- *PI name and contact information:*

Name: Samuel Chang, MD, MS
Assistant Professor, Chief
Division of Abdominal Imaging, Department of Radiology
University of Colorado School of Medicine
Address: Mail Stop L954
12401 East 17th Avenue
Office at AOP, Room 1615
Aurora, Colorado 80045
Office: 720 848 1875
Fax: 720 848 7315
e-mail: samuel.chang@ucdenver.edu

- *Other key personnel:* Burcu Akpinar, MD

- *Project title:* **3T MR Angiography of the Hepatic Vasculature: A pilot comparison study of new non-contrast techniques to post-contrast technique and CT angiography in liver donors.**

- *Project period:* 6 months from the opening of fund

- *Summary and Relevance:*

Currently, all potential liver donors are evaluated with both computed tomography (CT) for the evaluation of hepatic vasculature and magnetic resonance (MR) including MR pancreato-cholangiography (MRCP) for the evaluation of biliary tree anatomy. CT involves the risk of radiation, allergic reactions to contrast, and contrast induced nephropathy. The final goal of this study is to eliminate CT from the pre-transplantation evaluation of potential liver donors by performing the evaluation of hepatic vasculature on MRI.

We propose to evaluate the utility of two new noncontrast MR angiography (MRA) techniques, which do not involve ionizing radiation or exposure to contrast; Inhance 3D Velocity and Inhance Inflow IR. These techniques are available in the GE Signa HDXT 3T MR scanner (General Electric Healthcare, Milwaukee, WI). The Inhance 3D Velocity sequence is based on volumetric 3D phase contrast acquisition with parallel imaging, and the Inhance Inflow IR sequence, on 3D FIESTA (1). These new techniques have shown improved image resolution for imaging renal arteries. However, these techniques have not been evaluated for the hepatic vasculature.

We will recruit 10 potential liver donors who are scheduled for living liver donor CT angiography (CTA) and liver MR. We will obtain CTA and postcontrast MRA images of the hepatic vasculature as standards of care and additional Inhance 3D Velocity and Inhance Inflow IR noncontrast MRA images for study purposes. We will compare these two novel noncontrast MRA techniques to postcontrast MRA and CTA. We will analyze acquisition time, agreement of measurements of diameter among modalities, evaluate visibility of anatomic variations qualitatively and relative signal intensity of the hepatic vasculature quantitatively.

We expect that noncontrast MRA images are comparable to CTA and postcontrast MRA for the pre-transplantation evaluation of the hepatic vasculature. The four techniques will produce similar detection of the normal anatomic structures and potentially important anatomic variations. This result can provide an evidence for the removal of CTA from the current pre-transplantation evaluation process.

This is a pilot study, designed to obtain pilot data for a further, larger, confirmatory study.

- *Hypothesis and Specific Aims:*

Potential liver donors are currently evaluated with both CT including CTA for the evaluation of hepatic vasculature and MR including conventional liver MR and MRCP for the evaluation of biliary tree anatomy. CT evaluation of the potential liver donor requires intravenous iodine contrast administration and at least four-phase CT scanning. If the liver and its vasculature are well evaluated with conventional liver MR and MRA, CT including CTA may be removed from the pre-transplantation evaluation process. Elimination of CT from the pre-transplantation evaluation will remove radiation exposure to healthy candidates and unnecessary CT contrast injection, by which potential allergic reactions or contrast induced nephropathy can be avoided. To satisfy this requirement, MRA should be comparable to CTA in image quality and we will test the following hypotheses regarding CTA, postcontrast MRA, and two new noncontrast MRA techniques.

