

**Cardiac function and metabolism in young adults born premature
(PET/MRI)**

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Title: Cardiac function and metabolism in young adults born premature**PI:** Kara Goss, MD**Protocol version date:** V7 04/23/2019**Project Summary**

Adults born prematurely have evidence of cardiac dysfunction and pulmonary vascular disease. In preclinical models, this cardiac dysfunction has been associated with shifts in cardiac metabolic preferences/substrate utilization as well as mitochondrial dysfunction. The purpose of this study is to determine the effects of premature birth on cardiac function, cardiac metabolism, and oxidative stress in a cohort of young adults born prematurely using cardiac positron emission tomography/magnetic resonance imaging (PET/MRI) and mitochondrial respiration studies.

Background and Significance

Preterm births are steadily increasing in the United States, accounting for up to 12% of deliveries.¹ As our ability to care for premature infants improves, the number reaching adulthood is also rising. Unfortunately, the mechanical ventilation and supplemental oxygen often required to sustain life following extreme preterm birth can also disrupt normal lung development, resulting in simplified distal airspaces, reduced pulmonary vascular surface area, and ultimately chronic lung impairment and the clinical entity of bronchopulmonary dysplasia, or BPD.²⁻⁵ Premature infants, especially those with BPD, are at increased risk for developing pulmonary hypertension (PH) and right ventricular (RV) dysfunction in the postnatal period, with up to 1 in 6 extremely preterm infants affected.⁶⁻⁸ However, although many of these changes may be reversible, the long-term effects of premature lung disease on the pulmonary vasculature and RV are poorly understood. Even though the majority of premature infants with persistent lung disease have only mild pulmonary function abnormalities in adulthood, increasing evidence suggests that the heart and pulmonary vasculature may be primed for later malfunction.⁹⁻¹¹ For example, Lewandowski et al recently demonstrated that young adults born premature exhibit structural RV abnormalities and dysfunction more than two decades after the initial insult, though this was not coupled with an assessment of severity of pulmonary vascular disease.¹⁰ In addition, Sartori et al demonstrated that young adults with a history of persistent PH of the newborn develop significantly more hypoxic pulmonary vasoconstriction when taken to altitude than aged-matched healthy controls, suggesting a persistent perinatal imprinting on hypoxic pulmonary vasoconstrictor responses later in life.¹² While these studies demonstrate that perinatal vascular insults do affect RV and pulmonary vascular function later in life, the mechanisms of these alterations are unknown. Our work has previously identified metabolic and functional adaptations in preclinical models of premature birth, and this study seeks to define these metabolic and functional cardiac changes in a cohort of adults born premature.

The purpose of this study is to determine the effects of premature birth on cardiac function, cardiac metabolism, and oxidative stress in a cohort of young adults born prematurely using cardiac PET/MRI, mitochondrial respiration studies, and analyses of blood biomarkers of heart failure and pulmonary vascular disease. Chronic RV pressure overload is accompanied by alterations in energy metabolism, with the heart shifting from a predominance of fatty acid metabolism to increased glycolysis and uncoupling of glycolysis from glucose oxidation.^{13,14} Such shifts in substrate utilization are detectable by novel imaging modalities such as cardiac PET imaging.^{13,15-17} Interestingly, increased glucose utilization has also previously been demonstrated in RVs from patients with PH secondary to congenital heart disease, or Eisenmenger's syndrome, and may reflect an early postnatal cardiac priming event.¹⁸ A similar increase in glucose utilization in formerly preterm young adults has not previously been demonstrated, but may help explain their improved tolerance to hypoxic exercise and the more adapted RV phenotype noted in our animal studies.¹⁹⁻²¹ The University of Wisconsin has recently acquired a GE Signa PET/MR System, housed in the Wisconsin Institute for Medical Research PET Imaging Center, allowing for

