Contrast-Enhanced Magnetic Resonance Lymphangiography of the Upper Limbs in Breast Cancer Related Lymphoedema: An Exploratory Study.

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Introduction: Breast cancer-related lymphoedema (BCRL) remains one of the most common and distressing morbidities in breast cancer survivors treated with radical surgery and axillary nodal dissection [1]. Clinical imaging of the lymphatic system is limited: lymphoscintigraphy is currently the most widely utilized investigation for evaluating lymphoedema, but suffers from poor spatial resolution [2]. Near infra-red lymphangiography using indocyanine green is a recently introduced technique with high spatial resolution, but demonstrates only superficial lymphatic vessels [3]. Contrast-Enhanced Magnetic Resonance Lymphangiography (CE-MRL) can provide high resolution images of superficial and deep lymphatic vessels [4,5]. In this proof-of-principle study we have (1) demonstrated for the first time CE-MRL of the upper limbs in patients with BCRL; employed the contrast agent (CA) uptake curves to distinguish lymphatic vessels from veins; (3) reduced the CA concentration at the injection site to enable a dynamic quantitative examination; (4) used the CA uptake dynamic information to calculate lymphatic fluid velocity.

Materials and Methods: The study was approved by the institutional research and ethics committee, and written informed consent was obtained from all patients.

Clinical Examinations: Three patients with unilateral BCRL were recruited. Both the ipsilateral (affected) and contralateral (unaffected) arm were imaged at 1.5T (MAGNETOM Aera, Siemens AG, Erlangen, Germany), on separate visits. The imaging protocol included a high spatial resolution 3D fast-spoiled gradient-echo pulse sequence (TE/TR = 2.77/6.14 ms, flip angle = 12°, voxel size = 1×1×1 mm, SPAIR fat suppression). The whole arm was imaged in 3 stations, covering the anatomy from the hand to the axilla (total acquisition time = 3:54 minutes), once pre-injection and several times post-injection over a period of 45 minutes. A mixture of gadoteridol (ProHance®, Bracco Diagnostics Inc., Princeton, USA, [Gd] = 0.5 M) and anaesthetic (1% lidocaine) was administered with a 1 ml total volume intradermal injection for each of the 4 inter-digital spaces. Two injection protocols were adopted:

Morphological: 1 ml of injected volume contains 0.9 ml of gadoteridol and 0.1 ml of anaesthetic [4], with resulting [Gd] = 0.45 M.

Quantitative: 1 ml of injected volume contains 0.02 ml of gadoteridol, 0.1 ml of anaesthetic and 0.88 ml of saline, with resulting [Gd] = 0.01 M.

The *morphological* protocol was administered to the first 2 patients, the *quantitative* protocol to the 3rd patient.

