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Ultra High Field (7T) Magnetic Resonance Imaging of Intracranial Vessel Wall

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Graduate Program in Medical Biophysics

A thesis submitted in partial fulfillment of the requirements for the degree in Master of Science

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ULTRA HIGH FIELD (7T) MAGNETIC RESONANCE IMAGING OF INTRACRANIAL VESSEL WALL

(Thesis format: Monograph)

by

Pablo López Ojeda, MD

Graduate Program in Medical Biophysics

A thesis submitted in partial fulfillment of the requirements for the degree of Master of Science

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London, Ontario, Canada

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Abstract

Intracranial vessel wall imaging may be accomplished with high-field (7T) magnetic resonance (MRI). To determine its feasibility, a 7T MR protocol was defined using Polyvinyl-alcohol cryogel (PVA-C) phantom vessels and healthy subjects.

A 2D matrix construct of PVA-C vessel phantoms of different diameters and wall thicknesses was scanned. Three observers measured the phantom images, one of which three times. Physical measurements were performed using a digital caliper. Ten volunteers were scanned using three different MRI sequences (TSE-3D, FLAIR, MPRAGE). Imaging assessment was performed in different circle of Willis (COW) segments. Reliability and accuracy of the measurements was analyzed by inter and intraobserver correlation and by comparison to physical measurements.

Phantom measurements showed overall high inter and intraobserver reliability and accuracy (ICC≈0.9). However, precision diminished for smaller vessels (<3mm). TSE was superior on vessel wall definition compared with FLAIR on both, phantoms and volunteers. On healthy subjects, vessel wall was recognized consistently, but precise definition of distal COW segments was not achieved. Vessel wall was significantly overestimated (p<0.05) when comparing to intracranial vessel diameters from prior studies due to partial volume effects.

Vessel wall imaging is feasible with 7T MR. However, precision and definition decreases consistently with the vessel caliber. PVA adequately mimics 7T MR vessel wall imaging properties.

Keywords

Vessel wall imaging, High-Field (7T) MR, Polyvinyl-alcohol cryogel (PVA-C), intracranial vasculopathy.
Co-Authorship Statement

Conception and Design: Boulton

Acquisition and Imaging data postprocessing: Gati, Szekeres, Wang, Lopez-Ojeda.

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Chapter 1

1 Background

1.1 Introduction

Stroke is the third leading cause of death in Canada and affects around 50,000 people in Canada each year. Also known as cerebrovascular accident (CVA), it is the rapid loss of brain function due to disturbance in the blood supply to the brain. This can be due to either ischemia (lack of blood flow) caused by blockage of the vessel (thrombosis, arterial embolism) or hemorrhage as a result from rupture of a blood vessel or an abnormal vascular structure. It is intimately related to the health of the blood vessels in the brain, and therefore to the vessel wall pathology (i.e., intracranial atherosclerosis, vasculitis, and other vascular abnormalities). However, intracranial vessel wall imaging still remains one of the elusive frontiers of stroke and vasculopathy research, as contemporary clinical imaging is confined to luminal study. Vessel wall pathology must be inferred from either the morphology of the lumen, or the displacement of surrounding cerebrospinal fluid signal and brain parenchyma. Assessment of the lumen solely, it has been demonstrated to be insufficient, especially during the early stages of vasculopathy, when vessel remodeling and wall alterations can occur without compromising luminal size. Luminography-based methods therefore may underestimate the presence of intracranial arterial pathology. Intracranial atherosclerosis, dissection, vasculitis, and early aneurysm formation could yield similar appearances with either: catheter angiography; computed tomographic angiography (CTA); or standard magnetic resonance angiography (MRA). The inability to correctly diagnose these pathologies could lead to adverse treatment events or unnecessary surgical exploration. With conventional MRI techniques only pathological conditions, such as enhancement of the intracranial vessel wall with vasculitis and significant luminal narrowing with severe atherosclerosis can be detected. Studies have shown a high prevalence of atherosclerotic changes of intracranial arteries. However, the most important cause of ischemic cerebral infarcts is still thought to be embolic, and is not well known the role of intracranial vessel
wall atheroma (atherosclerosis) in their occurrence. An important reason for this lack of knowledge might be the absence of imaging methods to depict the intracranial vessel wall. Intracranial arterial aneurysm pathogenesis has been debated for many years and remains unclear. These lesions can suppose life threatening risks to patients, so understanding their cause and progression is important for choosing the adequate treatment. The general assumption is that the arterial blood flow generates an aneurysmal herniation of the vessel wall that can eventually rupture. Thin aneurysm wall thickness (AWT) is thought to carry an elevated risk of intracranial aneurysm rupture. Obtaining information about the AWT might help to predict the risk of rupture for these lesions, and therefore an adequate management avoiding unnecessary preventive treatments. Moreover, a better understanding of aneurysms might be obtained on evaluation of the morphological characteristics of the vessel wall and might help to distinguish among the diverse diseases that generate intracranial aneurysms. Distinguish between more conventional saccular aneurysms and intracranial dissecting aneurysm (IDA) that involve different natural histories and different wall pathological features (e.g., double lumen, intimal flap, and intramural hematoma on IDA) might be also of great importance for the clinical decision-making process. Overall, accurate visualization of vessel wall could help in the understanding of underlying pathological features and potentially guide treatment choices for intracranial vascular diseases.

1.2 Intracranial vessel wall imaging

Standard 1.5T magnetic resonance imaging (MRI) has been used to study extracranial carotid arteries and vessel wall morphology for atherosclerosis and dissection. Novel imaging protocols allow visualization of the vessel wall, plaque, and blood. When applied to the intracranial circulation, the resolution is not sufficient and the reliability of the images diminishes. The intracranial vessels are smaller and located deep in the brain, and need a higher resolution than used for carotid vessel wall imaging. Moreover, circle of Willis (COW) vessels do not have a single orientation, which prohibits the use of thick slices perpendicular to the vessel orientation, as is normally done in imaging of the
carotid artery wall. The extracranial carotid arteries measure 7-10 mm in diameter, and taper intracranially to range from 4-5mm in diameter proximally to 1-2mm more distally, throughout the Circle of Willis. Only 13 studies to date have attempted to visualize both healthy and diseased intracranial vessel walls, compared to over eighty publications per year on the extracranial carotid arteries. Small vessel size prevents accurate visualization at 1.5T. Eleven of the 13 studies utilize 3T MRI, and only 2 studies explored 7T MRI. Brain vessel wall MRI has been demonstrated, but again, in most of the cases, the spatial resolution utilized so far makes it difficult to assess contrast or structure inside the wall thickness. Although 3T MRI could provide imaging resolution to resolve some pathologies that produce a thickened vessel wall, 7T MRI has superior signal to noise, and contrast to noise characteristics compared to 3T, and thereby providing better spatial resolution and visualization of intracranial vessel walls.

1.3 Imaging at High Field (7T) MRI

Imaging at high magnetic field strengths has many advantages, such as increased signal-to-noise ratio (SNR) and spatial resolution. An increase in the field corresponds to an increase in SNR, that follows a linear relation with the value of the field. An increase in SNR results in a higher image quality, higher speed of image acquisition, and higher spatial resolution. Also, longer T1 and T2 relaxation times at higher fields result in higher blood/tissue contrast.

However, there are certain concerns regarding the effects of magnetic fields of such high strength on human tissue. At ultra high field, there is a rapid increase in the quantity of RF (radiofrequency) energy deposited; which is proportional to the square of the value of the main magnetic field. During an MR procedure, the patient absorbs a portion of the transmitted RF energy, which may result in tissue heating and other adverse effects, such as alterations in visual, auditory and neural functions. The Specific Absorption Rate (SAR), measured in Watts/kg, is the RF power absorbed per unit mass of tissue. Strict limits to the SAR levels are imposed by patient safety international regulations and SAR measurements must be monitored during a scan to ascertain that levels do not approach the limit.
1.4 Study hypothesis and objectives

Hypothesis:

We hypothesize that using an ultra high field (7T) magnetic resonance imaging a fine resolution, such that intracranial vessel wall at the level of the circle of Willis can be precisely define, could be accomplished.

Objectives:

1. Using an ex vivo phantom model of simulated intracranial vessels, define a 7T MR protocol to approximate the signal characteristics, determine its precision and accuracy and delimit an image resolution threshold.

2. Optimize the MR protocol on human volunteers, maximized for spatial resolution, with the aim of obtaining reliable intracranial vessel wall imaging, and defining in-vivo achievable cerebral vessel limits on MRI, in terms of image contrast and spatial resolution.
Chapter 2

2 Polyvinyl alcohol (PVA) phantoms

2.1 Introduction

2.1.1 Hypothesis and objectives
We hypothesize that polyvinyl alcohol cryogel (PVA-C) phantoms could simulate imaging characteristics of intracranial vessels at ultra high field (7 tesla) magnetic resonance imaging (MRI) with fine definition and good spatial resolution.

The objective is to develop a tissue-mimicking construct of the intracranial vessels using formulations of PVA-C that closely simulate the size, texture and imaging properties of vascular human tissue at 7T MR.

