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Multi-Modality Image Fusion to Guide Peripheral Artery Chronic Total Arterial Occlusion Recanalization in a Swine Carotid Artery Occlusion Model: *Unblinding the Interventionalist!*

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Abstract

Objectives—To demonstrate the feasibility of magnetic resonance imaging (MRI) to x-ray fluoroscopy (XRF) image fusion to guide peripheral artery chronic total occlusion (CTO) recanalization.

Background—Endovascular peripheral artery CTO revascularization is minimally invasive, but challenging, because the occlusion is poorly visualized under XRF. Devices may steer out of the artery which can lead to severe perforation. Merging pre-acquired MRI of the CTO to the live XRF display may permit upfront use of aggressive devices and improve procedural outcomes.

Methods—Swine carotid artery CTO's were created using a balloon injury model. Up to 8 weeks later, MRI of the carotid arteries was acquired and segmented to create 3D surface models, which were then registered onto live XRF. CTO recanalization was performed using incrementally aggressive CTO devices (Group A) or an upfront aggressive directed laser approach (Group B). Procedural success was defined as luminal or sub-intimal device position without severe perforation.

Results—In this swine model, MRI to XRF fusion guidance resulted in a procedural success of 57% in Group A and 100% in Group B, which compared favorably to 33% using XRF alone. Fluoroscopy time was significantly less for Group B (8.5 min ± 2.6 min) compared to Group A (48.7 min ± 23.9 min), p value<0.01. Contrast dose used was similar between Groups A and B.

Conclusions—MRI to XRF fusion guided peripheral artery CTO recanalization is feasible. Multi-modality image fusion may permit upfront use of aggressive CTO devices with improved procedural outcomes compared to XRF guided procedures.

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Introduction

Peripheral artery disease (PAD) is common, affecting twenty percent of adults over 55 years of age(1–5). Many patients will present with chronically occluded peripheral arteries, which can cause disabling claudication or critical limb ischemia. If exercise and medication therapy fail, surgical bypass or endarterectomy can provide symptom relief and limb salvage in eligible patients. However, peri-operative mortality, morbidity, and slow functional recovery are major limitations. Catheter-based, endovascular revascularization for chronic total occlusion (CTO) is more appealing; however, these procedures are technically challenging, and recanalization failure or perforation can occur.

Many operators who perform endovascular CTO revascularization procedures start with low to moderately aggressive guide wires and support catheters. If initial passage through the CTO is unsuccessful, more aggressive devices and re-entry methods may be employed. X-ray fluoroscopy (XRF) is typically used to guide these procedures, but the CTO segment does not highlight with x-ray contrast and therefore, abrupt bends in the artery may not be appreciated. Operators may unknowingly steer CTO catheters and guide wires through the artery wall, which can lead to life-threatening perforation. These procedures are often long in duration, suffer high ionizing x-ray radiation exposure, and require high doses of nephrotoxic iodinated contrast. Improved intra-procedural imaging may overcome these limitations.

Magnetic resonance imaging (MRI) has been shown to provide high resolution visualization of both patent and occluded artery segments(6,7). We previously demonstrated the feasibility of real-time MRI guided CTO recanalization; however, the lack of commercially available, MRI-compatible catheters and guidewires has prevented adoption of this technology into clinical practice(7). A hybrid approach, wherein high resolution MR images of the CTO and adjacent vasculature are registered and overlaid onto live XRF, could provide operators the imaging information they need to confidently steer commercially available CTO recanalization catheters and guide wires through the occlusion. Multi-modality image fusion guidance may improve CTO recanalization success, prevent perforation, reduce total procedure time, reduce x-ray contrast dose and reduce x-ray radiation dose. As an initial step, we hypothesize that a MRI to XRF fusion imaging system can be used to guide peripheral artery CTO recanalization in a swine model.