Figure 1. Morphological protocol

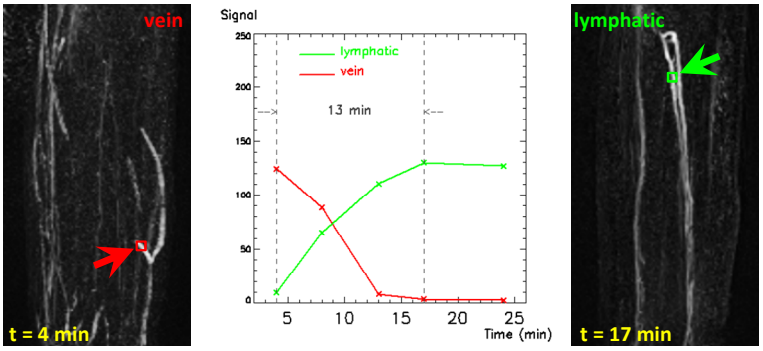

Figure 2. Quantitative protocol

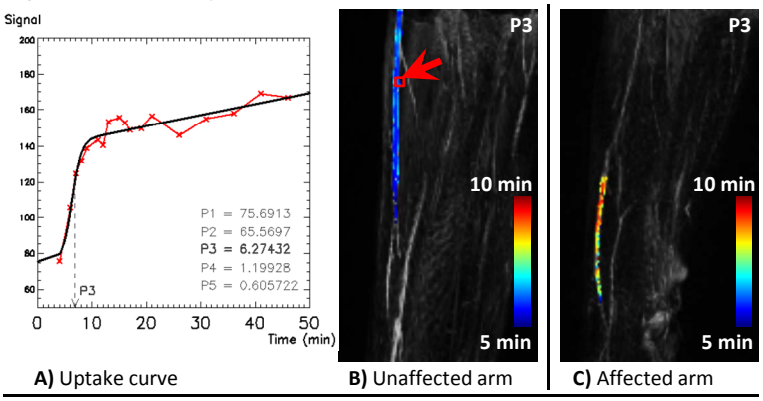

Figure 1. Morphological protocol: coronal Maximum Intensity Projections (MIP), at different times, of the forearm of Patient 2, showing lymphatic vessels and veins, and associated CA uptake curves.

Figure 2. Quantitative protocol: **A)** uptake curve for the voxel selected in B) and fit with the logistic model [6]; **B)** Distribution of the parameter P3 (onset time, minutes) within a main lymphatic vessel of the unaffected arm of Patient 3, superimposed, with colour scaling, to the MIP; **C)** Affected arm.

Data Analysis: Image processing was performed with in-house software developed in IDL (version 8.2, Exelis Visual Information Solutions). After performing image registration, each post-contrast volume was subtracted from the first volume with the purpose of visualizing the evolution of the enhancement. The software was designed to visualize the entire subtracted 3D data volume, producing, for each time point, a Maximum Intensity Projection (MIP) along a defined direction. Each voxel in the MIP was associated with the corresponding dynamic uptake curve, which plots the evolution of the signal across the subtracted series. The uptake curves were fitted with a five-parameter modified logistic equation [6] to enable identification of the onset time (time of arrival of the CA). The developed image processing tools were used to (a) differentiate veins from lymphatic vessels and (b) measure the lymphatic fluid velocity in the arms imaged with the *quantitative* protocol. The fluid velocity was calculated as the ratio between the distance travelled and the difference in onset of enhancement between two extremities of the vessel.

Results: Images were reviewed by an expert radiologist together with the clinical scientists to determine the presence and extent of lymphatic enhancement. Both protocols provided detailed images of lymphatic vessels. However, with the *morphological* protocol venous enhancement and T2*-related signal decay were observed, due to the high CA concentration at the depot of injection. The *quantitative* protocol prevented venous enhancement, and avoided spurious delay in lymphatic enhancement, due to short T2* values, therefore preserving the linear relationship between signal intensity and concentration of CA. These observations were independently confirmed by test object studies and by physiological modelling of the CA concentration. Considering a diffusion-limited transcapillary exchange in the injection depot, the maximal initial [Gd] in the venous system was estimated to be at least 10^{-3} times the injected [Gd]; this would produce an appreciable T1 shortening of venous blood immediately following injection only with the *morphological* protocol, as observed in the images. With the *morphological* protocol, different enhancing structures could be distinguished with the help of the uptake curves (Fig. 1). Structures which slowly take up contrast are lymphatic vessels, while veins show initial signal enhancement and subsequent signal decay due to CA wash-out. The uptake curves obtained with the *quantitative* protocol are not affected by T2*-decay, correctly reproducing the pattern of CA uptake, and could be described with a general heuristic model [6] (Fig. 2a). The parameter P3, which represents the time of onset of enhancement after injection, demonstrated progression of CA uptake along the main lymphatic trunk of the arm (Fig. 2b-c). The lymphatic fluid velocity was estimated to be 9.7 cm/min for the contralateral (unaffected) arm of the patient examined with the *quantitative* protocol, and 2.1 cm/min in the ipsilateral (affected) arm. These values are in agreement with the estimates reported using lymphoscintigraphy and near infra-red lymphangiography [2,3].

Discussion and Conclusions: We have extended the use of CE-MRL to upper limbs and produced high resolution MR images of lymphatic vessels at 1.5T. The *morphological* protocol produced images with complex signal behaviour, and may therefore not be the optimal method for quantitative studies. We propose a new *quantitative* protocol, which employs an intradermal injection with lower concentration of CA and prevents T2*-related signal loss, allowing correct modelling of CA uptake and minimizing venous enhancement. This protocol appears suitable for quantitative studies, enabling both structural and functional evaluation of the lymphatic system within the same examination.

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