Study Protocol

Title: Utility of MRI with ultrasound gating for advanced fetal monitoring

Institution: This Hospital for Sick Children

Team Members

Principal Investigator: Dr. Chris Macgowan (Imaging Scientist; SickKids)
Qualified Investigator: Dr. Mike Seed (Cardiologist; SickKids)
Research Coordinator: Natasha Milligan (Research Coordinator; SickKids)
Co-investigators: Fabian Kording (Scientist; University Medical Centre Hamburg-Eppendorf)
Dr. Greg Stortz (Research Analyst; SickKids)
Dr. Eric Schrauben (Postdoctoral Fellow; SickKids)
Christopher Roy (Ph.D. Student; University of Toronto)
Datta Goolaub (M.Sc. Student; University of Toronto)
Sharon Portnoy (Ph.D. Student; University of Toronto)

Study Period: 1 year

BACKGROUND AND SIGNIFICANCE

Abstract

This is a pilot study involving simultaneous magnetic resonance imaging (MRI) and ultrasound in pregnant participants with fetal congenital heart disease. The aim of this research study is to integrate non-imaging Doppler ultrasound to provide fetal cardiac gating during the MRI acquisition. This aim encompasses making clear images of the fetal heart and blood vessels, and reproducible measurements of fetal blood flow. MRI-derived blood flow waveforms in the fetus and anatomical images of the fetal heart will be compared with those from diagnostic ultrasound for validation.

Rationale

Fetal MRI can be used in adjunct to conventional obstetric ultrasound to assess and monitor the health of the fetus in the case of complicated pregnancies. For example, once the fetus is diagnosed with congenital heart disease (CHD) through initial ultrasound screening, the patients may be referred to our MRI program for additional fetal cardiovascular assessment. We would like to develop and apply MRI for advanced fetal cardiovascular assessment to better manage complicated pregnancies with the intent to improve patient care and postnatal health outcomes. Results from MRI may aid in the guidance of fetal interventions, managing optimal timing of delivery and planning for post-natal care.

Our group has studied the fetal circulation in healthy pregnancies and in the settings of CHD and intrauterine growth restriction (IUGR) [1]. Despite our early successes in studying the fetal heart and circulation by MRI, such studies have been limited by practical challenges including the small size of fetal structures, the high fetal heart rate and unpredictable motion of the fetus. For example, in late gestation the diameter of a normal left ventricle is only 15 mm and major vessels are even smaller with diameters less than 8 mm [2]. These small dimensions coupled with high heart rates (between 110-180 bpm) necessitate high spatial and temporal resolutions to capture cardiac dynamics [3].

To address these limitations, state-of-the-art MRI techniques originally designed for evaluating the adult heart must be translated to fetal imaging [4]. Phase contrast (PC) MRI is the gold standard for non-invasive measurement of blood flow in post-natal subjects. Cardiovascular anatomical MRI is an essential diagnostic tool in the evaluation of the heart post-natally. It is non-invasive, provides excellent soft tissue contrast and has the ability to perform multi-planar imaging in any orientation. PC MRI and anatomical MRI of the heart necessitate synchronization of image acquisition with the cardiac phase, which is most often facilitated by an electrocardiogram (ECG) signal.

In the case of fetal cardiovascular complications such as CHD, evaluation of the fetal heart is important for guiding treatment of disease, timing of delivery, and planning appropriate care after birth. Detection of the fetal heart beat through ECG has been done by placing electrodes on the mother's abdomen. Even after decades of developments in fetal ECG, detection of the fetal heart beat through ECG has been shown to be fundamentally unreliable due to the relatively small electric potentials generated from the fetal heart, interference from other potentials generated by the mother, and shielding from many layers of tissue [5]. A very low conductivity layer of tissue called the vernix caseosa which forms around the fetus between the 28^{th} and 32^{nd} weeks of gestation, makes detection of an fetal ECG signal particularly difficult [5]. Lack of an available ECG signal from the fetus necessitates the use of novel cardiac gating techniques for MRI. For this, we propose to investigate the use of an MRI-compatible Doppler ultrasound probe to produce a gating signal from the fetal heart. The Doppler ultrasound probe detects blood flow through the fetal heart, which can be used to trigger MRI data acquisition and produce dynamic images of the fetal heart. Our collaborators have successfully used this technique to produce a cardiac gating signal for MRI gating in non-pregnant adult humans [6], fetal humans [7], and fetal sheep [8].

