can be used to produce lysis of a thrombus which often forms at the site of stenosis, arising in the region of the distal anastomosis in aortofemoral bypass operations [3, 4]. By fitting a miniature magnet to the distal end of the prosthesis during the primary operation, magnetic targeting of a thrombolytic agent can be carried out. In some cases this will evidently help to avoid repeated operations to reconstruct the occluded region of the vessel. A permanent magnetic field created by a magnet in the region of

the distal anastomosis can be used to target and concentrate not only thrombolytics and disaggregants, but also, probably, agents inhibiting the proliferation and synthesis of connective tissue, so that it will be possible to prevent neointimal fibrous hyperplasia, the primary cause of postoperative reocclusion [4].

## LITERATURE CITED


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