Methods

Peripheral Artery CTO Model

Experiments were approved by the local Institutional Animal Care and Use Committee. A previously described peripheral artery CTO model was employed(7). Briefly, percutaneous balloon injury of the left carotid artery (LCA) was performed in lipid-rich diet fed swine. Four to eight weeks later, animals returned for MRI to XRF image fusion guided CTO recanalization. We previously demonstrated that pig carotid arteries have tortuosity similar to normal adult iliac arteries(7). Furthermore, the model carotid CTO consists of firm collagen deposition, fibrosis, and mature thrombus. In this prior experience, XRF-alone guided CTO recanalization was successful in only 33% of swine requiring over 45 minutes of fluoroscopy time and over 200mL of x-ray contrast.

MRI

Pre-operative MRI was performed using a clinical 1.5 T scanner (Signa HDx, GE Healthcare, Milwaukee, WI) with an 8 channel surface coil. The MRI system was located remotely from the XRF laboratory. MRI of the carotid arteries extending from the aortic arch to intracranial branch vessels was obtained using high resolution axial 2D T1 weighted

fast-spin echo sequences. Typical parameters were TR/TE/Flip/BW = 3.7ms/1.4ms/25°/375 Hz/pixel; FOV/Slice Thickness= 30×24cm/2mm; Matrix/Slices = 256×240×128. MR angiography (MRA) was performed using a clinically used Time Resolved Imaging with Contrast Kinetics (TRICKS) sequence with 0.15 mmol/kg Gadolinium-BOPTA (Multihance, Bracco Diagnostics, Princeton, NJ). The MRA simply provided a quick vascular roadmap to help the technician set the field of view parameters for the high resolution 2D T1 weighted fast-spin echo images. Following the MRI exam, the animal was transferred to the XRF cath-lab on an MRI compatible gurney.

3D surface rendered models of the patent right carotid artery (RCA) and occluded LCA were created from manually drawn contours on the high resolution 2D T1 weighted fast-spin echo images. Surface models of both carotid arteries were formed by connecting adjacent contours to create a surface mesh that minimized surface area using previously described methods(8).

Image Registration and Overlay

Registration and overlay of the 3D carotid model onto live XRF was performed using a dedicated workstation developed by our group(8). Excellent MRI to XRF registration accuracy was previously demonstrated in a swine cardiac validation study(8). Briefly, the system uses custom software running on commercially available hardware placed on a mobile cart. Live XRF from the frontal and lateral gantries of a bi-plane fluoroscopy system (Allura Xper FD10/10, Philips Healthcare, The Netherlands) is acquired by the workstation using a dual input frame grabber. Gantry orientation, source to image distance (SID), and previously acquired calibration data are used to accurately project the 3D carotid surface model onto the bi-plane XRF images (Figure 1).

MRI to XRF image registration for CTO recanalization was performed by aligning key anatomic features: the proximal CTO stump, the distally reconstituted artery, the curvature of the patent contra-lateral artery and the distal arterial branches (Figure 2) using established visual matching methods(9,10). Digital subtraction angiography (DSA) of the innominate artery and carotid arteries was performed using 5mL of iodinated contrast through a 5F JR4 catheter to highlight the patent RCA and the stump of the contra-lateral occluded LCA. The registration of the carotid artery surface models was manually adjusted with rigid transformations to account for table position and animal orientation with respect to the XRF system.

The swine carotid artery CTO was long, and extended beyond the 10 inch field of view limits of the biplane XRF system. Therefore, a second DSA acquisition was performed with the table moved cranially to capture the distally reconstituted artery at the terminal extent of the CTO. Table position was tracked in the images using x-ray visible tape with well-defined markings (Glow 'N Tell Tape, LeMaitre Vascular, Burlington, MA). The tape was fixed to the table under the animal. Changes in the x-ray visible tape position, and hence table position, were similarly applied to the carotid artery surface model to maintain the image registration. Once upfront image registration of both proximal and distal field of view was established, the operator could seamlessly translate the table cranially or caudally during the intervention, and the MRI to XRF image registration would hold.

Multi-Modality Image-Guided CTO Recanalization

Animals were pretreated with aspirin 325 mg and intravenous heparin 100 U/kg bolus was given initially and supplemented with 50 U/kg every 1 hour. After trans-femoral sheath insertion, the innominate artery was engaged with an 8F JR4 Guide catheter and angiography was performed. Procedures were performed by two fully trained interventional

cardiologists with advanced endovascular experience. Animals were separated into Group A and Group B (Table I).