This study will be conducted in compliance with this research protocol, GCP guidelines and with the Hospital for Sick Children's regulatory requirements.

Significance

Cardiac gated fetal MRI methods will enable accurate assessment of fetal cardiovascular function and development. The prospective gating provided by the Doppler ultrasound probe will allow direct translation of postnatal MRI techniques to the evaluation of pathologies like fetal heart disease and intrauterine growth restriction, to better guide treatments such as early delivery and to plan appropriate care after birth.

Hypotheses/Research Questions

Our proposal is geared toward method development and validation of MRI scanning techniques. We will compare dynamic cardiac images and blood flow patterns obtained using prospectively gated MRI with those obtained using conventional diagnostic ultrasound imaging. We will also compare MRI measurements made with the newly developed prospective gating method to un-gated and retrospectively gated MRI.

Our primary objective is to assess the feasibility of using Doppler ultrasound gated MRI for advanced fetal monitoring, which would include understanding the relationship between maternal-placental-fetal cardiovascular physiologies in utero. To achieve the primary objective, the following foundational objectives need to be accomplished:

(1) Incorporate fetal gating information from a novel Doppler ultrasound probe into our existing MRI pulse sequences and reconstruction software
(2) Validate Doppler ultrasound gated MRI by comparison to MRI images created without gating information from the Doppler ultrasound probe, in addition to measurements made with clinical ultrasound
(3) Assess utility of prospective Doppler ultrasound gating for fetal MRI compared to un-gated and retrospectively gated fetal MRI

Procedures

Pregnant volunteers carrying a fetus affected by congenital heart disease who are scheduled for a clinical fetal ultrasound examination at the Fetal Echocardiography Clinic at SickKids will be invited to undergo an MRI, where MRI techniques incorporating Doppler ultrasound gating will be tested. Participants will be scanned with the Siemens Prisma^{FIT} 3T MRI at SickKids. We will enroll 20 pregnant volunteers (10 in the 2nd trimester and 10 in the 3rd), allowing for method development and testing at different gestational ages, providing more dramatic variation in anatomy and vessel size and more variation in the types and magnitude of fetal motion. During scanning, pregnant mothers will be asked to remain still for periods of time on the order of 5 minutes as pulse sequences are run.

The Doppler ultrasound fetal gating device, which will be placed on the patient's abdomen by a registered MRI technician and held in place with a flexible elastic band, will be connected to the gating input of the MRI for either the entirety of, or a portion of the MRI examination. As is the case with all clinical ultrasound examinations, a water-based gel will be applied to the mother's skin below where the gating device is placed. The gating device will detect when each fetal cardiac cycle begins and trigger MRI acquisition. MRI examinations will be up to 60 minutes in length. The MRI examination will be scheduled on the same day that volunteers have their clinical ultrasound appointment, with both examinations occurring within the shortest time-period that can reasonably be achieved.

Data Collection / Analysis

Anatomic MR images of the fetal heart (be they single or multi-slice), phase-contrast MR images of blood flow in great fetal vessels, and T1 and T2 maps in great fetal vessels will be acquired using prospective gating information from the Doppler ultrasound probe. Similarly, anatomical images, phase contrast images, and T1 and T2 maps will be acquired without any gating input. From the ultrasound examination during the patient's visit to the Fetal Echocardiography Clinic, we will retrieve anatomical images of the fetal heart in addition to flow waveforms acquired in the great fetal vessels.

MR data acquired without the Doppler ultrasound gating signal will be reconstructed without any gating information, and will also be reconstructed using retrospective gating techniques that we have previously developed [9], [10]. Anatomic MR images will be compared quantitatively in terms of myocardial border sharpness, with the anticipated result that Doppler gated MR will show higher border sharpness than un-gated or retrospectively gated MR. Ejection fraction will be calculated from anatomical cardiac images. These estimates of ejection fraction will be compared to ejection fraction calculated from the ultrasound images, with the anticipated result that Doppler gated MR will agree better with ultrasound images than un-gated or retrospectively gated MR.