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simultaneous image acquisition with excellent PET sensitivity (3x higher sensitivity than conventional PET scanners on campus) and colocation of MR and PET images. This system will allow us to assess dynamic glucose uptake in a unique cohort of formerly premature young adults followed here at UW. Correlation of PET imaging in this cohort with MRI acquired measures of cardiac function will allow for assessment of metabolic efficiency. Furthermore, given that both our animal data and previous exercise studies show the most significant changes during hypoxia exposure, we will use hypoxic scanning conditions to accentuate differences in substrate utilization in formerly preterm young adults. Cardiac glucose utilization has previously been shown to acutely increase as much as 70% during hypoxia exposure in humans, despite unchanged glucose uptake in other tissues,²² and thus will serve as an appropriate myocardial stressor. We anticipate identifying an enhanced 'glycolytic reserve' in formerly preterm young adults, thus helping to explain their improved tolerance to hypoxic conditions.

Specific Aims/Objectives

Specific Aim 1: Identify alterations in cardiac metabolic substrate utilization and metabolic efficiency in formerly premature young adult human subjects using a rest (normoxia)-stress (hypoxia) protocol.

- SA1a: To demonstrate enhanced cardiac glucose uptake in adults born premature utilizing 18F-fluorodeoxyglucose (FDG) PET-MRI.
- SA1b: To correlate dynamic glucose uptake by positron emission tomography (PET) imaging with RV structural and functional measurements by cardiac MRI, providing a measure of metabolic efficiency.
- SA1c: Assess whether blood biomarkers (i.e. proteins) of heart failure and pulmonary vascular disease differ between adults born preterm and term.

Rationale: Formerly preterm young adults exhibit improved tolerance to hypoxic exercise, a phenomenon that exemplifies the relevance of our animal studies. Since increased glucose utilization has previously been demonstrated in RVs from patients with PH secondary to congenital heart disease, considered a protective early postnatal priming event, we propose that such an increase in glucose uptake will also be present in formerly preterm young adults, thus allowing for a more adaptive RV phenotype upon hypoxic RV stress.

Specific Aim 2: Assess the baseline and stressed bioenergetic health index in circulating monocytes from term-born and preterm-born adults as a measure of global oxidative stress.

Rationale: We hypothesize that young adults born premature have persistent chronic oxidative stress as a result of premature birth that predisposes them to the development of adult cardiovascular and metabolic disease. Isolated circulating monocytes from adults born prematurely and controls will be assessed for evidence of mitochondrial dysfunction using the Seahorse XF Flux Analyzer. Urine will also be collected and stored to assess later for markers of oxidative stress.

Research Design and Methods:Overall Design:

This prospective study will enroll 66 subjects and will include completion of 1 research visit. This study visit will include review of eligibility, consent, baseline screening labs (fasting glucose and

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pregnancy testing if applicable), followed by pulmonary function testing, lab draw for monocyte isolation studies (Aim 2) and biobanking (blood and urine) for future study. Next, subjects will undergo a PET/MRI imaging study as described below.

Subject population:

Preterm subjects (n=44) will be recruited from the general public or the Newborn Lung Project (NLP), a prospectively followed cohort of 265 subjects initially enrolled between 1989 and 1991 from neonatal intensive care units within Wisconsin and Iowa. This cohort is unique to the University of Wisconsin, and has been well studied over the past two decades by the Eldridge laboratory and collaborators.^{19,23} Subjects recruited from the general public will have gestation age of ≤ 32 weeks OR a birth weight $\leq 3\text{lb } 5\text{oz}$ if born premature. All NLP infants were born with very low birth weight, or $<1500\text{ g}$, and gestational age <36 weeks. Subjects who have previously expressed interest in participating in future NLP studies during IRB 2009-0212 or IRB 2013-1523 will be recruited. NLP subjects may also be recruited from the NLP Registry database (IRB 2018-0402). Non-NLP subjects aged 18-35 with birth weight $<1500\text{ g}$ OR gestational age of 32 weeks or less. Birth history for non-NLP subjects will be confirmed by hospital records.

Healthy, term-born age-matched controls (n=22) will be recruited from the general public. Preterm and control subjects recruited from the general public will be 18-35 years of age. Both groups (preterm and control) will undergo all portions of the described study.