In **Group A**, CTO recanalization was attempted using incrementally aggressive CTO recanalization devices. Initially, commercially available CTO recanalization devices and device combinations were categorized into 5 tiers based on guide wire tip load, catheter and wire stiffness and generally perceived perforation risk. These mutually agreed upon tiers were established prior to swine experimentation and were based on device availability and the interventionists' clinical experience. Operators were instructed to spend 5 minutes per tier before advancing to the next tier. Any number of devices within a tier could be used within the allotted 5 minutes. Specific guidewire-support catheter combinations were chosen based on availability and preference of the operator. In the fourth tier, a classical "step-wise" guidewire-in-laser catheter approach was used. The laser catheter was chosen as an example of an aggressive CTO crossing device, as it can penetrate through most human tissue with relative ease. With the "step-wise" technique, a stiff CTO guidewire is steered 3–4 mm ahead of a 0.9 mm over-the-wire (OTW) Turbo Elite Laser (Spectranetics, Colorado Springs, CO), the laser catheter is advanced over the wire, and the process is repeated. Calibration settings were 45 Fluence, 25 Hz repetition rate, and recanalization settings were 60 Fluence, 45 Hz repetition rate. After the fourth tier, operators were free to select from any of the available devices without time limit. Devices were re-directed if they were observed to reach the carotid artery surface model border limits.

In **Group B**, operators were instructed to use a 0.9mm Turbo Elite Laser catheter telescoped in an angled Cross-Pilot support catheter (Spectranetics, Colorado Springs, CO) as a "directed" laser recanalization method (Figure 3). Unlike the "step-wise" approach, a leading guide wire is not used, until after the CTO has been successfully traversed. The laser catheter was chosen as an example of an aggressive CTO crossing device, as it can penetrate through most human tissue with relative ease.

Procedural success was defined by i) luminal or sub-intimal position of guidewire or catheter in the distal reconstituted artery in two XRF projections AND ii) absence of severe "storm cloud" perforation by angiography or necropsy. Small, contained perforations (<5mm) were considered acceptable.

Necropsy

Following the procedure, swine were sacrificed and the carotid arteries were visually examined for evidence of perforation.

Statistical Analysis

Group variables were reported as mean $\pm$ SD. Comparisons for statistical significance were performed using a 2-tailed Student t test for equal variances, p value <0.05 for statistical significance. (Excel 2010, Microsoft).

Results

Peripheral artery CTO models were attempted in 19 swine; however, 8 swine were excluded for the following reasons: 4 had no CTO at follow-up, 1 had a lethal carotid rupture when creating the balloon injury CTO model, 1 had no angiographic evidence of any reconstituted artery/branches distal to the occlusion, and 2 had lethal anesthesia/intubation related complications.

The remaining 11 swine were divided into two groups; Group A consisted of 7 swine, and Group B consisted of 4 swine. Overall mean weight was 79 kg $\pm$ 20 kg with no difference

significant between Group A and B (p value=0.1). Mean number of days from balloon injury model and recanalization attempt was not significantly different between Group A (47 days $\pm$ 38 days) and Group B (33 days $\pm$ 5 days), p value=0.5. Mean CTO length measured by MRA did not differ significantly between Group A and Group B (Group A: 146 mm $\pm$ 47 mm; Group B: 173 mm $\pm$ 15 mm; p value=0.3). Similarly, mean CTO diameter was measured 70 mm cranial to the carotid bifurcation point and was not significantly different between groups (Group A: 5.1 mm $\pm$ 0.7 mm, Group B: 5.1 mm $\pm$ 0.4 mm; p value=0.1). Pre-procedure, the time required to contour the 2D T1 weighted fast-spin echo MR images and created carotid artery surface models was less than 15 minutes. The time required to advance a diagnostic catheter, create a DSA roadmap, and register MRI to XRF was less than 10 minutes in all animals.