T1 and T2 maps will be compared in terms of the standard deviation of T1/T2 values in ROIs placed in the larger great fetal vessels, with the anticipated result that Doppler gated MR will provide a tighter distribution than un-gated or retrospectively gated MR. From the ungated, retrospectively gated, and Doppler ultrasound gated cardiac images, we will calculate *ejection fraction*.

Flow waveforms in great fetal vessels derived from retrospectively gated and Doppler ultrasound gated phase contrast images will be compared to flow waveforms measured with clinical Doppler ultrasound during the patient's visit to the Fetal Echocardiography Clinic (which we view as a gold standard). We anticipate that flow waveforms derived from Doppler ultrasound gated MR will prove to be more similar to the gold standard than flow waveforms derived from retrospectively gated MR.

Once enrolled, participants will be assigned a study number and all data and images gathered from the study procedures will be de-identified so to be identifiable only by this number and not any personal health information. Results of this study will be published in conference presentations and proceedings, peer reviewed journals, and academic rounds.

Inclusion and exclusion criteria

Inclusion criteria:
-pregnant adults (age 18 and up) with fetus affected by congenital heart disease
-singleton pregnancy in their 2nd and 3rd trimesters
-scheduled for a clinical fetal ultrasound examination at the Fetal Echocardiography Clinic at SickKids

Exclusion criteria:
Exclusion criteria that prevent the mother from having an MRI
-claustrophobia
-cardiac pacemaker
-non-MRI compatible implants

Other exclusion criteria
-non-singleton pregnancy
-obesity (BMI > 30)

Possible harm to the patients:
Fetal MRI has been used for more than 25 years and poses no risk to the fetus in the 2nd and 3rd trimesters of pregnancy [11]. MRI does not use ionizing radiation, which is known to be harmful to the fetus, and risks are primarily related to the rise in body temperature due to absorption of radio-frequency energy. The UK National Radiological Protection Board suggests that MRI be restricted to the 2nd and 3rd trimester because of theoretical concerns about teratogenesis with MRI in early pregnancy [12], however recent studies of incidental MRI use in 1st trimester pregnancies have demonstrated no increase in adverse outcomes in these cases when no MR contrast agent is used [13]. In fetal MRI, current data and research studies have failed to demonstrate any reproducible harmful effects on pregnant women and their fetuses at magnetic field strengths of 3T or less [14]. The *International Commission on Non-Ionizaing Radiation Protection* concludes that "adverse developmental effects [on the fetus] will be avoided with a margin of safety if the body temperature of pregnant women does not rise by more than 0.5 ˚C and the temperature of the fetus is less that 38 ˚C" [15].

MRI manufacturers have adapted the *International Electrotechnical Commission* (IEC) standard IEC 606-1-2-33, which defines three levels of MRI RF exposure risk. The lowest risk level, *normal mode*, sets a maximum specific absorption rate (SAR) of 2 W/kg and a maximum temperature rise of 0.5 ˚C. Before any MR pulse sequence is run on the Siemens Prisma^{FIT} 3T MRI, an estimate of whole-body SAR and temperature rise is made, which accounts for the patient's height, weight, ambient temperature and humidity, and details of the MR pulse sequence. When operating in normal mode, the scanner will simply not run a pulse sequence if the estimated SAR or temperature rise exceeds the thresholds defined by IEC normal mode. It is known that the fetal temperature rests ~0.5 ˚C above the maternal body temperature (which is 37 ˚C) due to limited pathways for heat transfer [16]. Numerical simulations suggest that fetal temperature will not pass 38˚C when a mother is scanned in *normal mode* [16], giving assurance that we will operate within internationally recognized safety limits.

Concerns related to the loud noises generated by the MR coils and their potential to cause acoustic damage to the fetus have been dispelled by several studies [11].

In addition to the ultrasound that volunteers will undergo to validate our MRI techniques, ultrasound is the enabling technology behind the Doppler ultrasound probe used for fetal cardiac gating. Doppler ultrasound detects blood velocity by transmitting acoustic waves into the patient and then detecting waves that reflect back from moving red blood cells. Ultrasounds are included in routine prenatal care around the world and no harmful effects have ever been detected. Theoretical concerns are related to tissue heating (as in MRI) in addition to ultrasonic gaseous cavitation [17]. The Doppler ultrasound probe will be built by our collaborators from the Department of Diagnostic and Interventional Radiology at the University Medical Centre in Hamburg, Germany where they have received ethics approval for use in non-pregnant adult human volunteers [6] and later, for fetal imaging in pregnant adult volunteers [7]. The transducer transmits acoustic energy at a maximum (pulse averaged) power of 1.5 mW/cm^2, which is well below the limit of 20 mW/cm^2 set by Health Canada for Doppler ultrasound based fetal heart rate monitors [18].

This study will not proceed before we receive Health Canada approval to use this new medical device.

It is known that use of ultrasonic gels carries a small risk of spreading bacterial infections [19]. Health Canada mandates that sterile gels be used in all procedures that pass a device through tissue (such as ultrasound guided tissue biopsy) or where the ultrasound transducer makes contact with a mucus membrane. Because we will only put the ultrasound gel on intact skin, there is minimal risk of spreading infection. The ultrasound transducer will be cleaned with an antibacterial disinfectant after each use, and Health Canada guide-lines regarding use of non-sterile ultrasound gels, as outlined in [20] will be followed.

Any adverse events (such as injury during MRI examination) will be reported to the SickKids Research Ethics Board.

Possible benefit to the patient:
Fetal cardiac MRI provides a way of making pictures of the fetus, in addition to conventional ultrasound screening, and may result in visualization of previously undetected abnormalities. The probability of such benefits to the patients is very small because such abnormalities would likely have been detected by ultrasound during normal standard of care. In such a situation, Dr. Mike Seed, who is in the patient's circle of care, will be informed of the findings and will take appropriate action.

Possible benefit to society:
Fetal cardiac MRI methods will enable more accurate assessment of fetal cardiovascular function and development. The imaging techniques provided by the methods we develop will allow for early evaluation of fetal heart and/or placental disease to better guide treatments such as early delivery and to plan appropriate care after birth.

Data collection and storage:
The source images from the study will be de-identified and stored on the secure hospital research PACS system with password-protected access. The de-identified data will be associated with a code, and the key-code will be stored in password-protected files on an internal hospital directory. The data will be destroyed after a period of 7 years. De-identified MRI and ultrasound data will be shared with our collaborator (Fabian Kording) at the University Medical Centre Hamburg-Eppendorf in Hamburg, Germany. Data will be transferred using the SickKids RIT-FTP service. Only the study team identified will have access to the patient data.

Withdrawal from study participation:
Participants can withdraw from the study at any point, for any reason, specified or unspecified, without penalty. No new data will be collected or linked to other data from that point on. Upon request any processed and unprocessed data can be destroyed.

Research budget and funding:
The main cost of this study is the cost of the MRI examinations, which are $500 per hour. Each participant will be reimbursed for travel and parking, costing up to $33.50. We will pay to make our publications open access, for which we will allocate $2000. The total cost of this project could reach $12,670. A total sum $30,000 is available through CIHR funding.

References

[1] M. Y. Zhu, N. Milligan, S. Keating, R. Windrim, J. Keunen, V. Thakur, A. Ohman, S. Portnoy, J. G. Sled, E. Kelly, S. J. Yoo, L. Gross-Wortmann, E. Jaeggi, C. K. MacGowan, J. C. Kingdom, and M. Seed, "The hemodynamics of late-onset intrauterine growth restriction by MRI," *Am. J. Obstet. Gynecol.*, vol. 214, no. 3, p. 367.e1-367.e17, Mar. 2016.

[2] G. R. DeVore, "Assessing fetal cardiac ventricular function.," *Semin. Fetal Neonatal Med.*, vol. 10, no. 6, pp. 515–41, Dec. 2005.

[3] H. F. Sandmire and R. K. DeMott, "Electronic fetal heart rate monitoring: research guidelines for interpretation.," *Am. J. Obstet. Gynecol.*, vol. 179, no. 1, pp. 276–277, 1998.

[4] Y. Li and X. Zhang, "Advanced MR Imaging Technologies in Fetuses," *Omi. J Radiol*, vol. 1, no. (4), pp. e113-119, 2012.

[5] R. Sameni and G. D. Clifford, "A Review of Fetal ECG Signal Processing; Issues and Promising Directions.," *Open Pacing Electrophysiology Therapy J.*, vol. 3, pp. 4–20, 2010.

[6] F. Kording, B. Schoennagel, G. Lund, F. Ueberle, C. Jung, G. Adam, and J. Yamamura, "Doppler ultrasound compared with electrocardiogram and pulse oximetry cardiac triggering: A pilot study," *Magn. Reson. Med.*, vol. 74, no. 5, pp. 1257–1265, Nov. 2015.

[7] J. Yamamura, B. Schoennagel, M. Tavares, M. Kladeck, G. Adam, C. Ruprecht, and F. Kording, "Fetal cardiac MRI and Flow-measurement using Optimized Doppler-Ultrasound Sensor (DUS) gating," *ISMRM Conference Record*, 2016, p. abstract 0974.

[8] F. Ueberle, E. Dettmann, C. Eden, J. Jayakumar, M. Jelinek, C. Much, B. Schönnagel, M. Tavares de Sousa, U. Wedegärtner, and J. Yamamura, "Cardiac MR: Imaging of the Foetal Heart Dynamics using Doppler Ultrasound Triggering.," *Biomed TEch*, vol. 57, no. Suppl.1, pp. 1–4, 2012.

[9] M. S. Jansz, M. Seed, J. F. P. Van Amerom, D. Wong, L. Grosse-Wortmann, S. J. Yoo, and C. K. MacGowan, "Metric optimized gating for fetal cardiac MRI," *Magn. Reson. Med.*, vol. 64, no. 5, pp. 1304–1314, 2010.

[10] C. W. Roy, M. Seed, and C. K. Macgowan, "Accelerated MRI of the fetal heart using compressed sensing and metric optimized gating," *Magn. Reson. Med.*, vol. 0, pp. 1–11, 2016.

[11] F. V. Coakley, O. A. Glenn, A. Qayyum, A. J. Barkovich, R. Goldstein, and R. A. Filly, "Fetal MRI: A Developing Technique for the Developing Patient," *Am. J. Roentgenol.*, vol. 182, no. 1, pp. 243–252, 2004.

[12] National Radiological Protection Board, "Principles for the Protection of Patients and Volunteers during Clinical Magnetic Resonance Diagnostic Procedures," *Ann. N. Y. Acad. Sci.*, vol. 649, no. 1, pp. 372–375, 1992.

[13] J. G. Ray, M. J. Vermeulen, A. Bharatha, W. J. Montanera, and A. L. Park, "Association Between MRI Exposure During Pregnancy and Fetal and Childhood Outcomes," *JAMA*, vol. 316, no. 9, p. 952, 2016.

[14] S. Tocchio, B. Kline-Fath, E. Kanal, V. J. Schmithorst, and A. Panigrahy, "MRI evaluation and safety in the developing brain," *Seminars in Perinatology*, vol. 39, no. 2., pp. 73–104, 2015.

[15] International Commission on Non-Ionizing Radiation Protection, “Statement on medical magnetic resonance (MR) procedures: protection of patients,” *Health Phys.*, vol. 87, no. 2, p. 197, 2004.

[16] J. W. Hand, Y. Li, and J. V Hajnal, “Numerical study of RF exposure and the resulting temperature rise in the foetus during a magnetic resonance procedure,” *Phys Med Biol*, vol. 55, pp. 913–930, 2010.

[17] D. L. Miller, “Safety Assurance in Obstetrical Ultrasound,” *Semin. Ultrasound, CT MRI*, vol. 29, no. 2, pp. 156–164, 2008.

[18] Health Canada, “GUIDANCE FOR INDUSTRY - Device Licence Applications for Ultrasound Diagnostic Systems and Transducers.,” 2006, url: http://www.hc-sc.gc.ca/dhp-mps/md-im/applic-demande/guide-ld/ultrasound_ultrasons-eng.php

[19] S. C. Oleszkowicz, P. Chittick, V. Russo, P. Keller, M. Sims, and J. Band, “Infections Associated with Use of Ultrasound Transmission Gel: Proposed Guidelines to Minimize Risk,” *Infect. Control Hosp. Epidemiol.*, vol. 33, no. 12, pp. 1235–1237, 2012.

[20] Health Canada, “Notice to Hospitals: Important Safety Information on Ultrasound and Medical Gels.”, url: http://www.healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2004/14290a-eng.php?_ga=1.243051650.1024799928.1416943151