Eligibility and Exclusion Criteria:

Subjects with known metabolic disorders that would affect FDG uptake (i.e. diabetes) or contraindications to PET/MR imaging (i.e. pregnancy, claustrophobia, implanted devices) will be excluded. Subjects with a personal history of type I or II diabetes will be excluded. Control subjects may not have a personal history of known cardiovascular or pulmonary disease.

Subject Identification and Recruitment:

Some preterm subjects will be former participants in Newborn Lung Project cohort. The Newborn Lung Project (IRB 1997-152) (NLP; Mari Palta Ph.D., Director) is a multicenter population-based cohort study of infants with birth weight of $\leq 1500\text{g}$ who were born between 08/01/1988 and 06/30/1991 and admitted regional to Neonatal Intensive Care Units (NICUs) in Wisconsin and Iowa.

Preterm subjects who have previously participated in research in the Eldridge laboratory (IRB 2009-0212 and 2013-1523) and who have previously given consent for contact will be recruited for participation. We have mailing addresses, email addresses, and phone numbers for these members of the NLP cohort. NLP subjects may also be recruited from the NLP Registry database (IRB 2018-0402).

Using contact information provided by the subjects for re-contact, potential subjects from the NLP cohort will receive a recruitment email, letter, or phone call, asking if they would like to be part of the study. Subjects will not be contacted more than 3 times total by any single method if we don't receive a response. Messages left on phones will not include health information. If the subject is not reached, the message will give our contact information for them to call back.

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Recruitment of preterm subjects who are not a part of the NLP cohort will be done via internet posting such as at the Jobcenter and Craigslist Madison, or by a mass UW email. Interested individuals will contact the study coordinator.

Recruitment of healthy controls will be done through internet posting such as at the Jobcenter and Craigslist Madison, by a mass UW email, or via flyers announcing the study posted at UW or UW clinics. Interested individuals will contact the study coordinator.

Consent:

Oral consent will be obtained as part of the phone screening process and will include consent for a pre-visit fast and other pre-visit restrictions on diet and exercise described below under "Research Procedures." Consent forms will be sent to subjects by mail or email for review prior to meeting with research staff. Oral consent for use of email for communications will also be obtained, where applicable, prior to use of email for delivery of consent forms.

Preterm subjects that are not NLP registered will provide additional authorization for the release of their neonatal records (from birth hospitals). These records will be used to confirm gestational ages and birth weights. We will also review any major diagnoses from newborn hospital stays, typically found in admission notes or discharge summaries. This may include prenatal characteristics, pregnancy complications, maternal conditions that can affect pregnancy outcomes, including use of alcohol and tobacco during pregnancy, birth characteristics, and postnatal medical care. If the neonatal records indicate subject eligibility (based on confirmation of gestational age and birth weight), we will store the neonatal information in a password-protected database or locked file cabinets. If the neonatal records indicate ineligibility, we will contact the subjects and destroy all information collected from the records.

The written consent process will occur prior to the administration of any research procedures. Potential subjects will meet with a study team member to review the information in the consent form including study procedures, risks associated with participation, alternatives to participation and whom to contact for additional information. Any questions will be addressed prior to the start of any research procedures and all subjects will be reminded that participation is optional, and they can change their mind at any time.

Research Procedures:

After initial recruitment contact, subjects will be screened for eligibility. Those with a history known metabolic disorders that would affect FDG uptake (i.e. diabetes) or contraindications to PET/MR imaging (i.e. pregnancy, claustrophobia, implanted devices) will be excluded. Subjects with a personal history of type I or II diabetes will be excluded. Control subjects may not have a personal history of known cardiovascular or pulmonary disease. Eligible subjects will be asked to provide oral consent as part of phone screening for a pre-visit fast. Subjects completing initial eligibility screens will be asked to fast overnight (or a minimum of 8 hours) prior to arrival for their study visit. To ensure best PET radiotracer uptake, subjects will also be provided the following instructions: A complete fast is required, including candy/gum. Only water is permitted (and encouraged); flavored water is not allowed. No caffeine, alcohol, or nicotine for 12 hr prior to scan. A high protein, low carbohydrate diet the day prior to imaging is strongly encouraged. Strenuous activity (including but not limited to jogging, cycling, weight lifting, yard work, sexual activity) should be avoided for 24 hr prior to imaging.