We will test no difference between the four modalities for the following outcomes:

#1. A Likert scale for the visibility of hepatic arterial anatomic variations to the level of left and right hepatic arteries as shown on the maximum intensity projection (MIP) images.
#2. Detection rates of accessory or replaced left or right hepatic arteries, major branch of the middle hepatic vein draining the right lobe, or accessory inferior right hepatic vein(s).
#3. Correct classification rate of major anatomic variation in portal vein branching pattern.
#4. Measurements of the diameter and length of the hepatic arteries, portal veins and hepatic veins, including
    a. The proper, right, middle, and left hepatic arteries.
    b. The right portal vein at the branching point from the main portal vein.
    c. The main portal vein diameter 1 cm distal to the bifurcation.
    d. The right, middle, and left hepatic veins.
    e. The major branch of the middle hepatic vein draining the right lobe at the insertion to the middle hepatic vein main stem.
    f. The accessory inferior right hepatic vein at the insertion into the inferior vena cava.
#5. A Likert scale which rates the examination for how badly the artifacts prevented evaluation by the reader.
#6. The percentage of examinations with the presence of significant artifacts interfering interpretation.
#7. The relative signal intensity of the hepatic vasculature on noncontrast and postcontrast MRA.
#8. Acquisition time.
#9. The percentage of examinations that caused adverse events, including contrast reactions or claustrophobia.

- *Background and Detailed Research Plan*

Potential living liver donor candidates have been evaluated for the liver and its vasculature and biliary anatomy, mostly by use of CT and CTA, which requires intravenous contrast administration and at least four phase CT scanning including CT cholangiogram. Recently, the intravenous agent for CT cholangiogram has become withdrawn from the market and unavailable. Instead, the biliary anatomy is being evaluated with MR cholangiopancreatography (MRCP). Given the ability of evaluating hepatic parenchyma and characterizing focal hepatic lesions better, MR examinations are usually performed with dynamic liver MR and MRCP protocols prior to and following the administration of intravenous gadolinium contrast. Thus, the candidates are currently being evaluated by CT, CTA, MR and MRCP, which requires high cost and at least two sessions of examinations.

If the liver and its vasculature can be well evaluated with MR and MRA, CT and CTA

may be removed from the pre-transplantation evaluation process. Elimination of CT from the pre-transplantation evaluation will remove radiation exposure to healthy candidates and unnecessary CT contrast injection, by which radiation hazard and potential allergic reactions or contrast induced nephropathy can be avoided. Since MR is considered better than CT for the evaluation of hepatic parenchyma and the characterization of focal hepatic lesions and can also evaluate the upper abdomen for incidental abnormalities, MR can replace CT for the evaluation of the liver and the characterization of focal hepatic lesions. If MRA can evaluate the hepatic vasculature comparably to CTA, thus, MRA can replace CTA and potential living liver donors can be completely evaluated by use of a single modality, MR, by performing conventional liver MR, MRA, and MRCP. Therefore, the purpose of this study is to test MRA sequences for their comparability to CTA in the preoperative evaluation of potential living liver donors.

MRA sequences can be performed with or without intravenous contrast material. Postcontrast MRA sequences are not applicable to patients with poor renal function due to the fear of nephrogenic systemic fibrosis. Noncontrast MRA sequences can be applied regardless of patient's renal function, but have had poor image quality and resolution. However, two new Inhance sequences recently designed by GE Healthcare, including Inhance 3D Velocity and Inhance Inflow IR, provide high-resolution images of the vasculature with short acquisition time and excellent vessel detail (1).

Inhance 3D Velocity is designed to acquire angiographic images in brain and renal arteries with excellent background suppression in a short scan time. By combining a volumetric 3D phase contrast acquisition with parallel imaging, efficient k-space sampling, and pulse sequence optimization, Inhance 3D Velocity is faster than previous generations. Background suppression is improved the optimized pulse sequence design, resulting in better visualization of small branches (1).

Inhance Inflow IR is an angiographic method developed to image renal arteries with the ability to suppress static background tissue and venous flow. Inhance Inflow IR combines the benefits of the inflow effects of time-of-flight (TOF) MRA and the bright luminal signal of the FIESTA sequence. This sequence based on 3D FIESTA improves SNR while producing bright blood images. A relative inversion pulse is applied over the region of interest, which inverts arterial, venous and static tissue. At the null point of the venous blood, an excitation pulse is applied to generate a signal. The net result is an angiographic image with excellent background suppression and virtually no venous contamination. Uniform fat suppression is achieved using a spectrally selective chemical saturation (SPECIAL) technique (1,2). Both techniques have respiratory gating compatibility (1,2).