2.1.2 Phantoms
Phantoms are used in medical imaging research to replace real tissue in studies where in vivo models are inappropriate or as a first step to allow initial stages of the investigation without directly subjecting in vivo models. Phantoms can be modeled on anatomical features, like vessels and vascular trees, or mechanical structures that behave appropriately, such as a pulsating vessel wall. One benefit to modeling these features instead of using anatomical specimens is that the phantom can be made accurately, with a known structure that is used as ‘truth’. Other benefits to phantom use include their long-term structural stability, the ease of registering multiple phantom images to one another in subsequent studies, the ability to perform long imaging procedures without concern for subject motion or discomfort and also to test and develop new medical methods\textsuperscript{27}. Also, phantoms usually have a simpler structure than anatomical models. This allows for a simplification of the problem, by restricting the number of experimental variables. The structure can be focused to a specific problem, or the role of the phantom can be limited to a single process in question\textsuperscript{27}. 
2.1.3 PVA-C ideal vascular mimicking phantom material

Desired properties of a tissue-mimicking phantom material for imaging include: comparable relaxation times to those of human tissue, robustly processable, non-hazardous, stable for long periods of time, readily available, inexpensive, and easy to handle. Polyvinyl alcohol cryogel (PVA-C) is an ideal material fulfilling all of these characteristics.

Polyvinyl alcohol (PVA) is a widely used, non-toxic, industrial compound, often employed in papermaking, textiles, glue in food packaging or for a variety of coatings. It is white (colorless) and odorless and could be supplied as beads, powder or as solutions in water.

When using the appropriate PVA and water solution, this material can be easily formed into a gel possessing tissue-mimicking properties. This gel solution of PVA (PVA hydrogel) can be submitted to a cross-link process by the formation of crystallites during repeated freeze–thaw cycles to become polyvinyl alcohol cryogel. Effects of varying the concentration of PVA powder in the aqueous solution or the number and/or timing of the freeze/thaw cycles (FTC) used in its preparation can be easily exploited to tweak the properties of the resulting material to suit the desired application. PVA-C as a synthetic polymer with tissue-mimicking capability, has been used in constructs that simulate liver, brain, heart valves, stomach, bladder and prostate for research and teaching purposes. It has also demonstrated to be an ideal vascular phantom material due to its excellent properties such as signal intensity, relaxation times, elasticity, and strength.

PVA-C vascular phantoms have been previously used for imaging purposes in 1.5T and 3T MR, but there is no previous experience using high field 7T MR. Therefore this project represents the first attempt to experiment with PVA-C in high field strength MRI.
2.2 Methods

2.2.1 PVA preparation

2.2.1.1 PVA liquid solution preparation

Commercial PVA powder, Aldrich 341584 Poly(vinyl alcohol) powder \([\text{Mw} 180,000; 99+% \text{ hydrolyzed}]\) (Sigma-Aldrich Co. LLC. Saint Louis, MO, USA) was used to make our PVA liquid solutions. To make 10% PVA liquid solution, 40 g of PVA powder and 360 g of de-ionized water were mixed in a 1 litre flat bottom flask, along with a stir bar. A biocide was added (0.2% Germall Plus powder) to avoid biological contamination. The mixture was stirred to break any aggregates of powder. To fully dissolve the powder, the solution was brought to 85-90 °C for 2 hours using a Heating mantle (Resin reaction flask mantle. Glas-Col, LLC. Terre Haute, USA). During this process the mixture was continuously stirred with an automatic mixer blade (Fig 1). The resulting clear gel, PVA hydrogel (PVA-H), was transferred to a beaker container for its storage and was cooled to room temperature for at least 1 to 3 hours. This cooling stage was important to ensure the formation of a homogeneous gel. When the PVA-H was cool, the beaker was covered with a plastic wrap to prevent air drying the surface. The same process was repeated to make 15% PVA liquid, this time mixing 60 g of PVA powder and 340 g of de-ionized water.
2.2.1.2 PVA cryogel (PVA-C)

The PVA-H was allowed to rest for 12–24 h for air bubbles to rise to the surface (thin crust) and be removed. To form the PVA hydrogel solution into a solid phantom, the PVA gel was first poured into the appropriate moulds taking care to avoid forming bubbles. If the PVA-H seemed still to present an excessive amount of bubbles the beaker glass containing the gel was placed on a hotplate (Thermolyne® Cimarec® 2 –stirring hotplate. Sigma-Aldrich Co. St Louis, MI, USA) and slowly stirred until reach a temperature of around 50-60ºC. Around 1 hour after that, it was feasible to use the gel solution to fill the moulds.

The phantoms were kept well sealed (zip lock bag) in order to maintain some humid environment, so that they will not dry during the freeze-thaw cycle stage. Phantoms were placed in a Temperature Environmental Chamber (TestEquity 107 Benchtop Temperature Chamber). The desired number of cycles was chosen (Fig 2). Every cycle cooled the
phantoms from 20°C to -20°C at 0.1 degree C per minute, for a total freeze-thaw stage time of 15 hours for every cycle. Adequate temperature variations were recorded during the process and checked once the cycles were completed. This monitoring was performed with a temperature and humidity datalogger (Reed C-342/345. Center Thermo recorders) obtaining a numerical and graphic reading on a PC interface program (“Slim-Com” RS-232. Test link SE342 version 2.2.1.0) (Fig 2). The resulting PVA-C phantoms were carefully removed from the moulds and stored in clean, de-ionized water. With care, the phantoms can be kept almost indefinitely this way. In particular, replacing the water regularly, helps to extend the useful life of the phantoms.

Figure 2: Freeze-Thaw cycle process. a) Temperature Chamber selected for 2FTC. b) 2FTC graph (30h) showing the recorded temperature and humidity during each cycle.

2.2.2 Selecting PVA optimal formulation

In order to choose the optimal formulation of PVA for our vessel phantoms and characterize this material in terms of its imaging properties at 7T, we decided to construct cylindrical solid phantoms. Plastic tubing, with inner diameter of 27 mm, outer diameter of 28.5 mm and a length of 11.5 cm for a 50cc volume capacity, was used as mould for the phantoms. Three phantoms were created using 10% PVA solution and another set of
three using 15% PVA solution (Fig 3). Both PVA formulations were subjected to different freeze-thaw cycles, from 2 (30 hours) to 4 (60 hours) cycles. The resulting cylindrical phantoms were scanned at the 7T MR (T1 and T2 sequences) to obtain the different relaxation times (see table 1). A CPMG sequence was used for T2 and an inversion-recovery method for T1.

![Figure 3: Solid cylindrical phantoms. a) Plastic tubing mold + PVA-C phantoms. b) Solid cylindrical phantom sample (10% PVA, 3FTC)](image)

<table>
<thead>
<tr>
<th>T1 times</th>
<th>10% PVA</th>
<th>15% PVA</th>
<th>T2 Times</th>
<th>10% PVA</th>
<th>15% PVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 FTC</td>
<td>1542 ms</td>
<td>1633 ms</td>
<td>2 FTC</td>
<td>128ms</td>
<td>115ms</td>
</tr>
<tr>
<td>3 FTC</td>
<td>1627 ms</td>
<td>1388 ms</td>
<td>3 FTC</td>
<td>115ms</td>
<td>91ms</td>
</tr>
<tr>
<td>4 FTC</td>
<td>1527 ms</td>
<td>1290 ms</td>
<td>4 FTC</td>
<td>100ms</td>
<td>81ms</td>
</tr>
</tbody>
</table>

Table 1: T1 and T2 times at 7T MR as a function of FTC and PVA-C concentration (%).
As expected, based in other MRI studies (on 1.5 and 3T MR) using PVA, T1 and T2 values decreased with the number of freeze-thaw cycles\textsuperscript{27,32} (See Fig 4).

The measured relaxation T1 and T2 times were also found reasonable and biologically relevant to human brain tissue and to ex vivo intracranial vessels relaxation times at 7T MR obtained from previous experiments\textsuperscript{8,21}.

![Figure 4: MR relaxation coefficients, T1 and T2, for 10% PVA-C at 1.5T (from Surry et al\textsuperscript{27})](image)

To decide the ideal formulation for our purpose we took into account the T1,T2 relaxation times, the mechanical workability of the material and the effects of the freeze-thaw cycles on the wall thickness. It is known from other research studies that PVA-C vascular phantoms wall thickness decreases with freeze-thaw cycles. This results from PVA crystallites growing in size after each freeze-thaw cycle and hence, expelling free water from the gel. A shrinkage from around 2% after two cycles to approximately 25% after five cycles has been documented\textsuperscript{32}.

Considering an adequate range of T1 and T2 times, ideal mechanical and manageability properties, making it more convenient for its manipulation, and trying to minimize the
non measurable and non controllable shrinkage factor, it was decided 10% PVA-C subjected to 2FTC to be the optimal formulation for our study.

2.2.3 Intracranial vessel phantoms. 2D matrix construction

2.2.3.1 2D matrix construction

Several published papers have tried to measure the geometry of the circle of Willis (COW) and to elucidate the intracranial vessels diameter as well as their wall thickness. Most of them are post-mortem and histopathological studies\(^{36-40}\), although different techniques have been used including various imaging techniques\(^{37,41-44}\). In general, intracranial arteries have a lower wall:lumen ratio than extracranial arteries\(^{36}\). Some of these studies suggest a mean wall thickness of 0.6 ± 0.12 mm and 0.51 ± 0.08 mm in the basilar and middle cerebral arteries, respectively\(^{36,42,44-47}\). Considering the average outside diameter (OD) of this 2 vessels from those literature sources (middle cerebral artery: 2.8-3.5mm [2.59mm], basilar artery: 2.6-3.4mm [3.24mm]), it is estimated a wall thickness/OD ratio of around 15-20% in the intracranial vessels. The diameters of our phantoms were based on this averaged values obtained from the different sources found in the literature\(^{36-47}\).