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After informed consent is obtained, subjects will undergo baseline screening labs (fasting glucose and pregnancy testing if applicable) to confirm subject eligibility. Questionnaires, health history, and anthropometric data will be collected. Pulmonary function testing and baseline electrocardiogram (EKG) will be completed to characterize the cohort. Two venous catheters will be placed, one to be used for FDG infusion and a second to be used for blood draws. Blood will be drawn for monocyte isolation studies (Aim 2) and biobanking for future study. Urine will also be collected for biobanking for future study. Subjects will then undergo a PET/MRI imaging study as described below, including a rest-stress (hypoxia) protocol.

PET-MRI Imaging: The subject will be escorted to the GE Discovery 750W 3T MR scanner containing the PET insert, located in the basement level of WIMR Tower 1, where they will undergo simultaneous cardiac PET/MR scanning. 3.7 MBq/kg (with a maximum 10 mCi dose) of ^{18}F -fluorodeoxyglucose (FDG) will be administered intravenously at a constant infusion rate of 0.01ml/s – 0.05ml/s in a large-bore indwelling catheter in the arm (preferably in an antecubital vein) by a nuclear medicine technologist. The continuous infusion will be maintained by a Medrad® Spectra Solaris syringe pump. The injection site will be inspected by the technologist to assess for any possible infiltration. Simultaneous PET/MR scanning will be conducted during ^{18}F -FDG administration.

After a period of obtaining baseline resting normoxic images (10-20 minutes of scanning time), the subject will breathe hypoxic gas (FiO_2 0.12) through a low-resistance two-way non-rebreathing mouthpiece for the remainder of the scan (total duration of scan estimated at 60-90 minutes, with a maxi of 120 minutes, and hypoxic portion estimated at 40-45 minutes, with a max of 60 minutes) to enhance glucose uptake, similar to what has previously been described by Chen and colleagues.²²

Heart rate, oxygen saturation, and blood pressure will be monitored periodically during MRI scanning, and approximately every 10 minutes during PET scanning. Oxygen saturations and heart rate will be monitored throughout the study, and hypoxic challenge terminated early (transitioned to normoxia) in the event the subject experiences sustained oxygen saturations <75% or heart rate sustained above 100 beats per minute associated with symptoms of dyspnea, chest pain, or palpitations. Decisions to terminate the study altogether will be made by the PI (Kara Goss) or other qualified research personnel (MD or RN). A qualified research team member will be present for scans. When an MD is not physically present in the imaging suite, a physician will be available by phone/pager for all studies and able to physically respond if needed. Given that the Eldridge lab has previously conducted exercise testing in similar degrees of hypoxia in this population, we anticipate this degree of hypoxia during rest will be well tolerated.¹⁹ Serum glucose and lactate levels, as an indicator of increase in anaerobic metabolism and lactic acidosis, and thereby suggesting decreased glucose oxidation, as well as serum for FDG activity level, will be obtained approximately every 10 minutes during PET scanning.²²

All PET imaging data will be corrected for scatter and measured photon attenuation. PET data will be collected in list mode enabling flexible retrospective reconstruction of images. Images will be reconstructed in six 10-minute images and exported for offline analysis with Mirada (Mirada Medical, Oxford, UK). Regions of interest (ROIs) will be manually drawn over the RV and left ventricle (LV) (apical, mid-ventricular, and basal short axis slices) and standardized uptake value (SUV) determined to quantify ^{18}F -FDG uptake. Endpoints assessed will include the mean and

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maximal SUV within RV and LV, and ratio of RV:LV ^{18}F -FDG uptake (previously correlated with RV function²⁴) for each of the six PET images.