Although the arteries of interest by non-contrast MRA in the abdomen were mostly renal arteries, the investigators have started to apply non-contrast MRA techniques to the hepatic arteries (3-6). To our knowledge, however, these improved techniques of Inhance sequences on 3T MR scanners are not yet evaluated for the hepatic vasculature. This pilot study will enable us to optimize these improved non-contrast MRA techniques for the evaluation of the hepatic vasculature and, if successful, will provide us with the benefit of performing pre-transplantation evaluation with MR only, avoiding CT contrast injection and radiation exposure and decreasing cost in potential living liver donors. Hopefully the study will advance to the evaluation of hepatic transplant anastomosis studies later. In our daily practice, there is also a substantial clinical need for detailed angiographic examinations of the hepatic vasculature, without injection of intravenous contrast materials such as in recipients with poor renal function post-transplant.

If the subjects fulfill the criteria for living liver donation and are evaluated for the procedure with CT and MR, they will be included in this study. We will recruit 10 potential living liver donors who had CT and CTA for the evaluation of the liver and hepatic vasculature and will undergo MR and MRCP. Contraindication for MR contrast material is a cause for exclusion from the study. Two healthy volunteers will be examined with MR to optimize the inversion time (TI) and other MRA parameters for the best evaluation

of the hepatic vasculature. After obtaining informed consents, 6 sequences of noncontrast MRA that are optimized to evaluate hepatic arteries, portal veins, and hepatic veins (2 techniques each for three structures) will be acquired additionally to MR and MRCP for each subject. The 3D spoiled gradient echo (GRE) sequence with fat suppression and parallel imaging acceleration (Liver Acquisition with Volume Acceleration, LAVA, GE Healthcare) will be used for the post-contrast MRA. This sequence will also be optimized to evaluate the hepatic vasculature in terms of timing and spatial resolution and acquired after the intravenous administration of a gadolinium based intravenous contrast, Eovist (gadoxetate disodium, Bayer HealthCare, Berlin, Germany).

Five readers will evaluate the hepatic vasculature for the evaluation criteria described below. The readers will be Drs. Chang, Pokharel, Meier, Clark, and Akpinar. The readers will evaluate four examinations per patient. The four examinations are CTA, Inhance 3D Velocity noncontrast MRA, Inhance Inflow IR noncontrast MRA, and postcontrast MRA. The order of reading the examinations will be randomized.

Each reader will evaluate each examination on the following outcomes.

1. A Likert scale for the visibility of hepatic arterial anatomic variations to the level of left and right hepatic arteries as shown on the maximum intensity projection (MIP) images.
2. Detection of accessory or replaced left or right hepatic arteries, major branch of the middle hepatic vein draining the right lobe, or accessory inferior right hepatic vein(s).
3. Classification of major anatomic variation in portal vein branching pattern.
4. Measurements of the diameter and length of the hepatic arteries, portal veins and hepatic veins, including
   a. The proper, right, middle, and left hepatic arteries.
   b. The right portal vein at the branching point from the main portal vein.
   c. The main portal vein diameter 1 cm distal to the bifurcation.
   d. The right, middle, and left hepatic veins.
   e. The major branch of the middle hepatic vein draining the right lobe at the insertion to the middle hepatic vein main stem.
   f. The accessory inferior right hepatic vein at the insertion into the inferior vena cava.
5. A Likert scale which rates the examination for how badly the artifacts prevented evaluation by the reader.
6. The relative signal intensity of the hepatic vasculature on noncontrast and postcontrast MRA.

Readers will be asked to evaluate the visibility of hepatic arterial anatomic variations using a 5 point Likert scale, where 5 represents complete visibility of the anatomic variations at the level of the left and right hepatic arteries, and 1 represents a completely inadequate image (#1).

The readers will evaluate the branching pattern of the hepatic artery, portal vein and hepatic veins and categorize according to the known variations (#2 and #3).

The diameter or length of the hepatic arteries, portal veins and hepatic veins will be measured by each reader as follows:

1. The proper, right, middle, and left hepatic arteries.
2. The right portal vein at the branching point from the main portal vein.
3. The main portal vein diameter 1 cm distal to the bifurcation.
4. The right, middle, and left hepatic veins.
5. The major branch of the middle hepatic vein draining the right lobe at the insertion to the middle hepatic vein main stem.
6. The accessory inferior right hepatic vein at the insertion into the inferior vena cava.