We decided to create several vessel-like phantoms with decreasing diameter and wall thicknesses to obtain a 2D matrix model that could cover the whole spectrum of the intracranial vasculature. A total of 24 vessel phantoms of different calibers were built from 8mm as the largest outside diameter to 2mm as the smallest diameter. A total of three pig vessels (common femoral artery) (Fig 5) were also harvested and included in the model for tissue characterization and comparison with the phantoms.
To create the phantoms, clear acrylic and stainless steel (SS) multi-component vessel molds were constructed. The acrylic material was used as a cast for the SS tubing (Precision Miniature Stainless Steel Tubing. McMaster-Carr. Cleveland, OH, USA). Each vessel mold had an OD tube that fit on a preformed cavity on the side pieces of the acrylic cast, and an ID tube slide fitting into the OD tube. The acrylic cast consisted of 3 pieces with the central part containing the support for the OD tube. In the right end piece a threaded hole was made to suit a barbed plastic tube connector made to inject the PVA solution. The molds were designed to obtain a vessel length of approximately 5cm. With disassembly these molds allowed us to create the walled vessel phantoms and remove them fairly easily from the molds for their later use. (Figure 6)

Four different molds were created for each OD vessel. By varying the ID tube size we obtained four different wall thicknesses, 25%, 20%, 15% and 10% (OD/wall thickness ratio), that should represent the average diameter of the intracranial vessels wall.
Figure 6: Walled vessel phantom. a) PVA-C vessel showing the average length of 5cm. b) Vessel phantom mold partially disassembled.

PVA-H was carefully injected into each mold using a 5cc syringe (Fig 7a). The molds were again placed in sealing bags to avoid drying out during the freeze-thaw cycle stage, and submitted to 2 FTC in the Temperature Chamber. Adequate temperature variations were again recorded during the process and checked once the cycles were completed (Fig 7b). The resulting PVA-C phantoms were carefully removed from the moulds and stored in labelled containers in clean de-ionized water.
Figure 7: Making of vessel phantoms. a) Filling the mold with PVA-H b) Phantoms in the temperature chamber ready for the freeze-thaw cycle stage with the temperature recorder (arrow).

2.2.3.2 2D matrix assembling: Supporting fixtures. Agarose solution.

To complete the 2D matrix construction a customized supporting fixture for the phantoms was designed and built with a stereolithography (SLA) 3D printer (SLA-5000 3D Systems, Inc. Rock Hill, SC, USA). The model consisted of a total of 27 cylindrical rods of acrylic-like material. These rods had coincident diameter with the inner diameter of the vessel phantoms and served as the vessel lumen contrast on the phantoms imaging. Three extra rods were added to fit the pig vessels. The phantoms were positioned, such that ‘axial’ slices, as defined by the head coil orientation, could show a circular cross-section of each vessel and cylinder in the image. (Fig 8)
Figure 8: 2D matrix model. a,b) 2D matrix model design for its SLA 3D printing. c,d) 2D matrix customized supporting fixture. Two vessel phantoms were placed in their respective rods as an example (see arrows).

The vessel phantoms and the pig vessels were placed on their respective rods on the supporting fixture. In order to obtain image contrast it was decided to embed the phantoms with a surrounding material that could mimic the brain tissue and give us good differentiation between tissue classes. Although many different types of brain phantom materials have been proposed, agar and agarose are the most commonly used\textsuperscript{48-51}. T2 relaxation time of both agarose and agar gel have demonstrated to be similar to that of human and brain tissue (40–150 ms human tissue equivalent on 3T MR and 45-55ms brain tissue equivalent on 7T MR)\textsuperscript{26,48}, with the possibility of being adjusted by altering the consistency of the gel (i.e. the concentration of agarose or agar)\textsuperscript{48,52}. Previous experience\textsuperscript{26} using agarose as brain tissue mimicking material used a concentration of 2%. Therefore, we opted to prepare a 2% agarose gel solution as our imaging contrast
tissue. The required quantity of agarose gel powder (A6013 Sigma-Aldrich Agarose Type I, Low EEO) was weighed accurately using an electronic balance (MS1062-S Precision Balance. Mettler-Toledo Canada Inc. Mississauga, ON, Canada) and the powder was dissolved in distilled water. The solution was mixed well with a stirrer and heated to a temperature of 85-90 °C using a hotplate (Thermolyne® Cimarec® 2 –stirring hotplate. Sigma-Aldrich) until the mixture became viscous, but trying to avoid many bubbles. The agarose solution was then poured into the mold embedding the vessels and allowed to cool down to room temperature.

With this last step the 2D matrix model construction was finished and the phantom was ready to be scanned. (Fig 9)

Figure 9: Different pictures of the 2D matrix construction after its completion (a and d without the outside part of the mounting fixture). The phantom has all its components (PVA-C walled vessels and acrylic-like mounting fixture, embedded in the agarose gel) and is ready for scan.
2.2.4 7T MR phantom imaging

MRI scanning was carried out on a 7-Tesla Agilent/Siemens human neuro MRI System (Siemens Healthcare, Erlangen, Germany) using a 31-channel receive coil and 10-channel head-only transmit coil for transmission (Figure 10).

Three different sequences were used: Turbo spin-echo (TSE) 3D (SPACE)-725um isotropic (Iso) sequence, fluid attenuated inversion recovery (FLAIR) 3D-800um Iso sequence and magnetization-prepared rapid gradient echo (MPRAGE)-750um Iso sequence. The acquisition parameters for the TSE 3D sequence were TR = 3750ms and TE = 435ms, with a bandwidth of 463Hz. Scan orientation was axial and sagittal for this sequence and the scan duration 7 minutes and 52 seconds. The parameters for the FLAIR sequence were TR = 6000ms and TE = 269ms, with a bandwidth of 625Hz and Inversion Recovery pulse. Scan orientation was sagittal for this sequence and the scan duration 9 minutes and 54 seconds. The MPRAGE parameters were TR = 7.78ms, TE = 2.57ms, a bandwidth of 260Hz, inversion recovery pulse and Sagittal scan orientation, for a total acquisition time of 6 minutes and 3 seconds. The MR sequences and parameters are outlined in Table 6.

These sequences applied to the phantoms were the same sequences used later on the healthy subjects.
2.2.5 Imaging postprocessing and measurements

The obtained imaging was stored in nifti file format. Imaging post processing was performed with OsiriX image viewer (version 4.1.2 32-bit).

With the aim of defining the spatial resolution of the system (i.e, the ability to discriminate between two adjacent image values or objects) and therefore calculate the size of the smallest vessel phantom that can be resolved with detail, and, to calculate objectively the accuracy and reliability of the obtained imaging we decided to measure the phantoms in both TSE 3D and FLAIR sequences. Since the MPRAGE was deemed to be an adjunctive angiographic sequence for the final protocol with subjects, the sequence was obtained to assess its feasibility but measurements were not performed.

The saved images were loaded in the OsiriX viewer for its initial analysis and preparation for the measurements. This digital tool displays a 3-panel window containing sagittal, axial, and coronal reconstruction views (3D MPR reconstruction) of the nifti data in addition to the corresponding model. In order to blind the measurements, every vessel was individualized and randomized. This way, the potential bias from measuring the phantom vessels directly from the whole 2D matrix model was avoided. The
individualization of the vessels was performed by selecting every vessel as the region of interest (ROI), propagating the selected ROI in the desired image range and nulling the pixels outside the ROI. With the vessel individualized and propagated, a single frame was selected for the measurements, exported as a DICOM (digital imaging and communications in medicine) format and stored. (Fig 11)

Figure 11: 7T MR imaging of the 2D matrix phantom. a) FLAIR sequence b) TSE 3D sequence. On the bottom more detailed view of one of the rows in each sequence.

Since by definition the reliability or precision of a measurement, also called reproducibility or repeatability, is the degree of stability exhibited when a measurement is repeated under identical conditions\textsuperscript{53-55}, we chose 3 different observers to make the measurements. A previous training session was performed until each examiner felt comfortable with the use of electronic measurement tools on the OsiriX image viewer. A package with the image files, an Excel working sheet (Microsoft\textsuperscript{®} Excel\textsuperscript{®} version 12.0) and a scheme of the required measurements was provided (Fig 12). One of the observers performed the measurements 3 times on 3 different dates (intraobserver) while the other two only once (interobserver).
Figure 12: Scheme of how measurements were performed (OD, ID and vessel wall diameters). This model was provided to every observer. a) Measurements done on acquired phantom image. b) Graphic representation of the measurements.

The accuracy of a measurement is defined as the estimate measuring of the true value\(^5^4\) - \(^5^6\). In our case, the degree of closeness of measurements of the obtained images to the actual (true) value. To define our dimensional truth, physical measurements of the phantoms were performed using a high-precision digital caliper (Pro-point. Metal Fractional digital caliper ) that measured up to 0.1mm (accuracy +/-0.3mm, Repeatability +/-0.01mm, range 0-150mm). Detailed measurements were achieved with the aid of a surgical microscope (OPMI PENTERO\textregistered 900 surgical microscope. Carl Zeiss Meditec) (Figure 13). The measurements of the phantom were performed using a replication of the 2D matrix phantom that was scanned. That allowed an easier and more precise measurement by enabling the sectioning of the PVA vessels to obtain cross-sectional measurements. This sectioning was performed with a pathology trimming knife (4786-Trimming Knife. Tissue-Tek\textregistered Accu-Edge. Sakura Finetec USA, Inc. Torrance, CA,}
USA). Measurements were performed twice and the mean of the 2 measurements was designated as the reference standard or dimensional truth.

![Image](image.png)

**Figure 13:** a) Digital caliper (range 0-150mm). b) Microscope screenshot showing cross-sectional view of one of the PVA phantoms mounted on its respective rod.

### 2.2.6 Statistical Analysis

All statistical analysis and data processing were performed with a standard statistical software Package, SPSS statistical program version 15.0 for Windows (SPSS, Inc, Chicago, Illinois).

