# Changes in placental and fetal organ perfusion during chronic maternal hypoxia: assessment by BOLD MRI during brief hypercapnic and hyperoxic challenge

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**Background & Aims** Preeclampsia and intrauterine fetal growth restriction are common disorders of pregnancy where clinical management may be improved by non-invasive imaging of uteroplacental blood flow (UPBF) and fetal organ perfusion. Ultrasound is routinely used to assess the preplacental circulation (uterine arteries) and the postplacental circulation (umbilical and fetal middle cerebral arteries), but is unable to assess these vessels simultaneously, to perform dynamic studies, or to assess tissue oxygenation. The use of DCE-MRI with gadolinium to assess UPBF is limited in humans by the slow placental transfer, by the large doses required for fetal imaging and by the potential for renal injury. Blood oxygen level dependant *f*MRI (BOLD-*f*MRI) has been used to image changes in uterine perfusion without contrast agent administration during hypoxia in pregnant sheep.[1] We further developed the BOLD-*f*MRI method by utilizing brief challenges of hypercapnia followed by hyperoxia for monitoring acute changes in organ perfusion without contrast administration.[2-3] In this study we use this technique to assess uteroplacental and fetal organ perfusion, in order to assess the acute fetal responses to hypercarbic and hyperoxic challenge, and to assess whether these responses are affected by chronic maternal hypoxia, as a model of intrauterine fetal asphyxia.[4]

**Methods** Pregnant female ICR mice were either exposed to chronic hypoxia (12% $O_2$) by placing them in a hypoxic chamber (Coy Laboratory Products) or kept under normoxic conditions on days 13-18 of gestation (n=6 mice/group). On the 18th day, anesthetized mice (pentobarbital) were scanned in a 4.7-T Bruker Biospec spectrometer. Changes in placental and fetal perfusion were analyzed from T2*-weighted GE images (TR/TE=147/10 ms) acquired during breathing of air (4 min), air-carbon dioxide (5% $CO_2$) (4 min), and carbogen (95% $O_2$-5% $CO_2$) (4 min). Different regions of interest (placenta, and fetal heart, liver and brain) were identified on True-FISP images using IDL software. Percentage change in signal intensity induced by hypercapnia ($\Delta S_{CO2}$) and hyperoxia ($\Delta S_{O2}$) was calculated and presented by color maps and time curves. After MRI fetuses and placentas were taken for histological evaluation.

**Results** BOLD-*f*MRI provided simultaneous assessments of placental and fetal organs (brain, heart, liver) perfusion in pregnant mice. We observed that acute maternal hypercapnia caused reproducible and reversible reductions in UPBF, fetal hepatic perfusion and fetal cardiac perfusion. Fetal cerebral perfusion, however, was unchanged; suggestive of the described phenomenon of fetal "brain sparing" (Fig 1). The acute hypercapnia challenge using BOLD-*f*MRI was able to distinguish between chronic intrauterine asphyxia (induced by maternal hypoxia) and normal controls, with lower % change in UPBF and less fetal brain sparing (Figs 1, 2).

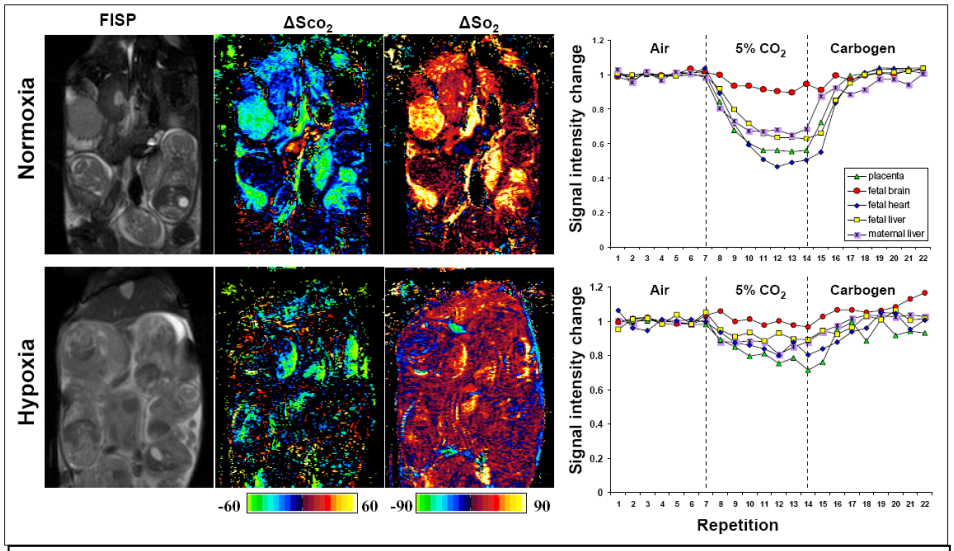


**Fig 1** Representatives coronal FISP images (**left**); the corresponding *BOLD-fMRI* (ΔS) maps (**middle**) and the related time courses of SI change from the different regions obtained from normoxic (**Top**), and hypoxic (**Bottom**) pregnant ICR mice (day 18 of gestation – E18).

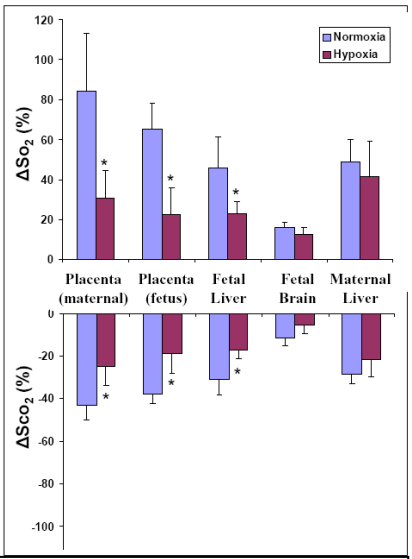


**Fig. 2** Mean *ΔS* values of different fetal and maternal organs obtained from normoxic (n=6) and hypoxic (n=6) pregnant ICR mice E18 (*p<0.001 compare to normoxia).

**Conclusions** The BOLD-*f*MRI hypercapnic challenge test was able to differentiate between normal and chronically asphyxiated pregnancies. Further preclinical and clinical investigation is required to assess whether these observations may herald the use of this non-invasive diagnostic tool to determine if the severity of chronic intrauterine fetal asphyxia justifies interventional delivery.

**References**: [1]Wedegärtner U, *Radiology* 238:872,2006;[2] Barash H, *Radiolog* 243:727,2007**;** [3]Barash H, *Hepatology* 48:1232, 2008. [4] Tomlinson T, *Am J Physiol Regul Integr Comp Physiol* 298: R312, 2010.