Multi-contrast high spatial resolution black blood inner volume three-dimensional fast spin echo MR imaging in peripheral vein bypass grafts

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Abstract The purpose of this study is to primarily evaluate the lumen area and secondarily evaluate wall area measurements of in vivo lower extremity peripheral vein bypass grafts patients using high spatial resolution, limited field of view, cardiac gated, black blood inner volume three-dimensional fast spin echo MRI. Fifteen LE-PVBG patients prospectively

underwent ultrasound followed by T1-weighted and T2-weighted magnetic resonance (MR) imaging. Lumen and vessel wall areas were measured by direct planimetry. For graft lumen areas, T1- and T2-weighted measurements were compared with ultrasound. For vessel wall areas, differences between T1- and T2-weighted measurements were evaluated. There was no significant difference between ultrasound and MR lumen measurements, reflecting minimal MR blood suppression artifact. Graft wall area measured from T1-weighted images was significantly larger than that measured from T2-weighted images ($P < 0.001$). The mean of the ratio of T1-versus T2-weighted vessel wall areas was 1.59 (95% CI: 1.48–1.69). The larger wall area measured on T1-weighted images was due to a significantly larger outer vessel wall boundary. Very high spatial resolution LE-PVBG vessel wall MR imaging can be performed in vivo, enabling accurate measurements of lumen and vessel wall areas and discerning differences in those measures between different tissue contrast weightings. Vessel wall area differences suggest that LE-PVBG vessel wall tissues produce distinct signal characteristics under T1 and T2 MR contrast weightings.

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Introduction

Lower extremity surgical bypass graft failure has high clinical significance; almost half of patients have either a lesion or failure within 1 year [1, 2] with resulting mortality, limb loss, further interventions, and diminished quality of life. Doppler ultrasound evaluates increased blood flow velocity, often a late finding. Magnetic resonance (MR) [3–32] capitalizes on inherent soft tissue contrast to further characterize vessel wall components. Despite success in larger vessels such as the carotid artery, the small dimensions and large craniocaudal extent of peripheral vein bypass grafts pose significant challenges for MR surveillance. To date there is no data to confirm that MR graft lumen area measurements correlate with sonography.

This study tests two hypotheses in 15 consecutive peripheral bypass graft patients. The primary hypothesis is that there is no statistical difference between graft lumen area measured from T1-weighted images, fat suppressed T2-weighted images, or gray scale ultrasound. The 1.5T MR approach is a multi-contrast double inversion recovery (DIR) black-blood [5] three-dimensional high sampling efficiency [33] inner-volume [34] FSE protocol (3D IV-FSE) [10, 35–37]. The secondary hypothesis is that the wall area measured on T1-weighted images is greater than the area measured on T2-weighted images at three distinct time points between 1 and 12 months after implantation, and independent of cardiovascular imager performing the measurements. The validation of consistent, accurate MR lumen measurements supports this MR approach to further study the biology of vein graft wall maturation and disease.

Materials and methods

With approval from the institutional human research committee, written informed consent was obtained in 16 consecutive patients in an imaging substudy of a completed clinical outcomes trial after LE-PVBG [38, 39]. One patient was excluded; the patient was unable to finish the exam and those images acquired were degraded by motion artifact. The post-operative time at imaging for the remaining 15 patients (10 M, mean age = 66.4 ± 10.4 years) was as follows: 5 patients, 1 month; 7 patients, 6 months; 3 patients, 12 months.

Seven (47%) patients had coronary artery disease, 8 (53%) had diabetes mellitus, and 13 (87%) had hypertension. Four of the 7 patients imaged 6 months after implantation have been previously reported [37].

Surgery

The indication for arterial reconstruction was critical limb ischemia (rest pain, ulceration, or gangrene) in five patients and lifestyle limiting claudication in ten patients. The source of inflow was the common femoral artery in ten patients and the superficial femoral artery in five patients, while the outflow consisted of popliteal in ten patients and tibial vessels in five patients. Bypass in fourteen patients was constructed with single-segment, non-reversed greater saphenous vein. One bypass was constructed with two pieces of spliced greater saphenous vein. A Mills valvulotome rendered the valves incompetent. There were no bypass graft occlusions, although two patients underwent revision in a location not examined by ultrasound and MR imaging (as defined in the next paragraph).