Means, standard deviations and 99% confidence levels were calculated for all the measurements, including direct caliper measurements and imaging measurements by the observers. As a measure of reliability, the intraclass correlation coefficient (ICC) for absolute agreement based on a 2-way random effects analysis of variance (ANOVA) was
calculated. ICCs of the repeated imaging measurements tested the reliability of the measurements. Interobserver reliability of the measurements was determined by comparison of the measurements of the 3 observers. Intraobserver reliability of the measurements was determined by comparison of the repeated measurements of observer 1. Because the direct caliper measurements were regarded as the reference; the accuracy of the system was determined by comparison of the observers measurements to the direct caliper measurements. ICCs of these 2 different measuring methods were obtained. A table of confidence intervals (CI 99%) was created. Cronbach’s Alpha was calculated as a measure of internal consistency.

In order to determine the image resolution threshold, multiple comparisons between the measurements according to the caliber and according to the diameter of the vessel wall were calculated using the Wilcoxon Signed Ranks Test for paired variables. Results were adjusted for multiple comparisons using the Bonferroni adjustment procedure.

2.3 Results

MR images of the vessel phantoms revealed high contrast between the high signal of the PVA-C phantoms and the low signal of the acrylic-like rod inner lumen and the medium-intensity agarose background. Better definition and contrast imaging of the vessel phantoms was obtained with TSE imaging comparing with the FLAIR sequence. Quantification of vessel dimensions (OD, ID and wall thickness) was feasible in all 27 vessels (24 phantoms + 3 pig vessels) for both sequences.

PVA-C mimicked the imaging characteristics of the vascular tissue remarkably well at 7T MR, both in TSE and FLAIR sequences, when compared with the imaging of the pig vessels included in the model (Fig 14)
2.3.1 Accuracy and reliability: Validation of the system

2.3.1.1 Reliability

Measurements made by the observers over the phantom imaging were overall very reliable. Outside diameter and inner diameter measurements showed the highest agreement in both series (ICC: 0,987-0,998). High reliability was maintained for the wall diameter measurements in TSE sequences (ICC: 0,858-0,950). However, in FLAIR sequences the reliability of the measurements decreased significantly (ICC: 0,675-0,819), showing more variability of vessel wall diameter measurements. Interobserver and intraobserver reliability showed minor differences, with TSE sequence measurements being more reliable on average. The interobserver reliability for the vessel wall thickness in TSE was high with a mean ICC of 0,923 (0,832-0,955; 95% CI). Intraobserver repeated measurements were also very precise in TSE sequence with a mean ICC of 0,892 (0,764-0,955; 95% CI). For the FLAIR Imaging the interobserver correlation for wall diameter measurements was less consistent with a mean ICC of 0,742 (0,421-0,883; 95% CI). Intraobserver measurements also showed increased variability with an average ICC of 0,767 (0,485-0,894; 95% CI). High internal consistency of the measures was demonstrated with a Cronbach’s alpha of 0,874. Reliability is reported in a detailed intraclass correlation coefficients (ICC) table (see table 2).
Table 2: Intraclass correlation coefficients (ICC); interobserver and intraobserver reliability (average measures of OD, ID and Wt (lower bond-upper bond) 95% CI) for TSE and FLAIR sequences.

<table>
<thead>
<tr>
<th>TSE</th>
<th>Observer 1 (1)</th>
<th>Observer 1 (2)</th>
<th>Observer 1 (3)</th>
<th>Observer 2</th>
<th>Observer 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>OD</td>
<td>0.997 (0.994-0.999)</td>
<td>0.996 (0.991-0.998)</td>
<td>0.997 (0.994-0.999)</td>
<td>0.998 (0.995-0.999)</td>
<td>0.996 (0.990-0.998)</td>
</tr>
<tr>
<td>ID</td>
<td>0.994 (0.986-0.997)</td>
<td>0.993 (0.985-0.997)</td>
<td>0.998 (0.996-0.999)</td>
<td>0.997 (0.994-0.999)</td>
<td>0.993 (0.984-0.997)</td>
</tr>
<tr>
<td>Wt</td>
<td>0.837 (0.642-0.925)</td>
<td>0.827 (0.619-0.921)</td>
<td>0.925 (0.835-0.966)</td>
<td>0.921 (0.826-0.963)</td>
<td>0.885 (0.748-0.947)</td>
</tr>
<tr>
<td>FLAIR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OD</td>
<td>0.990 (0.978-0.995)</td>
<td>0.992 (0.984-0.997)</td>
<td>0.989 (0.977-0.995)</td>
<td>0.987 (0.972-0.994)</td>
<td>0.987 (0.971-0.994)</td>
</tr>
<tr>
<td>ID</td>
<td>0.994 (0.986-0.997)</td>
<td>0.996 (0.942-0.998)</td>
<td>0.991 (0.981-0.996)</td>
<td>0.989 (0.976-0.995)</td>
<td>0.993 (0.985-0.997)</td>
</tr>
<tr>
<td>Wt</td>
<td>0.675 (0.287-0.852)</td>
<td>0.807 (0.572-0.913)</td>
<td>0.819 (0.597-0.918)</td>
<td>0.732 (0.410-0.878)</td>
<td>0.727 (0.369-0.876)</td>
</tr>
</tbody>
</table>

2.3.1.2 Accuracy

There was close agreement between MR derived measurements and phantom dimensions overall. The highest agreement was shown by outside diameter and inner diameter measurements in both TSE and FLAIR sequence (ICC: 0.983-0.997). Consistently with the reliability results, high closeness between the dimensional “truth” and the MR measurements was observed for the vessel wall measurements in TSE sequence with a mean ICC of 0.869 (0.698-0.944; 95% CI). FLAIR measurements showed a remarkable decrease in agreement values for vessel wall measurements with a mean ICC of 0.630 (0.156-0.842), showing significant variability. Accuracy is reported in detail in an intraclass correlation coefficients (ICC) table (see table 3).
A graphical illustration of mean measurements (MR derived measurements + phantom dimensions) expressed as a table of confidence intervals (99% CI) is shown in Fig 15. Table 4 shows mean of measurements expressed as absolute means and standard deviations (SD).

<table>
<thead>
<tr>
<th></th>
<th><strong>Observer 1</strong> (1)</th>
<th><strong>Observer 1</strong> (2)</th>
<th><strong>Observer 1</strong> (3)</th>
<th><strong>Observer 2</strong></th>
<th><strong>Observer 3</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TSE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OD</td>
<td>0.986 (0.967-0.994)</td>
<td>0.982 (0.958-0.992)</td>
<td>0.984 (0.962-0.993)</td>
<td>0.983 (0.960-0.992)</td>
<td>0.978 (0.950-0.991)</td>
</tr>
<tr>
<td>ID</td>
<td>0.998 (0.996-0.999)</td>
<td>0.997 (0.992-0.998)</td>
<td>0.998 (0.994-0.999)</td>
<td>0.998 (0.994-0.999)</td>
<td>0.995 (0.987-0.998)</td>
</tr>
<tr>
<td>Wt</td>
<td>0.894 (0.755-0.954)</td>
<td>0.865 (0.689-0.942)</td>
<td>0.817 (0.577-0.921)</td>
<td>0.878 (0.719-0.947)</td>
<td>0.892 (0.749-0.953)</td>
</tr>
<tr>
<td><strong>FLAIR</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OD</td>
<td>0.978 (0.948-0.990)</td>
<td>0.971 (0.933-0.987)</td>
<td>0.964 (0.958-0.985)</td>
<td>0.965 (0.918-0.985)</td>
<td>0.968 (0.927-0.986)</td>
</tr>
<tr>
<td>ID</td>
<td>0.996 (0.991-0.998)</td>
<td>0.996 (0.986-0.997)</td>
<td>0.995 (0.988-0.998)</td>
<td>0.987 (0.971-0.995)</td>
<td>0.990 (0.977-0.996)</td>
</tr>
<tr>
<td>Wt</td>
<td>0.714 (0.339-0.876)</td>
<td>0.501 (0.154-0.784)</td>
<td>0.622 (0.127-0.837)</td>
<td>0.666 (0.228-0.856)</td>
<td>0.672 (0.242-0.858)</td>
</tr>
</tbody>
</table>

**Table 3:** Intraclass correlation coefficients (ICC); agreement of MR derived measurements (TSE and FLAIR sequences) compared to reference values (phantom dimensions).
Figure 15: Graphical illustration of mean measurements (MR derived + phantom dimensions) for OD, ID and Wt in both sequences (TSE and FLAIR) expressed as a table of confidence intervals (99% CI).
Table 4: Mean of measurements (MR derived measurements and phantom dimensions) expressed as absolute means and standard deviations (SD).

