Response to Letter by Bendszus et al

**Response:**

We are grateful to Bendszus et al for their letter because their comments further improve the discussion of our article, raising important questions about the interpretation of MR signal loss at the early stage of focal cerebral ischemia. The authors indeed suggest that in this context the hypointense rim surrounding the ischemic lesion might be related to ongoing thrombus formation. This hypothesis seems likely to us because we did observe intravascular trapping of iron particles after Prussian blue staining at the early stages postischemia (<12 hours postinjury; authors' unpublished data, 2006), in line with their findings.

Nonetheless, our observations did not allow us to rule out the hypothesis of nonspecific iron leakage across the damaged blood-brain barrier. First, and in contrast to their studies, we used ultrasmall superparamagnetic iron oxide nanoparticles (USPIO) and not SPIO. One advantage of USPIO over SPIO is that the fact that they are not immediately recognized by cells of the mononuclear phagocytic system of liver and spleen and hence have a longer blood half-life, which widens the delivery time-window. On the other hand, owing to their smaller size, USPIO may cross the disrupted blood-brain barrier and enter the brain freely, whereas SPIO may be blocked by the basement membrane. Second, we could not exclude the possibility that the technical limitations of Prussian blue staining might have prevented detection of interstitial iron oxide particles. Therefore, no firm conclusion should be drawn from the fact that we did not observe free iron nanoparticles on Prussian-blue stained slices. In order to answer this crucial question, we are currently planning to investigate the hypothesis of passive iron diffusion, using other technical approaches including electronic microscopy.

In conclusion, the authors address a key issue in their letter, namely the differential interpretation of (U)SPIO-induced signal loss according to postischemia observation time. To date, a major limitation of the technique is clearly the inability to unequivocally discriminate between targeted cells and other phenomena, such as developing thrombi or interstitial nanoparticles. Because further exploitation of this technique will aim at studying the physiopathology of stroke, a major step forward would be to develop pulse-sequences that are iron-oxide specific (for instance, by using gradient echo acquisition for superparamagnetic particles with positive contrast [GRASP]) and perhaps sensitive to compartmentalization. Additionally, the combined use of contrast agents other than (U)SPIO (targeted at fibrin, for example, for thrombus identification?) may be necessary in order to increase the specificity of the approach. Such refinements are essential to realize the promise of clinical trials using USPIO-based imaging of macrophage activity.

**Disclosures**

None.

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**References**

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Marlène Wiart, Nathalie Davoust, Virginie Desestret, Norbert Nighoghossian and Yves Berthezène

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