A single team performed the surgery for all patients and prospectively identified a 5 cm long relatively straight “index segment” for imaging, chosen far away from either anastomosis to minimize turbulent flow. At surgery, meticulous identification of the index segment for precise image registration included marking the distance between the index segment and the proximal anastomosis plus at least one other landmark (e.g., scar, tibial tuberosity). The proximal aspect of the index segment was also noted at surgery by the placement of metallic clips on nearby side branches.

MR imaging

MR imaging was performed on a 1.5T Excite HD MR scanner (GE Medical Systems, Milwaukee, WI) using the body coil for radiofrequency (RF) transmission and a 12.7 cm (5 inch) circular surface coil for reception. Imaging included cardiac gated T1-weighted and fat-suppressed T2-weighted black blood imaging using a high sampling efficiency limited FOV 3D IV-FSE sequence [10]. For both contrast weightings, the cardiac trigger delay was set equal to the default DIR time for blood nulling, calculated based on the T1 of blood and the repetition time

(TR). Sequence parameters were TE = 17 ms, TR = 1 R-R, ETL = 12, and BW = ± 16 kHz for T1-weighted imaging, and TE = 60 ms, TR = 2 R-R, ETL = 18, and BW = ± 10 kHz for T2-weighted imaging. A 3×3 cm FOV encompassing the vessel was imaged at a resolution of 0.3×0.3 mm (zero-fill interpolated to 0.12×0.12 mm) at 32 s imaging time per slice for a heart rate of 60 bpm with four signal averages. Eighteen 2 mm thick slices were obtained over the index segment with each contrast weighting. Scan time at 60 beats per minute was 9.6 min per contrast weighting. Including patient setup and time-of-flight localizers, the total scan time was approximately 45 min per patient.

Sonography

On the same day, and immediately before MR imaging, gray scale US imaging orthogonal to the bypass graft was performed by a dedicated vascular imager with 10 years of experience using an Advanced Technology Laboratories 5000 vascular ultrasound machine with a 7.5 MHz linear array transducer. Two-dimensional cross-sectional LE-PVBG images were obtained at 1 cm intervals over the same index segment imaged by MR.

Image registration

To obtain data to test the first hypothesis, meticulous image registration over the index segment ensured precise comparison between MRI and ultrasound lumen area. The location of the anastomosis and the position of the clips placed for this study at the time of surgery were identified by sonography, and the skin overlying the proximal segment of the index segment was marked by pen (for proper placement of the circular surface coil), plus a vitamin E tablet that is readily identified by MR. The proximal end of the index segment was then confirmed with bright blood time-of-flight images that enabled careful measurement of the index segment with respect to the proximal anastomosis. Prior to the 3D IV-FSE sequences, these measurements were confirmed with data recorded at the time of surgery. Data acquired to test the second hypothesis, the comparison of wall areas between T1- and T2-weighted images, had far less potential for misregistration since the same images were prescribed for each contrast weighting.

Image analyses

Each patient had five ultrasound measurements separated by 1 cm that spanned the index segment. A cardiovascular imager with 6 years experience used an image post-processing tool (Vitrea workstation running 3.9 software, Vital Images, Minnetonka, MN, USA) to perform free-hand lumen measurements defined by the anechoic region on the 2D cross-sectional LE-PVBG images.

For MR, free-hand inner and outer vessel wall borders for each contrast were drawn on each of the consecutive 2 mm thick slices by the same imager, using the same software. A second imager with 4 years experience independently performed the same measurements using the same software to test interobserver variability. The lumen area was defined as the inner wall area on the T1- and T2-weighted images. The vessel wall area (computed for both T1- and T2-weighted images) was defined as the outer wall area minus the inner wall area. Ten to 16 contiguous slices were analyzed from each patient, depending on signal-to-noise ratio (SNR) limitations due to receiver coil placement with respect to the imaged portion of the LE-PVBG. To minimize bias, the imagers were blinded to all patient information, and all data was presented in a randomized fashion. In addition, the US measurements, also blinded and randomized, were performed 4 weeks after the completion of the MR image analysis. Finally, because of the very small FOV in the inner volume technique, neither the ultrasound nor the MR images have features that readily identify a patient, minimizing the potential for recall.