<table>
<thead>
<tr>
<th>TSE</th>
<th>Dimensional truth (digital caliper)</th>
<th>Observer 1 (1)</th>
<th>Observer 1 (2)</th>
<th>Observer 1 (3)</th>
<th>Observer 2</th>
<th>Observer 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>OD</td>
<td>4.44 +/- 2.00 mm</td>
<td>5.13 +/- 1.69 mm</td>
<td>5.18 +/- 1.67 mm</td>
<td>5.13 +/- 1.67 mm</td>
<td>5.04 +/- 1.65 mm</td>
<td>5.30 +/- 1.66 mm</td>
</tr>
<tr>
<td>ID</td>
<td>3.00 +/- 1.47 mm</td>
<td>2.71 +/- 1.47 mm</td>
<td>3.08 +/- 1.44 mm</td>
<td>3.22 +/- 1.45 mm</td>
<td>2.85 +/- 1.45 mm</td>
<td>2.87 +/- 1.44 mm</td>
</tr>
<tr>
<td>Wt</td>
<td>0.72 +/- 0.44 mm</td>
<td>1.08 +/- 0.34 mm</td>
<td>1.05 +/- 0.25 mm</td>
<td>0.97 +/- 0.25 mm</td>
<td>1.03 +/- 0.27 mm</td>
<td>1.13 +/- 0.33 mm</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>FLAIR</th>
<th>Dimensional truth (digital caliper)</th>
<th>Observer 1 (1)</th>
<th>Observer 1 (2)</th>
<th>Observer 1 (3)</th>
<th>Observer 2</th>
<th>Observer 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>OD</td>
<td>4.53 +/- 2.05 mm</td>
<td>5.54 +/- 1.74 mm</td>
<td>5.76 +/- 1.64 mm</td>
<td>5.66 +/- 1.71 mm</td>
<td>5.60 +/- 1.60 mm</td>
<td>5.46 +/- 1.67 mm</td>
</tr>
<tr>
<td>ID</td>
<td>3.02 +/- 1.51 mm</td>
<td>3.19 +/- 1.41 mm</td>
<td>3.62 +/- 1.42 mm</td>
<td>3.47 +/- 1.47 mm</td>
<td>2.73 +/- 1.32 mm</td>
<td>3.31 +/- 1.39 mm</td>
</tr>
<tr>
<td>Wt</td>
<td>0.75 +/- 0.41 mm</td>
<td>1.07 +/- 0.23 mm</td>
<td>1.08 +/- 0.16 mm</td>
<td>1.06 +/- 0.17 mm</td>
<td>1.37 +/- 0.22 mm</td>
<td>1.06 +/- 0.23 mm</td>
</tr>
</tbody>
</table>

2.3.2 Correlation by caliber and wall thickness.

Evaluation of OD and ID measurements showed no significant differences related to decreasing vessel caliber. Both, TSE and FLAIR sequences, showed ICC results maintained constantly over 0.9 (0.985-0.999) with high internal consistency measured by Cronbach’s alpha >0.9 (0.960-0.977).

In regards to vessel wall, when assessing the level of correlation of measurements in relation to the caliber of the phantoms, despite that the small size of the study sample did
not provide sufficient statistical power, also due to the high variability of vessel diameters, a tendency to obtain more accurate and reliable measurements in larger vessels (8-4mm) was observed with both sequences. Accuracy and reliability decreased generally in vessels of a size equal to or less than 3 mm. Internal consistency (Cronbach’s alpha) also diminished in this vessel caliber range. An illustrative graphic representation of this tendency is shown as a table of confidence intervals (99% CI). (see Fig 16)

Specifically for intraobserver precision, FLAIR measurements showed high variability and the pattern noted respect association with vessel caliber was less evident. The ICCs tend to be poorer, around 0.7 on average with a Cronbach’s alpha of 0,72 to 0,88. TSE ICC analysis demonstrated less variability and superior results in general. Trend to ICC decrease in the 3mm-2mm caliber group was more evident in this sequence with mean ICC of 0,940 (0,936-0,944) for the larger vessels and a mean ICC of 0,760 for the smaller ones. Interobserver assessment revealed similar results, and again some consistent tendency to reduction in the precision for the 3mm/2mm vessel size group. The obtained results are summarized in a table of ICCs values (table 5).

Analysis by groups of wall thickness (25%, 20%, 15%, 10%), associated or not to vessel caliber, showed no significant differences related to decreasing wall thickness, independently of the sequence. Standard errors (SE) appeared to be more prominent for vessels equal to or smaller than 4mm and with a wall thickness equal to or less than 20%. However, no evidence of a consistent pattern was demonstrated with some variability of SE independently of the wall thickness group.

The results were adjusted for multiple comparisons (Bonferroni adjustment test), with a total of 38 comparisons per each sequence (TSE and FLAIR), and this led us to have to accept as significant , p values equal to or less than 0.05/38=0.0013. Hence, the lack of sufficient statistical power.

Nevertheless, these results showed a trend to decrease on precision and accuracy in vessels with caliber equal or smaller than 3mm, independently of the wall thickness.
Table 5: Intraclass correlation coefficients (ICC); average agreement by vessel caliber (TSE and FLAIR)

<table>
<thead>
<tr>
<th></th>
<th>TSE</th>
<th>Intraobserver</th>
<th>Interobserver</th>
</tr>
</thead>
<tbody>
<tr>
<td>8mm/6mm</td>
<td>0.944</td>
<td>0.948</td>
<td></td>
</tr>
<tr>
<td>5mm/4mm</td>
<td>0.936</td>
<td>0.907</td>
<td></td>
</tr>
<tr>
<td>3mm/2mm</td>
<td>0.760</td>
<td>0.846</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>FLAIR</th>
<th>Intraobserver</th>
<th>Interobserver</th>
</tr>
</thead>
<tbody>
<tr>
<td>8mm/6mm</td>
<td>0.797</td>
<td>0.743</td>
<td></td>
</tr>
<tr>
<td>5mm/4mm</td>
<td>0.807</td>
<td>0.791</td>
<td></td>
</tr>
<tr>
<td>3mm/2mm</td>
<td>0.670</td>
<td>0.572</td>
<td></td>
</tr>
</tbody>
</table>
Figure 16: Graphical illustration of mean measurements by caliber groups (8mm/6mm, 5mm/4mm, 3mm/2mm) expressed as a table of confidence intervals (99% CI).
Chapter 3

3 Healthy volunteers

3.1 Introduction

3.1.1 Hypothesis and objectives

We hypothesize that using an ultra high field (7T) magnetic resonance Imaging (MRI) a fine definition of intracranial vessels wall could be accomplished.

The objective is to determine its feasibility by using and refining the 7T MRI protocol previously defined with the PVA-C vessel phantoms.

3.1.2 Importance of (scanning) Healthy subjects

Healthy volunteers have always played a vital role in medical research. They provide researchers with crucial data because their health information can be used as a base line for comparison. In some studies, researchers need to compare healthy volunteers with people who have a specific disease or condition, while when developing a new technique such as a blood test or imaging method or device, clinical research volunteers are needed to help define the limits of "normal." Research with healthy volunteers is primarily designed to develop new knowledge, and rarely provides direct benefit to study participants.

In our study, participants were subjected to an initial 7T MR protocol that was set up with the use of PVA-C phantoms as previously described. The information obtained imaging the volunteers should help to demonstrate the capabilities of 7T MRI to obtain detailed images of the intracranial vessels and serve as a starting point for future studies, based on the definition of the limits of normality, as well as for future comparisons with patients with intracranial vascular disease, and to improve imaging quality, definition and accuracy.
3.2 Methods

3.2.1 Subjects characteristics and demographics

10 healthy subjects (4 male, 6 female) in a determined group of age (26-34 years, Mean: 29.8, Median: 28) underwent a head 7T MRI applying the previously developed protocol. Patients were placed in supine position. The scanning session lasted approximately 50-60 minutes. The total length of each visit lasted less than 1.5 hours including consent, filling forms and screening. No incidental findings were noted when these volunteer subjects were scanned. All clinical subjects were healthy, ambulatory with no compromised functions.

Volunteers were recruited by means of advertisements distributed in the LHSC University Hospital and Western University campus. On the basis of their responses to questionnaires administered at screening before MR imaging about medical condition and history (see appendix 2), volunteers showed no evidence of medical abnormalities or contraindications for the MR scan. Prior to testing, the nature and purpose of the study, and the details of the test, including possible risks or discomforts, were explained to each volunteer, and informed consent was obtained.

3.2.2 Imaging of the healthy volunteers

MRI scanning was carried out on the same 7T MR suite used to scan the phantoms (7T Agilant/Siemens human neuro system). The same three sequences used for the phantoms were replicated for the subjects: TSE 3D (SPACE)-725um Iso, FLAIR 3D-800um Iso and MPRAGE-750um Iso. The acquisition was in the sagittal plane with 64mm in the readout direction (S/I) for all the sequences. The acquisition parameters for the TSE 3D were TR = 3750ms and TE = 435ms, with a bandwidth of 463Hz. Scan duration was 7 minutes and 52 seconds. The parameters for the FLAIR sequence were TR = 6000ms and TE = 269ms, with a bandwidth of 625Hz and Inversion Recovery pulse. Scan duration was 9 minutes and 54 seconds. The MPRAGE parameters were TR = 7.78ms, TE = 2.57ms, a bandwidth of 260Hz and inversion recovery pulse, for a total acquisition time of 6 minutes and 3 seconds. The MR sequences and parameters are outlined in
Any and all of the 7T MR acquisitions performed during the study did not exceed the FDA safety levels for static magnetic field, SAR (Specific Absorption Rate), dB/dT, sound pressure level or peripheral nerve stimulation as outlined in Westerns MRI guideline 2-G-004.

### 3.2.3 Image offline postprocessing and assessment

The obtained imaging was stored in nifti file format. Offline post processing and visual assessment was performed with OsiriX™ image viewer (version 4.1.2 32-bit) and an offline workstation.

The 3-dimensional (3D) reconstruction was used for final visualization to identify the vessel walls of the major arteries of the circle of Willis (COW) and its branches. This 3D format with isotropic resolution allowed multiple reformatting depending on local vessel orientation. It was sought to reorient perpendicular to the vessel under study, with the aim of better delineate the vessel wall boundaries (outboundaries), although it was not possible consistently, specially for distal vessels.

Both FLAIR and TSE scans acquired were registered to the MPRAGE at 750um Iso (isotropic) to help with data postprocessing options in order to improve the contrast of the imaging. A matlab registration script was applied for this purpose using the “PuTTY” system as a terminal emulator. MPRAGE data was also used to identify the observed vessels on the TSE and FLAIR images.

