

Hyperoxygenation in combination with susceptibility weighted imaging identifies vascular lesions in a model of multiple sclerosis

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Target audience: Those using susceptibility based MR imaging to study multiple sclerosis (MS) models and to image patients, and those interested in vascular involvement in MS.

Purpose: To develop a method that distinguishes between dark spots (or small phase changes) in susceptibility weighted imaging (SWI) caused by intravascular blood from those caused by perivascular or parenchymal iron/demyelination. We tested the effectiveness of changing inspired oxygen levels while imaging the experimental autoimmune encephalomyelitis (EAE) mouse model of MS. We showed previously that SWI detected two types of lesions in EAE: 1) vascular lesions, due to deoxyhemoglobin (dHb) and 2) parenchymal white matter lesions, due to iron deposition/demyelination. We hypothesized that lesions which change with high oxygen must be intravascular, caused by dHb.

Methods: Female C57BL/6 mice were immunized with EAE.² A 9.4T Bruker Avance II console with a 20mm surface coil was used. Lumbar spinal cords of EAE mice at peak disease (n=9) and long-term disease (n=5) as well as naive control mice (n=9) were imaged using 3D GEFC (matrix=192x128x32, FOV=0.92cmx1.28cmx1.28cm, TE/TR/α=4ms/50ms/15°, NEX=17, voxel size=48x100x400μm). Animals were imaged using 30% O₂/70% N₂, then with 100% O₂. A subset of mice was imaged again after perfusion (to remove blood). SPIN software was used to process images using a 32x32 Hanning filter and by multiplying the negative phase mask into the magnitude data four times to create SWI images.³ Lesions were counted and compared between control and peak EAE mice with 30% O₂ and the number of hypointensities were counted and compared between 30% O₂ and 100% O₂ data. Response types observed with 100% O₂ were also classified.

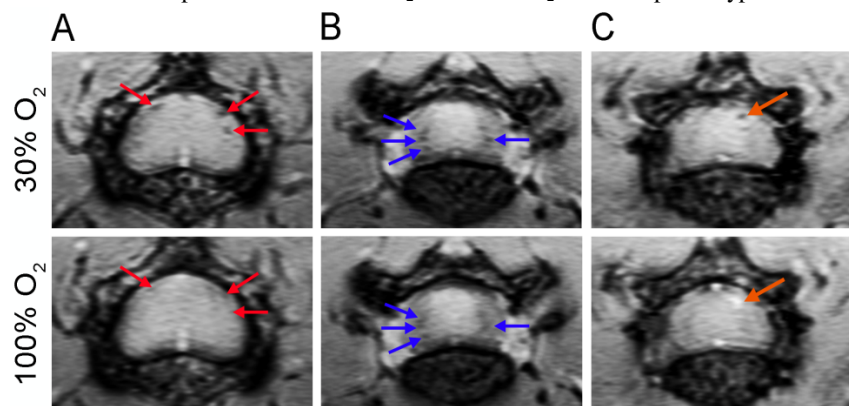


Fig 1. Vascular-based SWI lesions visible with 30% O₂ either disappear, become less dark but do not disappear completely, or become hyperintense upon administration of 100% O₂ in EAE mice. A shows a hypointensity visible with 30% O₂ which disappeared with 100% O₂ (red arrows). **B** shows hypointensities seen with 30% O₂ that became less dark but did not disappear completely with 100% O₂ (blue arrows). **C** shows a hypointensity seen with 30% O₂ that became hyperintense with 100% O₂ (orange arrow).

Results: Vascular lesions (hypointensities) visible with 30% O₂ showed different responses upon administration of 100% O₂ (**Fig. 1**). Some lesions seen with 30% O₂ disappeared with 100% O₂ (**Fig. 1A**); some lesions were less hypointense with 100% O₂ than with 30% O₂, but did not disappear completely (**Fig. 1B**); and some became hyperintense with 100% O₂ (**Fig. 1C**). Hypointensities that altered with 100% O₂ disappeared after perfusion, supporting that they are due to dHb (data not shown). Peak EAE mice had significantly more hypointensities visible with 30% O₂ than controls (**Fig. 2A**). The number of hypointensities seen with 30% O₂ was significantly greater than the number that did not change in appearance with 100% O₂ in both controls and peak EAE mice (**Fig. 2A**). Most hypointensities in control mice disappeared in the presence of 100% O₂, whereas most hypointensities in peak EAE mice became less dark but did not disappear completely with 100% O₂ (**Fig. 2B**).

Discussion: The different responses observed upon administration of 100% O₂ are likely related to the initial dHb saturation. Increased sensitivity may be obtained by adding CO₂. Hyperoxygenation alone is well tolerated and safe, making this a method that could be translated to patients.

Conclusion: Changing inspired oxygen in combination with SWI imaging can be used to identify vascular lesions. This method could be applied in MS patients to help differentiate between sources of lesions and relative amounts of vascular hypoxia.

References:

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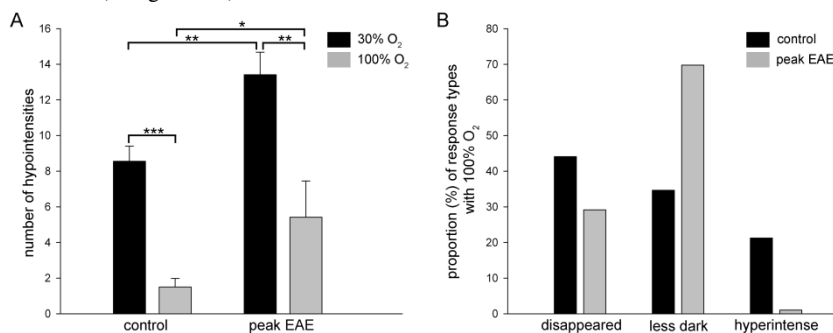


Fig 2. Number of hypointensities seen with 30% O₂ and 100% O₂, and proportion of responses to 100% O₂. A number of hypointensities seen with normal and high O₂. The number of focal hypointensities is higher in EAE when breathing either gas. High O₂ almost totally eliminates lesions in controls, but many remain in EAE. **B** shows a total count of response types in all animals seen with 100% O₂ for controls and peak EAE mice. **p*<0.05, ***p*<0.01 and ****p*<0.001 by t-test.