Procedural Success

For Group A, procedural success was achieved in 4 of 7 animals (57%) (Table II). CTO recanalization was successful in tier IV in $n=1$ pig, tier III in $n=2$ pigs, and tier I in $n=1$ pig. Re-entry into the true lumen was achieved in 2 pigs, and into a sub-intimal location beyond the occlusion in 2 pigs (Figure 3). The remaining 3 recanalization failures were due to arterial perforation and of these, $n=2$ reached tier III, and $n=1$ reached tier IV. Necropsy confirmed these findings. In all cases where perforation occurred, the CTO catheter/guide wire could be visualized exiting the CTO surface model boundaries.

For Group B, recanalization success was achieved in all 4 animals (100%) (Table II). Re-entry into the true lumen was achieved in 2 pigs, and into the sub-intimal location beyond the occlusion in 2 pigs. Necropsy confirmed no perforation in these swine.

Fluoroscopy Time and Contrast Dose

Total fluoroscopy time was less for Group B (8.5 min $\pm$ 2.6 min) compared to Group A (48.7 min $\pm$ 23.9 min), p value<0.01. Total contrast dose was similar for Group B (20 mL $\pm$ 7 mL) compared to Group A (24 mL $\pm$ 13 mL), p value=0.6.

When recanalization was considered successful, total fluoroscopy time was still less in Group B compared to Group A: [Group A ($n=4$): 41.5 min $\pm$ 26 min and Group B ($n=4$): 8.5 min $\pm$ 2.6 min, p value<0.05]. In this sub-group, total contrast dose remained similar between groups: (Group A ($n=4$): 23 mL $\pm$ 13 mL and Group B ($n=4$): 20 mL $\pm$ 7 mL, p value=0.7).

Discussion

Three key observations were made with this study. First, we demonstrated the feasibility of registering and overlaying an MRI roadmap to live XRF to assist with CTO recanalization using commercially available imaging systems and interventional devices in a relevant swine model. Second, we demonstrated improved recanalization success, reduced x-ray fluoroscopy time and reduced x-ray contrast volume by using MRI to XRF fusion guidance compared to a historical XRF-alone guided approach by the same operator and using similarly aggressive CTO devices(7). Finally, we demonstrated improved recanalization success and reduced x-ray fluoroscopy time by combining MRI to XRF fusion with an ultra-aggressive directed laser recanalization approach compared to an incrementally aggressive CTO device approach.

Percutaneous CTO recanalization can be challenging, time-consuming, and risky. The first step in these procedures is to safely traverse the occlusion with a guidewire. The next step is to re-enter into the true lumen. Although reports vary, procedural success is achieved in only 42–89% of highly selected cases, even when aggressive devices and methods are employed

(11–14). Imaging plays a critical role as devices are steered through the occlusion to re-enter the reconstituted artery. Our multi-modality image registration approach exploits anatomic landmarks visible on both MRI and XRF. Custom software tools and procedural adaptations, such as the use of the Glow ‘N Tell Tape, preserved image registration when the anatomy extended beyond the XRF field of view. This feature allowed the interventionalist to move the table to another field of view, yet maintain accurate image registration. In addition, our multi-modality imaging system is imaging vendor independent, and portable between different cath-labs(8). Therefore, this technology may be appealing to institutions that have cross-vendor imaging systems and multi-purpose interventional XRF laboratories with smaller cardiac detectors.

XRF is the clinical standard for endovascular CTO recanalization procedures; however, the course of the CTO segment is poorly visible to the interventionalist due to poor soft tissue contrast and poor penetrance of x-ray contrast. MRI provides excellent depiction of the CTO segment in this swine CTO model(7) and in humans(15,16). Additionally, the high resolution 2D T1 weighted fast spin-echo MR images that were used to generate the carotid artery surface models do not require gadolinium contrast, which is associated with nephrogenic systemic fibrosis in those with renal impairment. The contrast enhanced MRA performed in these experiments served only to assist the technician in setting up field of view parameters for the high resolution T1 weighted images. This step could be omitted entirely, or substituted for any clinically available and rapidly acquired, non-gadolinium contrast MRI pulse sequence such as for example, “Time of Flight” imaging(17). Computed tomography (CT) has been suggested to assist with CTO recanalization of primarily coronary arteries, due to the ability to visualize fibrotic/lipid plaque and calcium deposits which can help to outline the course of the CTO(18–20). However, CT requires high doses of radiation and x-ray contrast which can be problematic. Our multi-modality image fusion system is capable of registering and displaying CT generated coronary and peripheral artery CTO surface models onto XRF; however, it is our view that CT would be reserved for those patients who have a contra-indication to MRI.