Measurements of vessel caliber (OD), lumen size (ID) and vessel wall diameter of the distal internal cerebral artery, basilar artery, M1 segment of the middle cerebral artery and P1 segment of the posterior cerebral artery were performed in all subjects. Means and standard deviations were calculated for all the measurements (table 7).
<table>
<thead>
<tr>
<th>Parameters</th>
<th>TSE_3D (SPACE) -- 725um Iso</th>
<th>FLAIR_3D -- 800um Iso</th>
<th>MPRAGE -- 750um Iso</th>
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<td>Sagittal</td>
<td>Sagittal</td>
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<td>TR</td>
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<td>269,19</td>
<td>2.57ms (actual TE)</td>
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<td>Bandwidth</td>
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<td>Variable (target--45degrees)</td>
<td>10 degrees</td>
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<tr>
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<td>10ChTx / 31ChRx</td>
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</tbody>
</table>

Table 6: 7T MR acquisition parameters. (*RO=Readout, *PE=Phase Encode, *PE2=2nd Phase Encode, Tx = Transmit, Rx = Receive)
3.3 Results

3.3.1 TSE 3D

In TSE imaging, vessel wall of the distal internal cerebral artery, basilar artery, M1 segment of the middle cerebral artery, A1 segment of the anterior cerebral artery, and P1 segment of the posterior cerebral artery could be visualized and measured along their complete trajectories in all subjects (Fig 17,18). Also, in most volunteers the vessel wall of the proximal and smaller A2, M2, and P2 segments of the anterior cerebral artery, middle cerebral artery, and posterior cerebral artery, respectively, could be identified although with worse, irregular and non consistent definition along their course. It was significantly difficult to distinguish the vessel wall of these smaller branches, particularly when it was immediately adjacent to brain parenchyma. The quality of the vessel wall depiction decreased consistently with the vessel caliber. The best contour definition and wall depiction was observed in the ICA and Basilar branches where cross-sectional views were always accomplished and wall boundaries were less affected by brain tissue.

Measurements of wall thickness ratio (OD/Wt) seemed to correlate with vessel wall thickness from prior studies\textsuperscript{36-47} (postmortem measurements), showing a range between 14% to 28% (estimated intracranial vessel wall thickness from postmortem studies ≈15-20% OD/Wt ratio). However absolute measurements appeared to be oversized in comparison with data from those studies. A comparison of means (t-student test, 95% CI, p<0.05) was performed between MR derived measurements of healthy subjects (n=10) and the average measurements of the literature sources (n≈100) and significant differences were identified in line with the suspected oversizing (see Table 7). Oversized measurement affected more significantly those vessels surrounded by brain parenchyma.
Figure 17: Detailed vessel wall view of anterior circulation arteries. a) ICA terminus (ICA_T) b) ICA (cavernous segment). c) M1 (white arrow) and ICA_T (red arrow). d,e) MCA (M1).

Figure 18: Detailed vessel wall view of posterior circulation. a) Basilar artery. b) PCA. c) Basilar artery cross-sectional measurement. d) Basilar artery sagittal view.
3.3.2 FLAIR

In FLAIR imaging, vessel wall of distal internal cerebral artery and basilar artery could be visualized in all the subjects (Fig 19). However, vessel wall could not be visualized along their complete trajectories and distal branches (MCA, ACA and PCA). Measurements in these 2 intracranial segments gave the impression again to be overdimensioned in comparison with prior data from postmortem studies. Overall, it was a poor sequence to depict vessel wall beyond the proximal segments of the COW.

Figure 19: FLAIR. Detailed cross-sectional view of the distal ICA.
<table>
<thead>
<tr>
<th>Vessel</th>
<th>MR derived measures</th>
<th>Average literature sources</th>
<th>p</th>
<th>MR derived measures</th>
<th>Average literature sources</th>
<th>p</th>
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<tbody>
<tr>
<td></td>
<td>OD</td>
<td>OD</td>
<td></td>
<td>Wt</td>
<td>Wt</td>
<td></td>
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<tr>
<td>ICA</td>
<td>5.26 (±0.47)</td>
<td>4.20 (±0.90)</td>
<td>&lt;0.001</td>
<td>1.16 (±0.20)</td>
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<td>--</td>
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<tr>
<td>(Cavernous segment)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICA</td>
<td>4.26 (±0.51)</td>
<td>4.20 (±0.90)</td>
<td>0.863</td>
<td>1.02 (±0.15)</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>(terminus)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MCA</td>
<td>3.70 (±0.51)</td>
<td>2.96 (±0.47)</td>
<td>&lt;0.001</td>
<td>0.89 (±0.17)</td>
<td>0.51 (±0.08)</td>
<td>&lt;0.001</td>
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<tr>
<td>(proximal M1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Basilar</td>
<td>4.25 (±0.69)</td>
<td>3.08 (±0.42)</td>
<td>&lt;0.001</td>
<td>0.87 (±0.16)</td>
<td>0.60 (±0.12)</td>
<td>&lt;0.001</td>
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<tr>
<td>PCA</td>
<td>3.20 (±0.25)</td>
<td>2.10 (±0.70)</td>
<td>&lt;0.001</td>
<td>0.99 (±0.10)</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>(P1 segment)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 7: COW arteries diameters. Mean comparison between average MR measurements and average diameters described in the literature (expressed as mean +/- standard deviation, p<0.05). (OD: outside diameter, Wt: wall thickness, ICA: internal carotid artery, MCA: middle cerebral artery, PCA: posterior cerebral artery)

3.3.3 MPRAGE

The MPRAGE imaging was used as an adjunctive imaging tool to help improving the contrast of the imaging by realigning and co-registering to the other sequences, and also to better depict the corresponding vessels on the TSE and FLAIR images.

MPRAGE imaging showed high resolution with excellent vessel-to-tissue contrast
allowing us to delineate the vessels far distally into the periphery and even discriminate small vessels like brain perforators (Fig 20).

Figure 20: MPRAGE sequence. a) Axial view (COW). b) Axial view (Distal MCA branches). c) Coronal view (COW). d) Sagittal view (multiple intracranial vessels).
Chapter 4

4 Discussion

4.1 PVA-C phantoms: spatial resolution of the system. 
Aiming for an image resolution threshold.

A measurement system is considered valid if it is both accurate and precise (reliable). Measurements recorded from the phantom showed overall high inter and intraobserver reliability and accuracy. However, accuracy and precision were affected by the imaging sequence, with TSE measurements being, in general, more accurate and precise.

The reliability and accuracy were calculated and expressed as intraclass correlation coefficients (ICCs). In most research situations a reliability coefficient of 0,70 or higher is considered "acceptable", and some subjective guidelines suggest that an ICC from 0,81 to 1 is desired and indicates an “almost perfect” agreement.

On average, in terms of reliability for vessel wall measurements, while TSE showed high agreement with a mean ICC ≥0,9, FLAIR demonstrated fairly high variability with mean ICC slightly >0,70. For accuracy, TSE showed again high closeness values (ICC: 0,869) while FLAIR showed a correlation coefficient below the “acceptable” limits (i.e. <0,7).

This discrepancy in FLAIR sequences is consistent with the imaging contrast superiority of TSE for wall depiction demonstrated in the in-vivo imaging with healthy subjects.

The results obtained, specially for TSE, demonstrate that the imaging protocol assessed with the PVA-C phantom construct was overall a valid model for intracranial vessel wall assessment under ideal and controlled conditions, such as vessel and wall size, orientation and lack of motion artifacts.

Analysis of precision and accuracy as a function of vessel caliber and wall thickness was performed with the aim to define an image resolution threshold for intracranial vessels in the ideal conditions provided by the phantom. The obtained results, most likely due to a
lack of enough statistical power, did not allow us to draw a clear image resolution line with resounding significance. However, a trend for decreasing on accuracy and reliability was shown in vessels equal or smaller than 3mm. Interestingly, this was independent of the wall thickness expressed as a percentage (OD/Wt ratio %). Analysis by wall thickness showed no significant evidence of its impact in precision and accuracy. These findings suggest that the absolute vessel caliber, especially below certain size, is determinant in terms of accuracy and precision of the imaging. Therefore, is expected that precision below certain resolution threshold, that we estimate around 3mm, will be affected independently of the wall thickness, at least for the ratio range (25%-10%) explored in this study. It is unknown if wall thickness >25%, that could probably be expected for certain cerebrovascular pathologies, could impact positively and eventually improve the wall depiction precision.

In the light of these results, and obviating other potential sources of imaging bias that could be expected in real conditions with subjects, it should be anticipated to find some difficulties for a fine, precise and accurate visualization of intracranial vessel wall of smaller vessels, particularly with diameters below 3mm, like anterior cerebral arteries, distal middle cerebral artery branches and, in general, distal vessels of the circle of Willis.

4.2 Problems with subjects imaging: are we really seeing vessel wall?

In this study we evaluated a 3-dimensional (2 sequences) 7T MRI protocol for intracranial vessel wall imaging of normal non-diseased intracranial arteries. A total of 10 healthy subjects with not known cerebrovascular disease were scanned and vessel wall of the major intracranial arteries was consistently visible in all of them. However, the quality of vessel wall boundaries discrimination diminished correspondingly with decreasing in vessel caliber, and precise definition of distal COW segments was not satisfactorily achieved. It was particularly challenging to distinguish the vessel wall of these smaller branches, especially when surrounded by brain parenchymal tissue. Quantification analysis of major intracranial vessels was accomplished. The results of the
measurements, interestingly, showed calibers and vessel wall diameters significantly (p<0.05) overdimensioned in comparison with pre-existing intracranial vessel measurements from previous studies\textsuperscript{36-47}, thus questioning the capability of accurate intracranial vessel boundaries definition.