Statistical analyses

For each patient, the ultrasound lumen area, T1-weighted and T2-weighted inner wall area (i.e., lumen area), and both T1-weighted and T2-weighted wall area (outer wall minus inner wall areas for each contrast weighting) measurements were averaged over all available contiguous slices. To test the first hypothesis that the T1-, T2-weighted, and 2D gray scale sonography lumen areas correlate with each other, we examined whether the median differences between lumen area measured by the three methods are equal to zero using the exact Friedman test for k -rated samples. This method is an extension of the

Wilcoxon signed rank test. We subsequently quantified the magnitude of the differences in lumen area among the three data sets (T1 relative to US, T2 relative to US, and T1 relative to T2) based on the median absolute percent differences. Finally, we assessed the agreement between the three data sets using the intraclass correlation coefficient r . To test the secondary hypothesis, namely that PVBG wall areas measured on T1-weighted images are not different than their T2-weighted image counterparts, we examined whether the median difference of vessel wall area is equal to zero using the exact Wilcoxon signed rank test. Finally, we used the Pearson correlation coefficient r to assess interobserver variability for T1-weighted and T2-weighted lumen and vessel wall area measurements.

Results

High quality images were obtained in all 15 patients (Fig. 1), enabling accurate free hand measurements. Ultrasound images had no appreciable artifact. Seven of the 15 patients demonstrated minor artifacts (Fig. 2) presumed from slow flow. Artifacts were observed primarily in the T2-weighted images; one patient also had small artifacts in the T1-weighted images. In all patients there was sufficient contrast to identify an inner and outer boundary for the vessel

wall. No lesion suspicious of stenosis was identified on either the ultrasound or the MR images.

Interobserver agreement was excellent for all measurements; Pearson r was 0.89 and 0.99 for lumen area measurements from T1-weighted and T2-weighted images respectively, and 0.96 and 0.99 for outer vessel wall area measurements from T1-weighted and T2-weighted images, respectively.

The range of the vessel lumen areas was 10.6–30.9 mm² for US, 10.4–31.1 mm² for T1-weighted 3D IV-FSE, and 10.8–32 mm² for T2-weighted 3D IV-FSE. Evaluating the first hypothesis, there was no significant difference between the lumen area measured by sonography (mean = 17 mm²), T1-weighted images (mean = 17.3 mm²), and T2-weighted images (mean = 16.9 mm²) (Friedman, $P > 0.42$). Lumen areas were highly correlated among modalities: the intraclass correlation coefficient was $r = 0.97$ among the three data sets. The mean lumen area absolute percent difference was 5.7% comparing T1-weighted and ultrasound data, 5.1% comparing T2-weighted and ultrasound data, and 3.3% comparing T1- and T2-weighted measurements. As all comparisons were within 6%; the results suggest only small changes between the lumen area data sets.

The mean ($\pm$ SD) and range of the vessel wall areas were 14.9 ± 3.5 mm² and 9.7–21.3 mm² for the T1-weighted images, and 9.5 ± 2.8 mm² and

Fig. 1 **a, b** and **c** Peripheral vein bypass graft (**a**, left column) T1-weighted image, (**b**, middle column) T2-weighted image, (**c**, right column) cross sectional gray scale ultrasound image of the same slice in a 60 year old man, demonstrating the larger

wall area (outer wall minus inner wall) on T1-weighted images in comparison with T2-weighted images. The lower images in each column are identical to the upper images, except that the tracings are shown

Fig. 2 **a, b and c** Peripheral vein bypass graft (**a, left column**) T1-weighted image, (**b, middle column**) T2-weighted image, (**c, right column**) cross sectional gray scale ultrasound image of the same slice in a 58 year old man whose graft demonstrates outward expansion of the wall on the T1-weighted image

(arrow). Note that the T2-weighted image demonstrates slow flow artifact (arrowhead), but this does not obscure the visualization of the vessel wall. The lower images in each column are identical to the upper images, except that the tracings are shown