Other approaches for image guided peripheral artery CTO recanalization have been described. Gutierrez et al. demonstrated successful MRI to XRF image fusion to guide human superficial femoral artery CTO recanalization using a sophisticated combined MRI-XRF interventional suite with an inter-modality transport table(16). This registration method requires imaging fiducial beads which are visible on both MRI and XRF to be affixed to the patients’ skin. However, securing skin fiducials is cumbersome and the fiducial beads are easily displaced, especially in elderly and obese patients with loose skin. Further, the pre-acquired MRI must be done immediately prior to the intervention to minimize fiducial bead displacement and patient motion. Therefore, this approach may only be feasible in expensive combined, single vendor, MRI-XRF interventional suites. In comparison, our registration method registers off of the anatomy of interest and adjacent anatomic landmarks selected by the operator. Our approach permits MRI to be performed several days prior to the interventional procedure, and therefore does not interfere with independent MRI and XRF workflow. We previously demonstrated the feasibility of real-time MRI guided CTO recanalization in swine; however, the lack of commercially available, MR-compatible catheters and CTO guide wires is the current barrier to human translation(7). Duplex echo has been used to guide iliac CTO recanalization; however, limited acoustic windows and device interference have prevented wide clinical adoption(21,22).

Multi-modality fusion imaging could permit routine “upfront” use of aggressive peripheral artery CTO recanalization devices and techniques, rather than the traditional incremental step-wise aggressiveness approach. We demonstrated the feasibility of image fusion guided “directed” laser recanalization of the CTO, without a leading guidewire. This technique has

been described for short occlusions, but perforation risk would be significant if using XRF-alone(23,24). The guidewire “J” loop sub-intimal separation and retrograde access techniques have gained popularity but re-entry and distal access into the true lumen remain challenging (11,25–27). A variety of needle tip re-entry devices have been described; however, success is hinged on careful imaging to enable orientation of the needle tip trajectory to re-enter the true artery lumen (28–30). Multimodality fusion image would help the operator direct the re-entry needle in the correct orientation. Devices that employ blunt dissection, high frequency ultrasound energy (31–34) and radiofrequency thermal energy (35) have significant penetration power to traverse through firm plaque; however, perforation risk is high without robust imaging. Multi-modality fusion imaging could potentially improve safety, success and efficiency of CTO interventions when combined with any of the above listed aggressive devices and techniques.

Limitations

With our approach, unanticipated patient movement could lead to mis-registration. Unlike humans, swine in our study were fully anesthetized and restrained. Periodic check of registration accuracy by performing occasional angiography of patent adjacent arteries, careful patient positioning to ensure comfort, and “reminder” restraints could minimize this risk. Re-entry into the true lumen of the distal reconstituted artery was not always achieved in the pig CTO model because of lack of available re-entry devices. However, sub-intimal location of the guidewire or support catheter was clearly visualized with the registered and overlaid CTO surface model. This enhanced imaging could potentially improve the success of re-entry devices; however, this still needs to be tested.

Conclusions

Multimodality image fusion guided peripheral artery CTO recanalization using a vendor-independent, feature-based registration approach is feasible in swine. This imaging technology may one day permit safer, more successful, more efficient procedures with routine up-front use of aggressive CTO recanalization devices.