The measurements will be done on all modalities, recorded in millimeters (#4).

Readers will be asked to rate the degree of interference in image interpretation by artifacts using a 5 point Likert scale, where 5 indicates that the image is completely unaffected by artifacts, and 1 indicates that the severe artifacts prevent readers from interpreting images and recognizing anatomical structures (#5). We will categorize these scores into two groups; presence or absence of significant limitation that affected the confidence of interpretation (#6).

The relative signal intensity of the hepatic vasculature will be calculated as follows: First, the reader will measure the hepatic vasculature and liver parenchymal signal intensity by ROI (region of interest). Then, relative signal intensity (SI) will be calculated as: Relative Signal Intensity = $C_{vessel\text{-}liver} = (SI_{vessel} - SI_{liver}) / SI_{vessel}$ (#7).

The acquisition time of each MR sequence on the scanner monitor will be recorded in minutes (#8).

Adverse events will be evaluated by the study coordinator at the time of imaging and will be reported (#9).

Data for this study will be entered into a REDCap database, which uses a MySQL database via a secure web interface with data checks used during data entry to ensure data quality. REDCap is a free, secure, web-based application designed to support data capture for research studies. The system was developed by a multi-institutional consortium initiated at Vanderbilt University (7).

- *Statistical analysis plan*:

Power and Sample Size: The study will recruit 10 study participants. The study is designed to estimate parameters for a detailed power analysis for a further, larger, confirmatory study.

With 10 participants, the half width for the 95% confidence interval for the proportion of examinations with artifacts will be no more than 0.31.

We describe the analysis plan for Hypothesis #4. The other analysis plans are exactly parallel.

We will fit a general linear multivariate model with doubly repeated measures. The three within participant factors are imaging modality, location (hepatic vein, hepatic artery, and portal vein) and reader. The four imaging modalities are Inhance 3D Velocity noncontrast MRA, Inhance Inflow IR noncontrast MRA, postcontrast MRA, and CTA. The eleven locations of measurement are: The proper, right, middle, left hepatic artery, the right portal vein at the branching point from the main portal vein, the main portal vein 1 cm distal to the bifurcation, the right, middle, left hepatic veins, the major branch of the middle hepatic vein draining the right lobe at the insertion to the middle hepatic vein main stem, the accessory hepatic vein at the insertion into the inferior vena cava. We will average across the readers. We will use an alpha-spending approach to assure an overall 0.05 level for the experiment. At the 0.04 level, we will use a Hotelling-Lawley test to assess the null hypothesis of no modality effect on any of the 11 locations of measurement. If there is a difference, we will conduct two step-down tests to assess the difference between Inhance 3D Velocity non-contrast MRA and CTA, and the difference between Inhance Inflow IR non-contrast MRA and CTA. Finally, we will assess the difference between post-contrast MRA and Inhance 3D Velocity noncontrast MRA, the difference between post-contrast MRA and Inhance Inflow IR non-contrast MRA and the difference between post-contrast MRA and CTA.

We will examine jackknifed studentized residuals for the presence of outliers and strongly influential observations, using Cook's D to evaluate the significance of the outliers. We will conduct testing for multivariate normality. We will report p-values, parameter estimates, 95% confidence intervals, and produce graphs showing the relationship between the modalities.

We will use the parameter estimates to conduct a power and sample size analysis for a second, larger, confirmatory study, designed to show the non-inferiority of the new modalities to both post-contrast MRA, and CTA.

- *Detailed Budget and Justification:*

Two noncontrast MRA techniques for three vascular structures including hepatic artery, portal vein, and hepatic veins will add 6 sequences and 30 minute to MRI time.

$283.10 per patient for the additional MRI time (30 minutes) x 12 (2 optimization MRA scans and 10 subjects) = $3,397.20.