Fig. 3 Bland-Altman plot of the vessel wall areas measured by T1W MRI versus T2 MRI

6.7–18.2 mm² for the T2-weighted images. Evaluating the secondary hypothesis, unadjusted for any difference in lumen area, the vessel wall area measured from T1-weighted images was significantly different than that measured from the corresponding T2-weighted images (Wilcoxon signed rank, $P < 0.001$). The mean difference of the vessel wall area was 5.4 mm² (95% CI: 4.3–6.4 mm²), and the mean of the ratio of T1- versus T2-weighted vessel wall areas over all 15 subjects was 1.59 (95% CI: 1.48–1.69). This indicates that, for this patient group imaged over the first year after surgery, a significantly larger T1-weighted outer vessel wall boundary

accounted for wall area differences when compared to the T2-weighted images (Fig. 3).

Discussion

Further understanding of vein graft maturation and disease can potentially improve diagnoses at a time when effective repair can be performed safely. There is very little noninvasive high-resolution image data studying the complex changes in human vein graft morphology. Ultrasound is appropriate in symptomatic patients after intervention [40] because evaluation

of high grade lesions, based largely on velocity data, allows for prophylactic interventions to prolong secondary patency. However, routine sonography lacks the spatial resolution to demonstrate graft wall changes responsible for failure. Intravascular ultrasound (IVUS) has superior spatial resolution but is invasive and thus clinically limited.

After implantation, vein wall thickening has been attributed to increased wall tension [41]. As the wall thickens, it develops hyperplastic neointima that tends to normalize tangential wall stress [42]. With respect to pathophysiology, it has been postulated that excessive wall thickening, manifested primarily as intimal hyperplasia in contrast to medial hypertrophy, is a critical step in those grafts that succumb between 1 and 24 months [1, 43]. A single case has been reported with MR derived wall area changes between 1 and 6 months after implantation [35].

The high correlation between transcutaneous MR and ultrasound lumen area measurements argues that slow flow artifact does not compromise measurements performed with high interobserver agreement. Regarding T1- versus T2-weighted lumen area differences, the lumen is on average $0.4 \pm 0.9 \text{ mm}^2$ (95%CI: $0\text{--}0.9 \text{ mm}^2$) larger on T1-weighted images. This was not statistically significant, apparently contradicting earlier work [37] that studied a smaller population imaged at only 6 months after implantation. The earlier study found a statistically significant difference of $0.8 \pm 0.6 \text{ mm}^2$ (95% CI $0.7\text{--}0.9 \text{ mm}^2$). While actual differences are small, the current larger population with patients imaged at multiple time points likely accounts for the apparent discrepancy. Finally, lumen measurements for each of the three data sets differ by at most 6%; thus either contrast weighting can be used to determine lumen area. We generally use T1-weighted images to assess the lumen for clinical purposes.

Our current ultrasound and MR data correspond to the work of others using ex vivo IVUS to measure saphenous vein lumen area under physiologic pressures immediately after harvesting [44]. Our patients have long-standing grafts that may be outwardly remodeled, explaining why the wall areas are larger than those immediately after harvesting. This is further supported by peripheral graft ultrasound data suggesting that successful grafts undergo structural changes but maintain luminal caliber [45, 46]. Three-dimensional reconstruction of ultrasound images [47]

focused on lumen changes of peripheral vein graft revision (i.e., patch angioplasty) described negative remodeling of the lumen within the revision, with an average loss of 31% of the area over 35 weeks. However, translating this data to our patients is problematic since, after patching, the average post-operative lumen diameter was 7.5 mm. These grafts are considerably larger with more advanced disease than the unrevised vein grafts in this study.

