Angiogenesis and arteriogenesis evaluation by DCE-MRI and CE-MRA in a peripheral ischemia model

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Purpose

Dynamic contrast-enhanced MR imaging (DCE-MRI) and contrast-enhanced MR angiography (CE-MRA) were combined to evaluate angiogenesis[1] and arteriogenesis[1] in a rabbit model for peripheral ischemia[2]. Angiogenesis is the process of new blood vessel formation triggered by ischemia, and arteriogenesis is the growth of pre-existent arterioles into functional collaterals, for example in response to arterial occlusion. Combined DCE-MRI and CE-MRA may prove to be useful for both morphologic and functional evaluation of angiogenesis and arteriogenesis.

Methods

The left femoral artery was ligated in 12 New Zealand White rabbits, and X-ray angiography was performed prior to MR imaging. DCE-MRI (n=12) and CE-MRA (n=10) were performed in a clinical 1.5T MR system, at 1-2 hours after ligation (day 0^+) and after 7 and 21 days. DCE-MRI included a pre-contrast T_1 measurement and T_1-weighted dynamic contrast enhanced series (3D-FFE, TE/TR= 2.2/4.5 ms, FA 35°, voxel size 2.0×1.6×2.5 mm, FOV 256×192 mm, 200 dynamic scans, duration 10 min) [3]. Gd-DTPA was injected into the ear vein (0.5ml/15s) at the start of the 8th dynamic scan. The general pharmacokinetic two-compartment model was used to calculate the ratio of the endothelial transfer coefficient (K^{PS}) in the extensor- (anterior) and flexor muscles (posterior) in the lower ligated limb and non-ligated limb, individual vascular input functions were obtained at the aorta bifurcation. The contrast agent arrival in the aorta- and femoral artery bifurcation were obtained from the DCE-MRI data to obtain the arterial flow delay time in the ligated limb. CE-MRA was started 5 min after DCE-MRI (15 min after the 1st contrast injection) 3D FFE, TE/TR= 2.5/9.5 ms, 2:30 min, voxel size 0.6×0.6×0.7 mm, FOV 196×176 mm, centric k-space filling, and intravenous injection of Gd-DTPA (1ml/30s). Collaterals were scored on subtraction 3D rotational MIPs by the Longland criteria (defining stem-, mid- and re-entry zone), to allow anatomic distinction between collateral vessels and veins.

Results

At day 0^+, K^{PS} ratios significantly decreased (p=0.001) in the extensor muscles, which recovered in great part by day 7 (p=0.003) and recovered slightly more by day 21 (n.s. p=0.3). The flexor muscles reduced to a lesser extent (p=0.04), but also recovered by day 21 (n.s.) (Fig 1). CE-MRA showed growth of pre-existing arterioles, predominantly stemming form around the ligation, from day 0^+ to day 7 (p=0.01) and a small increase on day 21 (n.s.) (Fig 2). CE-MRA correlated well with X-ray angiography (Pearson r=0.68, p<0.001). The average arterial flow delay significantly reduced from day 0+ to day 7 (p=0.01) and day 21 (p=0.03) (Fig 3).

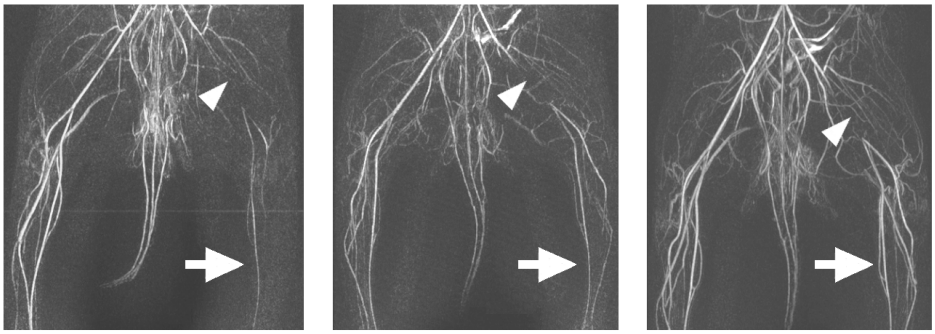

Figure 2: CE-MRA subtraction MIP images (used for creating the rotational MIPs) illustrate the growth of collateral vessels around the ligation (**arrowhead**), and blood-flow recovery to the distal arteries (**arrows**).

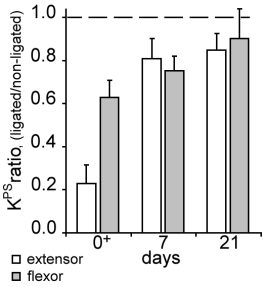

Figure 1: drop in K^{PS} recovers.

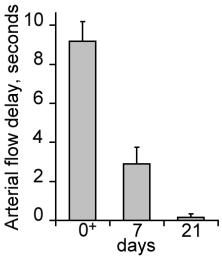

Figure 3: time from aorta to popliteal & saphenous artery.

Discussion

CE-MRA and arterial flow delay measurements establish the acute reduction in blood flow to the distal limb after femoral artery ligation, which recovers in 21 days by collateral growth in the upper limb (i.e. arteriogenesis). The K^{PS} measurements reflect the recovery of blood flow to the distal limb muscles, which is in concordance with recent reports [3] that K^{PS} is predominantly a measure for blood flow rather than microvessel permeability-surface area product (PS) when using a small molecular MR contrast agents like Gd-DTPA. Further work may show whether the observed differences in K^{PS} relate, for example, to muscle composition (e.g. fiber type) or correlate with other surrogate (e.g. histologic) markers of angiogenesis in these muscles.

Conclusion

Combined DCE-MRI and CE-MRA is a suitable non-invasive imaging technique for both morphologic and functional evaluation of arteriogenesis and angiogenesis in peripheral ischemia.

References

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