Measurement of reduced lymphatic flow velocity under conditions of obstructed lymphatic flow using spin labeling approach

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TARGET AUDIENCE: Breast oncologists and imaging physicists with an interest in novel spin labeling methodology

PURPOSE: *The purpose of this work is to (i) assess the sensitivity of a newly proposed lymphatic spin labeling approach for detecting variability in lymphatic flow to axillary lymph nodes, (ii) outline a quantitative framework for the interpretation of flow using this approach, and (iii) assess clinical potential in a cohort of advanced-stage lymphedema patients.* Lymphedema is a chronic, debilitating disease caused by lymphatic flow obstruction and affects nearly 89% of breast cancer survivors undergoing mastectomy with axillary lymph node removal. However, there are currently no MRI procedures that can be used to stratify lymphedema risk or to evaluate changes in the lymphatic system in response to therapy. Very recently, it was shown that spin labeling approaches, commonly applied to measure blood flow[1], can be adapted to quantify lymphatic flow as well[2]. However, significant gaps remain in our knowledge regarding (i) to what extent measurements are indicative of lymphatic flow, (ii) how measurements adjust in response to obstructed lymphatic flow, and (iii) how models should be adapted to allow for lymphatic flow quantification. This work addresses these questions by extending the lymphatic spin labeling approach to measure lymphatic flow under manipulated flow obstruction using a pressure cuff[2], in Stage II lymphedema patients with unilateral lymph node removal, and results are interpreted in the context of an adapted kinetic model.

METHODS: *Simulations.* Simulations were performed to visualize how the shape and behavior of kinetic curves describing inflow of lymphatic fluid to axillary lymph nodes vary compared to more common perfusion kinetic curves obtained from arterial spin labeling experiments. Simulations were performed using measured lymphatic T_1=3100 ms at 3T[2] and assuming the difference magnetization (ΔM) is proportional to the product of the flow, equilibrium magnetization, and convolution of a transit time and T_1-dependent input function and residue function describing flow into a simple, impermeable compartment with fixed residence time (Fig. 1). *Experiment.* All volunteers (n=6) provided informed consent in accordance with the local IRB and were scanned at 3T using a two channel parallel transmit body coil in conjunction with a 16-channel torso receive coil. Lymphatic spin labeling was assessed in three right-handed healthy volunteers and three Stage II lymphedema patients using (i) diffusion-weighted imaging with body signal suppression, DWIBS (TR/TE/TI= 8037/50/260 and b = 800s/mm^2; spatial resolution = 3x3x5 mm^3), and (ii) adiabatic pulsed spin labeling scan (spatial resolution=3x3x5 mm^2, SPIR fat suppression, inversion time, TI = 500, 1500, 2500, 3500, 4000–10,000 ms (500 ms intervals), averages=8, and single-shot gradient echo EPI readout). To simulate impaired flow conditions, lymphatic flow was obstructed in the left arm of healthy subjects, using a blood pressure cuff with pressure maintained at 60 mm Hg[3]. Blood pressure was recorded prior to imaging to ensure that the diastolic blood pressure > 60 mmHg. *Analysis:* Lymphatic flow curves (ΔM) were compared in left and right axillary nodes. The DWIBS scan was used to locate the lymph nodes and distinguish them from blood vessels. This protocol was a free breathing protocol, so respiratory motion in the chest cavity caused significant displacement of the nodes and distortion of the node shape. Motion correction was therefore performed and measurements of lymph node displacement over the duration of the experiment were measured and accounted for in post-processing. Signal to noise ratio (SNR) was calculated across all acquisitions for each TI. Unlike blood flow, lymphatic flow over several mm may take several seconds. To account for this, SNR measurements were recorded at each TI and ΔM values where SNR<0 were set to 0.

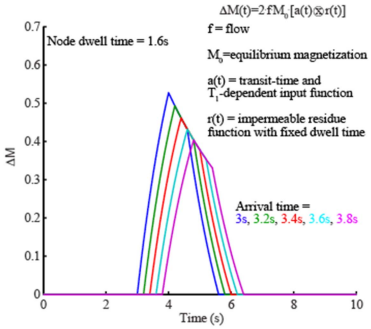

Figure 1: *Dependence of spin labeling difference contrast (ΔM) in lymph nodes for varying arrival time and long node residence time=1.6s. Note that the kinetic curves rise and fall quickly, analogous to the macrovascular component of signal in blood water spin labeling models.*

RESULTS AND DISCUSSION: Fig. 1 shows simulated kinetic curves for lymph flow into axilla; note the steep rise and fall of (ΔM). Fig. 2 shows representative DWIBS and spin labeling EPI images, along with the mean displacement of the lymph node across the ASL scan for different TIs, which on average was found to be 6 mm (2 voxels). The red region was common to all TIs and used for kinetic curve analysis. Lymph kinetic curves for a healthy subject show delayed lymphatic flow on the cuffed side relative to the uncuffed side (time-to-peak difference = 3s). The bottom graph describes lymphatic flow in the healthy arm (black) and the lymphedematous arm (red dashed) in a representative lymphedema patient. The lymphatic flow velocity into the node in the lymphedema arm was found to be slower (0.35 cm/min) than in the normal arm (0.61±0.13 cm/min) in all patient volunteers.

CONCLUSION: We extended preliminary lymphedema spin labeling studies to demonstrate sensitivity of this approach for measuring lymphatic kinetics under conditions of known lymphatic flow obstruction using both a pressure cuff to manipulate lymph flow in healthy volunteers and knowledge of physiological impairment in patients with Stage II lymphedema. Furthermore, algorithms have been developed that account for lymph node motion and flow quantification. Further development of this approach may expand abilities to assess lymphedema risk and patient response to therapy in this highly prevalent yet understudied condition.

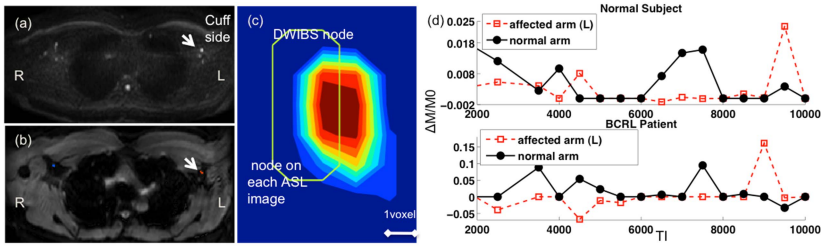

Figure 2*. (a) DWIBS image used to locate the lymph nodes and (b) corresponding control EPI image. Blue ROI depicts lymph node on the normal side and the red ROI depicts the lymph node on the cuffed side (left). Displacement and distortion of a representative lymph node due to respiratory motion. Color corresponds to a probability map (red=high location probability; blue=low location probability) of node location across all scans whereas the green outline shows the location in the DWIBS scan. (d) Lymphatic flow curves for the healthy volunteer and lymphedema patient show impairment in lymphatic arrival times on the compromised side.*

REFERENCES: [1]Detre JA, *et al*. MRM. 1992 Jan;23(1):37-45. [2]Rane S *et al*., *ISMRM 2012*, Abs 575. Melbourne, AU. [3]Modi S, *et al*. *J Physiol.* 583(1):271-285, 2007.