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Abbreviations and Acronyms

cath-lab	catheterization laboratory
CTO	chronic total occlusion
LCA	left carotid artery
RCA	right carotid artery
MRI	magnetic resonance imaging
PAD	peripheral arterial disease
XRF	x-ray fluoroscopy

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Figure 1. Imaging Flowchart

Axial T1 weighted fast spin-echo MR images are acquired, contoured and segmented to create 3-dimensional carotid artery surface models. These models are then registered to biplane DSA images in the cath-lab using common anatomic features. The registration is displayed onto live XRF, allowing for multi-modality image fusion guided interventions. MR=magnetic resonance, DSA= digital subtraction angiography, XRF=X-ray fluoroscopy

Figure 2. Imaging and Model Registration

(A) Pre-procedure MRA indicates an occlusion in the LCA. (B) The patent RCA (red) and occluded LCA (blue) arteries are both visible in T1 weighted MR axial images, and contours are used to segment the carotid arteries. (C–D) Intra-procedural biplane DSA from orthogonal views (45° RAO / 45° LAO) reveals the patent RCA and proximal stump of the LCA. (E–F) 3-dimensional models of the carotid arteries are registered to the DSA by aligning the luminal edges of the RCA with its model. MRA=magnetic resonance angiography, LCA=left carotid artery, RCA=right carotid artery, RAO=right anterior oblique, LAO=left anterior oblique, DSA=digital subtraction angiography.

Figure 3. MRI to XRF image fusion guided chronic total occlusion recanalization

(A) Digital subtraction angiography shows the guide wire near the distal stump of the LCA.

(B) The overlay of the registered MRI model onto the XRF image indicates the guidewire

has assumed a sub-intimal course. (C) Necropsy was performed with the wire in place,

showing a similar trajectory around the vessel lumen (dashed line). MRI=magnetic

resonance imaging, LCA=left carotid artery, XRF=X-ray fluoroscopy

Table I

Devices used for CTO recanalization categorized by aggressiveness level and perforation risk.

		GUIDE WIRES	SUPPORT CATHETER
Group A	Tier I	Hi Torque Pilot 150: 2.7g [*] Hi Torque Cross-IT XT: 1.7g [*] Hi Torque Pilot 200: 4.1g [*] ASAHI Fielder: 3.7g [*] ASAHI MiracleBros 3: 3.9g [*] ASAHI Miracle Bros 4.5: 4.4g [*] PT Graphix: 4g ^{*****}	Transit ^{***} Progreat Microcatheter ^{**} Fine cross ^{**}
	Tier II	ASAHI Confianza 9: 8.6g [*] ASAHI Confianza Pro 9: 9.3g [*] ASAHI Miracle Bros 6: 8.8g [*] 0.035" Standard Angled Glidewire ^{**}	Angled or Straight Glide Catheter ^{**} Transit ^{***} Progreat Microcatheter ^{**} Fine cross ^{**}
	Tier III	ASAHI Confianza Pro 12: 12.4g [*] ASAHI Miracle Bros 12: 13.0g [*] Shinobi Plus: 3–4g ^{***} 0.035" Stiff shaft, Angled Glidewire ^{**} Back end of a guidewire	5F Angled or Straight Glide Catheter ^{**} ASAHI Tornus [*]
	Tier IV	Step by Step Laser: ASAHI Confianza Pro 12: 12.4g [*] ASAHI Miracle Bros 12: 13.0g [*]	Step by Step Laser: 0.9mm Turbo Elite Laser ^{****}
	Tier V	Any combination of above equipment	Any combination of above equipment
Group B		Directed 0.9mm Turbo Elite Laser ^{****}	Directed: Angled Cross-Pilot ^{****}

^{*} Abbott Vascular, Redwood City, CA

^{**} Terumo, Somerset, NJ

^{***} Cordis, J&J, Bridgewater, NJ

^{****} Spectranetics, Colorado Springs, CO

^{*****} Boston Scientific, Boston, MA

Table II**Results Summary**

	Group A	Group B
Recanalization Approach	Incrementally Tiered	Directed Laser
n	7	4
Recanalization Success	4 (57%)	4 (100%)
Contrast Dose (mL)	24 ± 13	20 ± 7
Fluoroscopy Time (min)	48.7 ± 23.9 [*]	8.5 ± 2.6 [*]
CTO Length (mm)	146 ± 47	173 ± 15
CTO Diameter (mm)	5.1 ± 0.7	5.1 ± 0.4

Values are presented as mean ± standard deviation.

^{*}
p<0.01