Several factors could affect vessel wall imaging and explain the difficulties to obtain clear wall boundaries definition, especially in distal intracranial vessels. Although in general, most of the subjects tolerated the acquisition time without problem, the acquisition times were relatively long (7.5 to 9.5 minutes) and imaging could be limited by motion artifacts. These artifacts are more common during long image acquisitions, and can be caused by breathing motion, cardiac and brain pulsation, CSF flow at the subarachnoid spaces and involuntary head movements\textsuperscript{58}. Small motions, even below 1 mm, can result in obvious degradation of image quality and decrease the image resolution for finer details such as vessel wall\textsuperscript{59}. There may also well be partial volume effects particularly in vessels immediately adjacent to brain parenchyma, which may increase the difficulty in obtaining reliable MRI measurements, leaning towards overestimation of the vessel wall limits. All the healthy volunteers in our study were young (mean <30 years, range 26-34). Previous studies by van der Kolk\textsuperscript{5,20} showed that the vessel wall was more clearly visible in older healthy volunteers (and in diseased vessels). These findings could be a consequence of normal aging of the vessel or asymptomatic vessel wall pathology, and infer absence of significant atrophy in young subjects, making vessel wall depiction more difficult.

Efforts were also made to reduce the potential imaging contrast lost related to lack of sufficient contrast between vessel wall and surrounding CSF. The FLAIR sequence was performed with the aim of nulling CSF signal expecting to obtain significant contrast between vessel wall and adjacent CSF and/or explore the possibility of fuse or combine the data with the TSE in postprocessing and therefore completely remove the CSF in the TSE sequence. However none of the applied scripts resulted in significant improvements in contrast imaging, and FLAIR sequence showed no capability to image vessel wall beyond the ICA and basilar segments. This could also be related to the limited coverage of the FLAIR sequence (centered in the major COW arteries) in order to avoid longer
acquisition times, prolonging the time volunteers had to remain completely still. Overall, TSE demonstrated to be superior on vessel wall imaging contrast compared with FLAIR.

Although high field 7T MR represents a significant improvement in spatial resolution our results suggest there is still lack of certainty of accurate visualization of vessel wall, and, even though different sequence optimization and efforts have been made in ours and previous studies\(^5,20,21\) there is still the potential for vessel overestimation due to partial volume effects as mentioned before. Some studies demonstrated the tendency for wall thickness overestimation due to partial volume errors using MRI\(^{59-62}\). This suspected bias has been investigated and qualitatively described in carotid arteries and intracranial aneurysm at 3T MRI\(^{59-61}\). The accuracy limits of thickness determination in 3T MR images was investigated by Sato et al.\(^62\) and their results showed the measured thickness was overestimated by around 10\%. Our wall measurements go in line with these publications, and, albeit increased SNR should diminished this effect in light of a higher spatial resolution, the potential for vessel wall oversizing should be taken into account for future protocol optimizations and vessel wall studies in patients with cerebrovascular disease.

### 4.3 MPRAGE: 7T non-enhanced MR angiography

In our study MPRAGE was revealed, almost as an incidental finding, as a high-resolution non-enhanced magnetic resonance angiography (MRA).

It has been shown that MPRAGE sequence provides high signal intensity of blood vessels on contrast-enhanced images at 1.5T and 3T MR. However, it has no sufficient arterial vasculature signal when contrast agent is not administered. Therefore, other sequences have been used in order to obtain a non-enhanced MR angiography, being the time of flight (TOF) MRA the most commonly used. TOF MRA at 1.5T and 3T has evolved overtime to become a fairly reliable noninvasive angiographic technique, which is regularly used for detection and follow-up of some intracranial vascular pathologies like aneurysms.
When imaging at 7T, it has been observed that the MPRAGE sequence provides high signal in the arterial vasculature while the background shows intermediate signal, resulting in high vessel-to-background contrast potential\textsuperscript{23,63-65}. That resolution enables the intracranial vessels to be traced and delineated far into the periphery\textsuperscript{23}. Such intracranial vessel resolution on MPRAGE sequence, without contrast agent administration, is only possible with ultrahigh field strength MR\textsuperscript{23,66}. Moreover, when comparing the non-enhanced MPRAGE sequence at 7T with the potential benefit of adding contrast to it, studies revealed only minor or non-significant improvement\textsuperscript{66,67}.

A recent study\textsuperscript{66} also demonstrated the superiority of 7T MPRAGE over 7T (and 1.5T) TOF MRA in terms of image quality, vessel delineation and capability for simultaneous high quality assessment of related anatomical parenchymatous structures.

The MPRAGE imaging obtained in this study, goes in line with previous investigations, showing remarkably high resolution and excellent vessel-to-tissue contrast, which allowed us to identify the primary vessels of the COW and follow them distally along their course into the brain parenchyma. The resolution was such that it was feasible to even discriminate small vessel structures like perforating arteries. Due to the nature and primary objectives of the study, no comparison with other non-enhancing angiographic techniques neither with the gold standard angiography, digital subtraction angiography (DSA), was performed. Nevertheless, we believe that our imaging results and previous publications\textsuperscript{63-68} underline the high diagnostic and potential clinical application of 7T MPRAGE non-enhanced angiography for evaluation, management, screening and follow-up of several intracranial vasculopathies.

4.4 Limitations of the study

4.4.1 PVA-C phantom model

This study has several limitations. First, the model used to define our dimensional truth was a replica of the 2D matrix phantom that was scanned but not the original phantom itself. While the supporting fixture for the vessel phantoms, made in acrylic-like material, is less likely to significantly change in a replication, due to the nature of PVA-C and the
different factors involved in its process, it is impossible to completely ensure non
substantial changes in one or several vessel phantoms. Second, in the original model,
phantoms were surrounded by agarose gel, which could discretely affect the vessel
phantom boundaries for its measurement, while the replicated model was not embedded
in agarose. Third, for the ease and precision of the measurements the phantoms were
sectioned in order to obtain cross-sectional measurements. The very act of sectioning the
PVA phantoms may lead to tissue or wall deformations that result in underestimation of
the measurement. Fourth, although the physical measurements of the phantoms were
performed using a high-precision digital caliper with the adjunctive help of a surgical
microscope for better visualization, considering the elastic properties of the PVA-C and
the remarkably small caliber of some of the vessels, the same act of measuring could
represent some wall deformation which could lead to underestimate the measurements.
Fifth, another potential source of error and/or bias could be related to the fact that we
used the mean average of the measurements for the ease of the statistical analysis. This is
subjected to the assumption that the wall thickness is uniform in each vessel. Sixth, the
individualization of the vessels for their measurements could also represent some bias,
given the fact that FLAIR imaging was acquired exclusively in sagittal, whereas the TSE
was acquired also in axial, making the process of individualization, propagation and
frame selection more tedious, difficult and probably less precise. As a result this could
discretely impact in the final quality of each vessel imaging for the FLAIR sequence.

4.4.2 Healthy Subjects

In terms of subject imaging the current study has some limitations as well. Intracranial
vessels show tortuous course and don’t have a single orientation. Consequently, thick
slices perpendicular to the vessel orientation were not possible. During postprocessing
assessment (3D reconstruction) it was attempted to reorient perpendicular to the vessel
under study to better define the vessel wall limits but it was not feasible for each vessel,
affecting predominantly distal branches. Thus, some vessel obliqueness could lead to
measurement errors. It was difficult to distinguish the vessel wall boundaries in vessels
immediately adjacent to brain parenchyma and there may well be partial volume effects,
particularly for smaller branches embedded into brain parenchymal tissue, which may increase the difficulty of obtaining reliable MRI measurements and leading to their overestimation. Along with the beneficial increase in SNR, 7T also provides an increased artifact-to-noise-ratio (ANR). We used relatively long acquisition times, and imaging could be limited by motion artifacts. Imaging could also be affected by susceptibility artifacts. The presence of these artifacts, even if minor, could decrease the image resolution for finer details like vessel wall depiction. No specific cerebrospinal fluid suppression (CSF) method was used in TSE sequence during acquisition to improve contrast between cerebrospinal fluid and vessel wall, and therefore minimize possible misinterpretation of cerebrospinal fluid signal around a vessel for signal from the vessel wall. Postprocessing imaging was performed to fuse or combine the 2 sequences (TSE and FLAIR) and obtain improvement in contrast image and null the CSF signal but the results were non significantly better and/or unsatisfactory. Measurements of vessel diameters in healthy subjects were made by a single observer. Due to the high anatomic course variability and the required reorientation in most of the vessels to improve wall boundary definition for its measurement, the imaging postprocessing preparation it was deemed too complicated and observer dependent, and therefore subjected to bias. Consequently, no assessment of reliability for these measurements was made. There was no dimensional “truth” or standard reference for these measurements, although average data of previous postmortem studies was used as a reference for comparison.

4.5 Strengths of the study

There are four major strengths to this study. First, rather than proceeding with the assumption that 1.5 and 3T protocols would directly import to 7T, a protocol was defined as an initial stage, using an ex vivo phantom model that allowed us to infer an image resolution threshold for intracranial vessels in ideal and controllable conditions. Second, this study represents the first experience with PVA-C as a mimicking tissue material in 7T MR and we demonstrated its ability to mimic vascular tissue imaging properties at high field MRI. Third, this study is the first attempt to quantify intracranial vessel wall diameters and compare it to the existing literature data while questioning the capability of
depict exclusively vessel wall at 7T MR. Previous existent publications described their findings qualitatively, but none of the previous existent publications attempted quantification of the vessel diameters. Moreover, the design of the study evaluated vessel wall exclusively in healthy subjects (mean age <30) with the aim to obtain a base line assessment from non-diseased or aged vessels. Fourth, although it was not the goal of the study, MPRAGE imaging demonstrated high resolution and showed its potential for an immediate clinical use as a non-enhanced MR angiography.

