Ferumoxytol MR angiography: a novel technique for assessing iliac vasculature in potential kidney transplant recipients

Running Title: Ferumoxytol MRA for kidney transplant assessment

Sokratis Stoumpos MD, MSc[a,b], Pauline Hall Barrientos PhD[c], Douglas H Black MB ChB[c], Karen Stevenson MB ChB, PhD[a], Martin Hennessy MB ChB[c], Alex T Vesey MB ChB, PhD[a], William Strauss MD[d], Ram Kasthuri MB ChB[c], Aleksandra Radjenovic PhD[b], David B Kingsmore MB ChB[a], Giles Roditi MB ChB[c], Patrick B Mark MB ChB, PhD[a,b]

Corresponding Author:

Sokratis Stoumpos, MD, MSc

*University of Glasgow

Institute of Cardiovascular and Medical Sciences

126 University Place, Glasgow, G12 8TA

E-mail: sstoumpos@nhs.net

Keywords: ferumoxytol, ferric compounds, magnetic resonance imaging, angiography, kidney transplantation

Whilst kidney transplantation is the treatment of choice for suitable patients with end-stage kidney disease, approximately 25% of chronic kidney disease (CKD) patients have peripheral arterial disease (PAD)[1]. CT angiography (CTA) can identify patients requiring revascularization procedures before transplant listing, however its use has been limited because of the risk of nephrotoxicity in patients with residual renal function. Ferumoxytol (Feraheme®, AMAG Pharmaceuticals, Waltham, MA, USA) is an iron oxide nanoparticle used for treatment of iron deficiency anaemia that has superparamagnetic properties with high r1 relaxivity and a long intravascular half-life. We compared ferumoxytol-enhanced MRA (FeMRA) with CTA in assessment of potential kidney transplant recipients using anatomical and signal parameters as surrogates of diagnostic quality.

We prospectively enrolled 36 patients (54±11 years; 61% male; 47% with diabetic nephropathy) who had FeMRA and CTA of aortoiliac vasculature on the same day. The study was approved by the institutional review board (North of Scotland Research Ethics Committee reference: 16/NS/0099). CTA was performed with a 320-detector row CT scanner (Canon/Toshiba, Aquilion One Vision edition; USA) after injection of 100cc of iodine contrast (Omnipaque 350)**.** MRI studies were performed on a 3.0T Prisma MRI scanner (Magnetom, Siemens Healthineers, Erlangen; Germany) after infusion of 3mg/kg of ferumoxytol based on data from a dose-finding study[2]. For detection of arterial calcification, a specific MRI sequence [three-dimensional (3D) free-breathing (StarVIBE) fast low-angle shot (FLASH)] was performed before ferumoxytol administration.

CTA and FeMRA images were synchronized using anatomical landmarks and prespecified arterial and venous cross-sections (overall 216) were selected for comparative analysis. Regions of interest (ROI) were used for the infra-renal

abdominal aorta, right common iliac artery, right external iliac artery, inferior vena cava, right common iliac vein and right external iliac vein to estimate the a) arterial diameter, b) vein diameter, c) area of calcification and d) luminal enhancement (Figure 1). Two independent readers assessed the FeMRA (new technique) and a third reader the CTA (standard technique). Interclass correlation coefficients (ICC) with 95% confidence intervals (95% CI) were performed to test intra- and inter-reader consistency of agreement and mean differences (and 95% CI) were estimated.

There was excellent inter-reader agreement in assessment of the FeMRA across all vascular sections. ICC were 0.88 – 0.92 for the arterial diameter, 0.79 – 0.89 for the vein diameter, 0.88 – 0.91 for the area of calcification and 0.92 – 0.97 for the contrast-to-noise ratio (CNR). Among 12 patients that were selected at random for intra-reader agreement, ICC were between 0.79 – 0.99 for all parameters, indicating excellent agreement. Comparison of FeMRA with CTA showed no significant difference in arterial diameter and area of calcification (mean differences -0.36 – 0.89mm and -0.05 – 0.06mm^2, respectively), but there was significant systematic difference in vein diameter (mean difference 1.53 – 2.44mm). CNR values were significantly higher in FeMRA in both the arterial and venous vasculature (mean differences 3.16 – 7.44 and 16.78 – 24.70, respectively).

