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Title

Editorial for "Feasibility of Multimodal Perfusion Assessment in Diabetic Foot Ulcer Using IVIM and BOLD MRI

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Editorial for “Feasibility of Multimodal Perfusion Assessment in Diabetic Foot Ulcer Using IVIM and BOLD MRI”

Diabetes mellitus is one of the major risk factors for coronary and cerebrovascular disease as well as peripheral artery disease. Diabetes also causes peripheral sensory, motor, and autonomic neuropathy. Macro- and microvascular impairment and peripheral neuropathy may both lead to serious complications such as tissue inflammation, ulceration and infection, mainly in the lower limb.

In clinical practice, peripheral artery disease diagnosis and monitoring relies on clinical exams such as intermittent claudication, the ankle-brachial blood pressure index and doppler ultrasound, and imaging (angiography) techniques generally requiring the injection of radiopaque or paramagnetic contrast agents.

Assessment of the impact of peripheral artery disease and neuropathy on microvasculature and tissue microstructure is needed to predict the risk of tissue damage or the potential of tissue regeneration. Advanced non-invasive quantitative parametric imaging approaches have the potential to address such aims. Due to concerns related to allergic reactions, nephrotoxicity and gadolinium deposition in tissues contrast agent free approaches characterized by sufficient contrast to noise ratio and sensitivity are under development.

MRI perfusion and diffusion parameters can give valuable and quantitative insight into tissue integrity and function. For instance, autonomic neuropathy will impair endothelial function and therefore vasoreactivity, temperature regulation and tissue metabolism and may therefore lead to oedema and inflammation. IVIM yields diffusion constants attributable to slow diffusion in

tissue parenchyma, and to fast or pseudo-diffusion in microvasculature. The latter has been shown to correlate with dynamic susceptibility contrast MRI-accessible quantitative hemodynamic parameters such as blood volume and endothelial leakage coefficient (1). IVIM is sensitive to diabetes mellitus induced cardiac myopathy (2) and **Edwards et al (dummy reference)** shows diabetes mellitus induced alterations in foot angiosomes. Decreased perfusion fraction and pseudo-diffusion coefficients were observed in diabetic patients while increased diffusion and pseudo-diffusion coefficients were observed in patients with ulcers. This encourages further investigation of diabetes mellitus complications in muscle and cutaneous tissue using this technique. However, IVIM requires long acquisition times and is prone to motion artifacts and therefore poorly suited for the assessment of functional responses to exercise, and ischemic or pharmacologic challenge.

Blood oxygen level dependent contrast was initially proposed as a functional MRI technique for metabolic changes in brain tissue and for neural activation (3) based on the neurometabolic and neurovascular coupling. However, as BOLD contrast relies on hemodynamic and hemoglobin oxygenation changes, the response to a physiologic or pharmacologic stimulus of non-neuronal tissue such as liver, kidney and placenta has also been explored. Perfusion in myocardial (4), skeletal muscle (5) and neoplastic tissue (6) was the first to be studied.

BOLD MRI has the advantage of being a dynamic technique enabling monitoring of the response to stress activation and repeatable for treatment follow-up without exposure to ionizing radiation and contrast agents. However, so far, only 13 studies have taken advantage of this technique to study skeletal muscle tissue perfusion in patients with microvascular pathologies, with one study in diabetes mellitus patients (7). **Edwards et al (dummy ref)** realized the

potential of this approach and demonstrate decreased tolerance to vessel occlusion and a slowed reperfusion in diabetes mellitus patients with active foot ulcers.

Arterial spin labeling is another quantitative MRI approach for the non-invasive assessment of tissue perfusion and yields similar results in diabetes mellitus patients with foot ulcer (8).

Hyperemia in tissue surrounding ulcers was confirmed with ASL (9).

Despite worse methodological challenges in applying these MRI approaches to organs other than the brain, non-invasive mapping of quantitative perfusion parameters represents a promising tool to assess tissue alterations in diabetes mellitus in longitudinal studies. These techniques deserve further development and validation.

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