4.6 Future directions

Our results showed that vessel wall imaging is feasible. However, continuous research in order to better delineate the vessel wall boundaries and to visualize smaller and distal intracranial vessels is needed. Increasing knowledge and experience with brain imaging at 7T, improvement in coil designs and system upgrades will result in wider and better applicability. Immediate clinical usability of these technique it has not been demonstrated in this study, moreover, current regulations and safety rules regarding subject MRI at ultra high field strength are very strict when concerning metallic implants, like stents or surgical clips, which are not uncommonly present in patients with cerebrovascular disease. These patient contraindications imply a limited number of patients who could undergo imaging at 7T MR currently.

Nevertheless, future directions include application of these vessel wall imaging techniques to evaluate vessel wall in patients with intracranial vascular disease, particularly patients affected by intracranial atherosclerosis and patients with vascular malformations like aneurysms. Identify aneurysm wall thickness (AWT) could lead to estimate the risk of intracranial aneurysm rupture and provide a relevant information for its clinical management.

In future, vessel wall imaging at 7T will help to resolve the current limited imaging diagnosis of intracranial vessel wall abnormalities and vasculopathies.
Chapter 5

5 Conclusion

This study demonstrated the feasibility of vessel wall imaging at 7T MR using a TSE 3D (SPACE) sequence. However, precision and definition decreased correspondingly with the vessel caliber and surrounding brain tissue presence. Vessel wall tended to be overestimated most likely due to partial volume effects.

We also showed that PVA-C is a good vascular phantom material for ultra high-field MR studies that adequately mimicked intracranial vessel wall imaging properties. A trend to decrease in precision and accuracy for smaller vessels (<3mm) was also seen from the phantom.

MPRAGE sequence used to facilitate the tracing of the intracranial vessels revealed high resolution and its immediate future as a non-enhanced angiographic technique is expected.

These results are promising, and further investigation in patients with cerebrovascular disease is warranted.
References


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42. Gabrielsen TO, Greitz T. Normal size of the internal carotid middle cerebral and anterior cerebral arteries. *Acta Radiol.: Diagn.* 1970; 10, 1–10


54. Accuracy (trueness and precision) of measurement methods and reultts - Part 1: General principles and definitions. 1994. pp.1


Appendices

Appendix 1. Ethics Approval.

Use of Human Participants - Ethics Approval Notice

Principal Investigator: Mel Boulton
File Number: 10238
Review Level: Full Board
Approved Local Adult Participants: 10
Approved Local Minor Participants: 0
Protocol Title: Ultra High Field (7T) Magnetic Resonance Imaging of Intracranial Vessels
Department & Institution: Schulich School of Medicine and Dentistry/Clinical Neurological Sciences, Western University
Sponsor:
Ethics Approval Date: December 11, 2012
Ethics Expiry Date: September 30, 2013

Documents Reviewed & Approved & Documents Received for Information:

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<th>Document Name</th>
<th>Comments</th>
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<td>Letter of Information &amp; Consent</td>
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<td>Western University Protocol</td>
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This is to notify you that the University of Western Ontario Health Sciences Research Ethics Board (HSREB) which is organized and operates according to the Tri-Council Policy Statement: Ethical Conduct of Research Involving Humans and the Health Canada/IH Good Clinical Practice Practices: Consolidated Guidelines; and the applicable laws and regulations of Ontario has reviewed and granted approval to the above referenced study on the approval date noted above. The membership of this HSREB also complies with the membership requirements for REB’s as defined in Division 5 of the Food and Drug Regulations.

The ethics approval for this study shall remain valid until the expiry date noted above assuming timely and acceptable responses to the HSREB’s periodic requests for surveillance and monitoring information. If you require an updated approval notice prior to that time you must request it using the University of Western Ontario Updated Approval Request form.

Member of the HSREB that are named as investigators in research studies, or declare a conflict of interest, do not participate in discussions related to, nor vote on, such studies when they are presented to the HSREB.

The Chair of the HSREB is Dr. Joseph Gilbert. The HSREB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000940.

Ethics Officer to Contact for Further Information

Janice Sutherland
(sutherl@uwo.ca)
Grace Kelly
(grace.kelly@uwo.ca)
Shanele Walscott
(swalscott@uwo.ca)

This is an official document. Please retain the original in your files.
Appendix 2. MRI screening form

7T MRI ENVIRONMENT AND SCREENING QUESTIONNAIRE

Volunteer Number: __________ Date of Birth: ____________ Sex: [ ] M [ ] F

Do you have or have you ever had any of the following?

[ ] Yes [ ] No Cardiac Pacemaker.
[ ] Yes [ ] No Heart Surgery/Heart Valve
[ ] Yes [ ] No Implanted Cardiac Defibrillator (ICD)
[ ] Yes [ ] No Brain Aneurysm Clips/Brain Surgery
[ ] Yes [ ] No Shunts/Stents/Filters/Intravascular Coil
[ ] Yes [ ] No Eye Surgery/Implants/Spring/Wires/Retinal Tack
[ ] Yes [ ] No Injury to the Eye Involving Metal or Metal Shavings
[ ] Yes [ ] No Orthopedic Pins/Screws/Rods/Joints/Prostheses
[ ] Yes [ ] No Neurostimulator/Biostimulator
[ ] Yes [ ] No History of Cancer or Tumors: When: __________ Where: __________
[ ] Yes [ ] No Radiation Therapy/Chemo Therapy
[ ] Yes [ ] No Previous Back Surgery (Lumbar/Thoracic/Cervical): When: __________
[ ] Yes [ ] No Ear Surgery/Cochlear Implants/Hearing Aids/Stapes Prosthesis
[ ] Yes [ ] No Vascular Access Port/Catheter
[ ] Yes [ ] No Metal Mesh Implants/Wire Sutures/Wire Staples or Clips/Internal Electrodes
[ ] Yes [ ] No Electrical/Mechanical/Magnetic Implants: Type: __________
[ ] Yes [ ] No Implantable Drug Infusion Pump/Insulin Pump
[ ] Yes [ ] No Are you Pregnant?
[ ] Yes [ ] No Tattoo’s/Permanent Make-up/Body Piercing/Patches
[ ] Yes [ ] No Dentures/Partials/Dental Implants
[ ] Yes [ ] No Gunshot Wounds/Shrapnel/BB
[ ] Yes [ ] No Do you have pins in your Hair/Clothes/Hair Extensions/Hair Pieces/Wig

List any Drug Allergies: __________________________________________
List Previous Surgeries: __________________________________________
List any Medications you’re presently taking: _________________________

FOR INVESTIGATORS USE ONLY
---------------------------------------------------------------------
- Scanning time: __________________
- Sequences done: ______________
I attest that the above information is correct to the best of my knowledge. I give also consent to have a contrast agent administered to me for the completion of the study. I acknowledge that I am aware of the possibility of side effects with contrast and I have had the opportunity to ask questions related to this form, to ask questions regarding the MRI procedure and the study, and I understand the information presented to me.

__________________________________  __________________________  __________
Volunteer Subject Signature  Investigator Signature  Date
Appendix 3. Informed Consent

Participant's initials: ________________

Western

Letter of Information for Participants
Healthy Subjects

Magnetic Resonance Imaging of Intracranial vessels at 7 Tesla

Name of Principal Investigator: Mel R. Boulton, Ph.D., M.D.
Department of Neurological Sciences
The University of Western Ontario
London, Ontario
Office phone: 519-663-3602

Study Investigators:
Rob Bartha, MSc.
Robarts Research Institute

Joe Gati, MSc.
Robarts Research Institute

Pablo Lopez-Ojeda, MD.
Neurovascular Clinical Fellow, LHSC

Invitation to participate in Research

You are being invited to participate in a research study funded by the Department of Clinical Neurological Sciences (Internal Research Fund – IRF). This letter contains information to help you decide whether or not to participate. It is important for you to understand why the study is being conducted and what it will involve. Please take the time to read this carefully and feel free to ask questions if anything is unclear or there are words or phrases you do not understand.

Purpose of Research Study:

Stroke affects 1 Canadian every ten minutes, with upwards of 300,000 people remaining at risk for stroke throughout Canada. Stroke is intimately related to the health of the blood vessels in the brain, and can result from either the vessel blocking off vital blood flow, or from blood rupturing through a weak blood vessel wall. Current understanding of blood vessels comes from autopsy, or imaging studies of blood vessels in patients undergoing treatment. Unfortunately only autopsy allows full
Participant’s initials:______________

Magnetic Resonance Imaging of Intracranial vessels at 7 Tesla

Consent:

I have read the Letter of Information/Consent, have had the nature of the study explained to me and I agree to participate. All questions have been answered to my satisfaction.

Name: (please print)________________________

Signature:__________________________ Date:__________

Name of person obtaining consent: (please print)____________________

Signature:__________________________ Date:__________

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Curriculum Vitae

Name: Pablo López-Ojeda

Post-secondary Education and Degrees:
The Autonomus University of Barcelona, Barcelona, Spain
1998-2004 M.D

The University of Barcelona, Barcelona, Spain
2005-2010 Neurosurgery Residency

The University of Western Ontario, London, Ontario, Canada
2012-2014 Fellowship

Honours and Awards:
Charles Drake Endowed Fellowship in Neurointerventional and Cerebrovascular Surgery,
2012-2014

Western Graduate Scholarship
2012-2014

Grant for International Research Projects of the Fundación Alfonso Martin Escudero (FAME), Madrid, Spain
2012-2014

Related Work Experience:
Neurosurgeon
Bellvitge University Hospital,
Barcelona, Spain
2010-2012
Publications:


Abstracts:

