Study title: **Cardiac MRI for Metal on Metal Orthopaedic Prostheses**

List of Investigators:

- Dr. Paul Beaule (Principal Investigator),
- Dr. Girish Dwivedi (Co-Investigator)
- Dr. Alexander Dick (Co-Investigator)
- Dr. Rebecca Thornhill (Co-Investigator)

NCT02892448

Document date: 06 Jul 2017

Abstract: There may be a relationship between heart function and the metal ION levels in patients having undergone total hip replacement. The idea is to use results from a clinical cardiac MRI to assess heart function in a sample of 20 patients whom have also undergone metal-on-metal hip replacement, and 10 patients who have had hip replacement surgeries without metal-on-metal implants, to determine whether having undergone this procedure may be impacting heart function. In addition to the clinically used parameters, the images will also be retrospectively assessed using special software to assess amount of fibrosis and early changes affecting cardiac muscle contraction which may be indicative of impaired heart function. With these values we will compare to known, and previously collected, hip replacement and function data to determine whether there is any differences in how the heart works in those having had a hip replacement relative to a normal population.

Hypothesis:

Cardiac function in patients with previous metal-on-metal hip replacement will inversely correlate to the metal ion levels in the blood.

Introduction:

There has been some recent concern regarding possible systemic health effects resulting from elevated blood cobalt concentrations in patients with cobalt containing hip implants (1). To date there are no blood cobalt criteria to help guide physicians when evaluating an individual hip implant patient's risk of developing systemic health effects because historically there was little or no concern about systemic cobalt toxicity in implant patients. Included within this is heart function, for which we see a need to use this novel software to analyze heart function relative to Hip status and Metal Ion levels.

Patients with metal on metal hip prosthesis are subject to local and systemic release of cobalt and chromium ions which may increase the potential for locally aggressive ion-induced local tissue reactions such as pseudotumours, a type of Adverse Reaction to Metal Debris (ARMD) (2). Although there have been reports of local toxicity as well as cases of cobaltism (as seen during outbreak in Quebec of so called 'cobalt beer drinkers' cardiomyopathy) leading to cardiac and ototoxicity, it is unclear if chronic exposure to these ions can lead to impaired cardiac function (cardiotoxicity) in a well-functioning prosthesis.

The majority of the blood cobalt concentrations reported for hip implant patients appear to range from approximately 0.2 to 10 μg/L, and based on our review of the available literature, should not pose an increased risk for the development of systemic health effects.

The concern for systemic health effects is for the small number of patients with cobalt-containing hip implants with markedly elevated blood cobalt concentrations.

Extensive evaluations of these 'cobalt beer drinkers' have found that poor nutrition and underlying disease states caused by severe alcoholism were likely significant contributing factors to heart disease in this particular population. However, there remains a significant concern that cardiac function could be

affected in the long term. This is especially relevant as the majority of these implants are put in patients less than 50 years age.

Cardiac magnetic resonance imaging (CMR) is the gold standard method to assess cardiac function in patients at risk of cardiotoxicity. In addition to assessing cardiac function, CMR enables imaging of inflammation, and fibrosis (which may be secondary to the ion deposition) in the heart which may provide more specific information about the mechanism of injury in these patients.

The purpose of this study is to look at cardiac function in patients with a metal on metal hip prostheses.

Recruitment: 30 patients in total (10 unilateral and 10 bilateral) will be recruited which should provide indication of relationship both between either instances and heart function, as well as compared to one another. As well, 10 Total Hip Arthroplasty patients (who would not have metal-on-metal implants) will be case-matched by body surface area and age at surgery to already-recruited participants in either the unilateral or bilateral metal-on-metal participants. This will be used as the Control Group, as there is no evidence of elevated metal ions in this population. All patients will be undergoing clinical cardiac MRI and have previously undergone Metal on Metal hip arthroplasty or a non-Metal on Metal total hip arthroplasty. All patients will have extra images collected during their MRI and these images will be analyzed to determine any relationship between heart function and the possible metal ion levels from the hip implant. As part of the scan analysis they will be required to also have a 5mL vial of blood collected. Ultrasound values will be retrospectively collected, for analysis of soft tissue reaction, from a previous clinically ordered Ultrasound of the affected joint. Participants will be asked to complete blood testing to determine heart health after the scan.

Inclusion/Exclusion Criteria:

Inclusion:

- Undergoing clinical Cardiac MRI
- Have either unilateral MoM Hip replacement device if in Unilateral Group OR bilateral MoM hip replacement devices if in Bilateral Group OR have a total hip non-MoM device if in Control Group
- Willing to sign Informed Consent Form

Exclusion:

- Patient does not meet all ‘inclusion’ criteria.

Procedures:

A clinically indicated cardiac MRI will be performed at baseline to evaluate RV/LV function. At each imaging session, a single 5 ml blood sample is required for measurement of the hematocrit, to be used in conjunction with the T1 measurements to ensure accurate estimation of extracellular volume (3).

The CMR examinations will be performed using a 1.5 Tesla scanner (Magnetom Aera , Siemens Healthcare, Erlangen, Germany) and a phased array coil. A standard MR-contrast kit containing one syringe of gadolinium-based contrast (Gadovist, Bayer Canada, Toronto, Canada.) and another with saline will be assembled for use in the MR power-injector. The technologist will attach the gadolinium line to the patient's angiocath and check for any air in the tubing. After performing standard scout views, vector ECG-gated steady-state free precession (SSFP) breath-hold cines in sequential 8 mm/2 mm in short-axis oblique and axial planes will be performed.

Myocardial oedema will be assessed by T2-weighted black blood imaging using turbo spin echo (TSE) acquisition in SAO, 4C, 2C, 3C views.

Cardiac T2* imaging will be performed with a cardiac-gated, single–breath-hold, 8-echo sequence of a single midventricular short-axis slice.We will acquire T1 maps modified Look-Locker inversion recovery, “MOLLI” before administration of contrast to obtain native T1 values (4).

A single bolus of gadolinium (dose of 0.2 mmol per kilogram of body weight) followed by a saline flush by means of a power-injector will be administered for delayed enhancement imaging. We will perform standard phase-sensitive-inversion-recovery (PSIR) short axis oblique views starting 10 minutes after contrast administration.

15 minutes post-injection, we will again acquire post contrast T1 maps in short-axis oblique and four chamber views. T1 and T2 MyoMaps are approved by Health Canada. The commercial license number for MyoMaps on VE11 for a 1.5T system in Canada is 14441747.

Measurements of biventricular volumes, function and mass will be derived from the SSFP pulse sequence in the axial plane (RV) and short-axis plane (LV) on an Argus workstation (Siemens, Erlangen, Germany).

To determine if heart stress exists with these patients, we will also ask patients to consent to blood draws for 3 tests: a troponin test (determines heart stress via protein released when heart muscle is damaged), brain natriuretic peptide (BNP) test (checks for heart failure via a peptide that is released when there are pressure changes in the heart), and a biomarkers test. Each blood sample will consist of a 6mL tube. The biomarker tube will be held for up to 3 years for testing at the University of Ottawa Heart Institute.

Outcomes:

- Primary: A comprehensive cardiac function (i.e. right and left ventricular function, mass, volumes, fibrosis and heart health determined by blood tests) assessment by clinically indicated CMR. At the time of imaging, a single 5 ml blood sample will be required for measurement of the hematocrit, the latter will be used to perform post-hoc sophisticated analysis (such as T1 mapping) on the acquired MRI data sets for subclinical measures of cardiac dysfunction.

- Secondary: Cobalt and Chromium Ion level measurements in the blood as well as ultrasound of the hip to rule out soft tissue reaction.

Analyses:

Heart scan analyses:

We will generate pre-contrast and post-contrast T1 maps offline on an independent workstation. Following motion correction, we will compute T1 on pixel-by-pixel basis using non-linear curve fitting.[2] Given the linear relationship between gadolinium contrast concentration and T1, we can estimate the change in contrast-concentration between pre- and post-Gd using the corresponding T1 maps. We can then estimate extracellular volume (ECV) from the difference between [Gd-DTPA] in the myocardium relative to the LV blood pool, calibrating for the hematocrit as follows: (5)

$$ECV = 1 - hematocrit \frac{\frac{1}{T1_{myopost}} - \frac{1}{T1_{myopre}}}{\frac{1}{T1_{bloodpost}} - \frac{1}{T1_{bloodpre}}}$$

We will determine the mean ECV for both LV and RV.

Finally, the phase contrast images of the aorta and main pulmonary artery will be analyzed to calculate flow, velocities, stroke volume and cardiac output.

Further Analyses: With the MRI results they will be compared to the Control Group to investigate how both unilateral and bilateral metal on metal implants may impact heart function in these patients. Significance will be set to P=0.05 for all findings.

Risks/Benefits: Standard of care in this situation would involve a standard cardiac MRI. In this case the patient will undergo 10 to 15 minutes more of scanning time to capture required images for analysis, as well as have a single 5mL vial of blood collected. Blood sample will be collected by certified staff.

- Risks: As the scan will only be 10 to 15 minutes longer than the typical cardiac MRI patients may experience minor discomfort due to laying still for this small extension during the scanning process. They may also experience mild pain, bruising, or infection at the site where blood is drawn.

- Benefits: Patients will not receive any direct benefit from their participation in this study. Their participation may allow the researchers to have a better understanding of how Metal on Metal Prostheses affect heart function, which may benefit future patients.

Patients may withdraw from the study at any time without any impact on their current or future care at this institution.

Patients are not waiving any legal rights by agreeing to participate in this study. The study doctor and the Ottawa Hospital still have their legal and professional responsibilities.

References:

1. Kim, P. R., Beaulé, P. E., Dunbar, M., Lee, J. K., Birkett, N., Turner, M. C., ... & Krewski, D. (2011). Cobalt and chromium levels in blood and urine following hip resurfacing arthroplasty with the Conserve Plus implant. *The Journal of Bone & Joint Surgery*, *93*(Supplement 2), 107-117.
2. Pahuta, M. A., Smolders, J. M., van Susante, J. L., Peck, J., Kim, P. R., Beaulé, P. E. (In progress). Metal ion levels are not a useful test for failed metal-on-metal hip implants: a systematic review and meta-analysis
3. Moon, J. C., D. R. Messroghli, et al. (2013). "Myocardial T1 mapping and extracellular volume quantification: a Society for Cardiovascular Magnetic Resonance (SCMR) and CMR Working Group of the European Society of Cardiology consensus statement." Journal of cardiovascular magnetic resonance : official journal of the Society for Cardiovascular Magnetic Resonance **15**(1): 92
4. Messroghli DR, Greiser A, Frohlich M, Dietz R, Schulz-Menger J. Optimization and validation of a fully-integrated pulse sequence for modified look-locker inversion-recovery (MOLLI) T1 mapping of the heart. Journal of Magnetic Resonance Imaging 2007;26(4):1081–6.
5. Diesbourg LD, Prato FS, Wisenberg G, et al. Quantification of myocardial blood flow and extracellular volumes using a bolus injection of Gd-DTPA: kinetic modeling in canine ischemic disease. Magn Reson Med. 1992;23(2):239–253.