Research assistant: Burcu Akpinar. One 50% full time employed (FTE) research assistant who will work on the entire project during the 6 months. She is needed to help with participant appointment scheduling and do all the evaluation part of the donors and will be the one of the five readers, as she is a qualified radiologist. She will be responsible for researching as well as recording and managing the data, including measures, scores, files and health records. She will assist in ongoing literature review, document review for project, qualitative and quantitative data entry and management, data analysis and checking. She will be responsible for preparing the paper and presentation of the preliminary results for journals, meetings.

1 research assistant at 50% FTE salary for 6 months; $35,200 x 0.5 x (6/12) = $8,800 for 6 months.

Total amount: $3,397.20 + $8,800 = $12,197.20

- *Journals to which we plan to submit the study:*

Journals in which we wish to publish the results include: Radiology, Journal of Magnetic Resonance Imaging (JMRI), American Journal of Roentgenology (AJR), Hepatology and Journal of Hepatology.

- *Meetings at which we plan to present the study:*

Academic meetings at which we wish to present the results include: The International Society for Magnetic Resonance in Medicine (ISMRM), Radiological Society of North America (RSNA), The American Roentgen Ray Society (ARRS), Society of Abdominal Radiology (SAR), and American Society of Transplant Surgeons (ASTS).

- *Plans for a follow-up study, and the funding agency and grant mechanism to which a grant application would be submitted:*

If the non-contrast MRA turns out to be effective for the evaluation of hepatic vasculature with the healthy donors the study would be extended to the evaluation of liver transplant vascularity and anastomosis with non-contrast MRA sequences. The final goal of this study is to remove CT and CTA in the evaluation of potential living liver donors to avoid high dose radiation used for the production of high-resolution images and to see the possible use of the MRA for the evaluation of the hepatic vasculature in the patients with poor renal function such as hepatorenal syndrome or renal dysfunction. For these purposes a following grant application would be submitted to a larger funding agency, such as, GE- Radiology Research Academic Fellowship (GERRAF), or a small NIH grant with the preliminary results from this study.

- *Suggestions for independent reviewers:*

Until now the evaluation of hepatic vasculature has required excessive radiation in CTA or fluoroscopic angiography and injection of intravenous contrast material, which has a potential hazard and is a limiting factor for the use of these methods in patients with poor renal function. If this study of non-contrast MRA shows its potential to be comparable to CTA, this will make obsolete those clinical dilemmas and help the patient group to get appropriate imaging assistance.

- *References:*

1. Inhance Suite 2.0. Vascular Imaging, Magnetic Resonance Imaging, Products. GE Healthcare webpage.
2. Bley TA. Non-contrast enhance renal MRA. Vascular Imaging. A GE Healthcare MR publication. Autumn 2008.
3. Puippe GD, Alkadhi H, Hunziker R, et al. Performance of unenhanced respiratory-gated 3D SSFP MRA to depict hepatic and visceral artery anatomy and variants. Eur J Radiol. 2012 Aug;81(8):e823-9. doi: 10.1016/j.ejrad.2012.02.016. Epub 2012 May 10.
4. Shimada K, Isoda H, Okada T, et al. Non-contrast-enhanced hepatic MR angiography with true steady-state free-precession and time spatial labeling inversion pulse: Optimization of the technique and preliminary results. Eur J Radiol. 2009 Apr;70(1):111-7. doi: 10.1016/j.ejrad.2007.12.010. Epub 2008 Feb 4.
5. Shimada K, Isodo H, Okada T, et al. Non-contrast-enhanced MR angiography for selective visualization of the hepatic vein and inferior vena cava with true steady-state free-precession sequence and time-spatial labeling inversion pulses: Preliminary results. J MAgn Imaging. 2009 Feb;29(2):474-9. doi: 10.1002/jmri.21636.
6. Shimada K, Isoda H, Okada T, et al. Unenhanced MR portography with a half-fourier fast spin-echo sequence and time-space labeling inversion pulses: Preliminary results. AJR Am J Roentgenol. 2009 Jul;193(1):106-12. doi: 10.2214/AJR.08.1626.
7. Harris PA, Taylor R, Thielke R, etal. Research electronic data capture (REDCap) - A metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform. 2009 Apr;42(2):377-81.