We have demonstrated an MR imaging strategy for kidney transplant candidates, which provides reliable depiction of arterial lumen, accurate detection of arterial calcification and synchronous delineation of the venous vasculature. In addition, the favorable pharmacokinetics of ferumoxytol allow imaging of predialysis patients without concerns for iodine or gadolinium contrast toxicity. From a clinical standpoint,

FeMRA can complement or even replace currently used imaging methods in pretransplant assessment of CKD patients with known or suspected PAD.

Our study has limitations. Arterial-phase CTA combined with CT venography was not performed but this requires higher doses of iodine contrast, venous opacification can be suboptimal, and acquisition times vary considerably. This limits conclusions that can be drawn about venous anatomy in this study to some degree. In the steady state, ferumoxytol enhances arteries and veins equally and independently of bolus timing, however this attribute did not compromise diagnosis, as the arteries and veins of the abdomen and pelvis were readily distinguishable. Ferumoxytol is not currently licensed as a contrast agent for MRI and its commercial price (approximately $700 per 17mL vial) is not realistic for a routine deployment, limiting translation of our study protocol to clinical practice. However, its applicability in predialysis patients fills unmet clinical needs offering a safe and robust technique decisive to timely transplant listing.

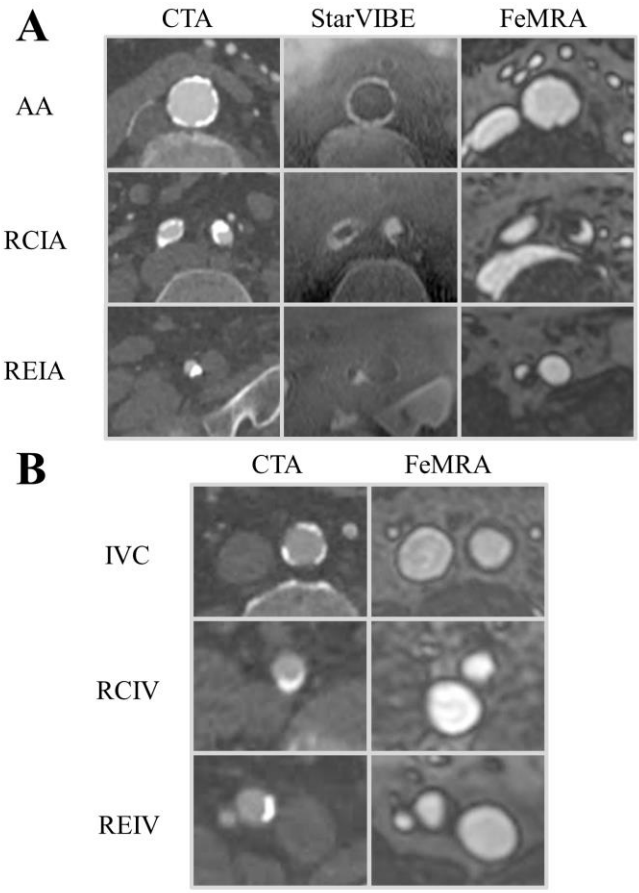

Figure 1. Method for the comparative analysis using arterial and venous cross-sections. Panel A. Arterial cross-sections at the level of infra-renal abdominal aorta (AA), right common iliac artery (RCIA) and right external iliac artery (REIA) used for comparisons between CTA and StarVIBE/FeMRA. Note the consistency in the presence and conformity of calcifications between CTA and StarVIBE and the intraluminal filling defects in FeMRA, which correspond to calcified plaques. Panel B. Venous cross-sections at the level of inferior vena cava (IVC), right common iliac vein (RCIV) and right external iliac vein (REIV) used for comparisons between CTA and FeMRA

References

1. Jones DW, Dansey K, Hamdan AD. Lower Extremity Revascularization in End-Stage Renal Disease. *Vascular and endovascular surgery.* 2016;50(8):582-585.
2. Stoumpos S, Hennessy M, Vesey AT, et al. Ferumoxytol magnetic resonance angiography: a dose-finding study in patients with chronic kidney disease. *Eur Radiol.* 2019.