Regarding graft vessel wall areas, these 15 patients (Figs. 1a, 2a) confirm earlier work [37] showing a bilayered appearance on T1-weighted images with a thinner, brighter inner ring and an outer ring of lower signal intensity; the latter accounts for the increased overall wall area on T1- versus T2-weighted images. Unique to this data (Fig. 3) is a trend of a larger difference (T1-weighted minus T2-weighted) in vessel wall areas as the overall wall area increases. Under the assumption that T1-weighted images include components of the adventitia not seen on T2-weighted images, this suggests that the adventitia plays a significant role in graft maturation. However, additional studies would be required for validation. While histology is required to assign in vivo graft signal intensities to wall components, ex vivo MR evaluation of specimens obtained 6 months after implantation has tentatively assigned the lower signal intensity outer ring visible on T1-weighted images to an expanded, predominantly fibrous adventitia [37]. The adventitia is characterized by not only fibrous tissue but also microvessels and, at least early after surgery, inflammatory cell infiltrates. Similarly, the inner high signal intensity ring, visible on both T1- and T2-weighted images, has been tentatively assigned to the media and matrix-rich neointima. Incorporating all data to date, the T1-weighted images most accurately assess the entire vessel wall area for future studies of full wall remodeling.

Unfortunately, histology is rarely obtained without graft failure. However, future work can use IVUS data for validation in patients who require a non-surgical graft intervention. High spatial resolution MR imaging of animal models [26] will allow serial imaging combined with histology data to further advance our understanding of graft disease.

High spatial resolution multi-contrast three-dimensional inner volume fast spin echo imaging may have a role in the assessment of bypass graft wall remodeling. While this will require sequential

Fig. 4 **a, b and c** Peripheral vein bypass graft with high grade stenosis imaged with 3D IV-FSE. Both T1-weighted (**a**, *left column*) and T2-weighted (**b**, *right column*) images demonstrate good flow suppression and image quality suitable for

quantitative analyses. The lumen (*asterisks*) measures 1.6 and 1.5 mm² on the T1-weighted and T2-weighted images, respectively

imaging over time [34], some patients have MR findings of outward remodeling, conjectured to be a flow-induced endothelial-dependent response to an acute increase in shear stress [39, 48]. The high spatial resolution data supports the growing body of literature that rapid lumen remodeling occurs early following surgery [45, 46], but to date the vast majority of reports are from IVUS studies of the heart, not lower extremity bypass graft imaging.

Noninvasive peripheral bypass graft imaging requires high spatial resolution and high tissue contrast. MR maintains superior tissue contrast for noninvasive graft wall studies. With respect to spatial resolution, computed tomography (CT) is not only well suited, but can also evaluate the entire craniocaudal extent of the graft [49]. Iodinated contrast can be used to determine lumen area. However, for CT the delineation of the outer vessel wall is problematic for grafts adjacent to or within muscle since the X-ray CT attenuations are similar. Moreover, bypass graft patients very often have chronic renal insufficiency, a relative contraindication to iodinated contrast media. Digital subtraction angiography has very high spatial resolution and low contrast volumes can be used to study the lumen. However, this method is invasive, uses iodinated contrast, and is not suitable for vessel wall area measurements. The superficial nature of vein grafts in the periphery makes them well-suited for MRI with a surface coil to enhance signal, and as described below, further development of MR methods are likely to improve craniocaudal coverage, the

current spatial resolution, or both, even with three-dimensional acquisitions.

Our main conclusion is that blood flow artifact for in vivo vein graft MRI over a limited FOV protocol with DIR blood suppression does not adversely compromise lumen measurements when compared with ultrasound. Future MR studies including patients with lesions (Fig. 4) will encounter greater blood flow velocities, presumably fewer artifacts, and are expected to have highly accurate lumen area measurements. The current MR protocol has no role in screening after bypass; the most significant limitation to more widespread clinical implementation is scan time to achieve sufficient craniocaudal coverage. The 1.5T protocol applied to these 15 patients could be used to study focal graft lesions localized by sonography. Regarding increased coverage, our results extend to DIR blood suppression for sequential volume acquisitions. At 3T, the 3.6 cm coverage could be extended fourfold given the reduced scan time assuming the same resolution and signal-to-noise ratio. Alternatively, other black-blood methods such as diffusion preparation could be used [6] to image the increased extent possible at 3T with a single three-dimensional acquisition. This would allow increased signal compared to sequential volume acquisitions. However, other black-blood methods would require validation of lumen area accuracy. Finally, expanded craniocaudal coverage, even to an entire lower extremity graft, could theoretically be achieved from continuous parallel imaging and pulse

sequence development improvements, such as longer FSE echo trains [26, 50].

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