EKG and respiratory gated cardiac MRI will be performed simultaneously with PET imaging, allowing for colocation of cardiac structures with ^{18}F -FDG uptake. RV and LV function will be evaluated using an EKG-gated, balanced steady-state free precession (SSFP) technique. Axial SSFP images will be acquired through the entire heart to minimize inter-observer and intra-observer variability.²⁵ Conventional short axis, 2-chamber, 3-chamber, and 4-chamber views will also be acquired, in accordance with standard clinical cardiac exam. Parameters for the SSFP images will be individually adapted to each participant's individual anatomy while optimizing image quality. In addition to a standard clinical cardiac exam, research sequences will include but not limited to: PC VIPR, SMART T1 map, 3D KAT-Arc Cine to provide detailed assessments of flow, T1, and cardiac functional morphology that are not routinely acquired in conventional clinical exams.

All PET/MRI hardware is FDA approved. Most software is FDA approved and used routinely in clinical care. Investigational MRI software developed by UW or GE Healthcare will be used for this research. The novel software will continue to meet the criteria for classification as Non-Significant Risk by FDA guidelines outlined in 21 CFR 812.3. Specifically:

1. It is not intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject;
2. It is not purported or represented to be for use supporting or sustaining human life and presents a potential for serious risk to the health, safety or welfare of a subject;
3. It is not for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety or welfare of a subject; or
4. It does not otherwise present a potential for serious risk to the health, safety, or welfare of a subject.

Image analysis will be offline. Using MATLAB (The Mathworks, Natick, MA) custom software or similar for quantitative modeling and analysis, RV and LV wall thickness and mass will be manually determined offline. RV end diastolic and end systolic volumes will be determined by semi-automated detection with fine manual adjustment of cardiac borders, allowing for calculation of RV ejection fraction and stroke volume. Finally, the Tei Index, a measure RV function previously correlated with glucose uptake in patients with PH, will be calculated as the isovolumetric contraction time plus isovolumetric relaxation time divided by the total ejection time.²⁶ Cardiac metabolic efficiency will be assessed as both a ratio of maximal SUV uptake to cardiac output and of maximal SUV uptake to Tei index.

Pulmonary function testing: Subjects will undergo non-invasive pulmonary function testing including spirometry, plethysmography (for lung volumes) and diffusion capacity, according to standard clinical testing. All procedures are performed according to standard clinical practice and all devices are non-investigational.

EKG: Subjects will undergo non-invasive EKG. Procedure is performed according to standard clinical practice and all devices are non-investigational. EKG will be reviewed by study personnel prior to imaging. Any subject not in a sinus rhythm will be excluded from imaging (sinus arrhythmia allowed), as hypoxia could exacerbate arrhythmias. Such findings will be discussed with the study participant immediately.

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Venous cannulation: Two intravenous (IV) lines will be placed by qualified study personnel. Blood for biobanking and monocyte studies will be collected at this time, typically during placement of one of the IV lines. Lidocaine may be administered as a local anesthetic. One IV will be used for FDG infusion, and the second used for initial laboratory draw as well as serial labs during the imaging scan. Alternatively, blood samples may be collected by finger stick or venipuncture (inserting a needle into a vein without a catheter). During the imaging scan, we will collect 0.5 – 2 ml blood every 10 minutes. Blood samples will be centrifuged to obtain plasma, and aliquot in a gamma counter calibrated to the PET scanner to measure activity during the experiment. We will also perform lactate and glucose assessment every 10 minutes during the study. The purpose of lactate measurements is to account for changes in lactate which is a measure of anaerobic metabolism during hypoxia. Entire amount of blood drawn will not exceed 80 ml.

Health questionnaires: The subjects will answers health questionnaires, a Pre-Session Questionnaire and Symptom Questionnaire.

Medical records: General information regarding birth history will be asked of all subjects (i.e. gestational age, birth weight). For adults born premature, additional birth history will be collected from Newborn Lung Project medical records or birth hospitals. This information will include prenatal characteristics (including but not limited to: maternal age, demographics, gravidity, comorbidities such as diabetes, hypertension, asthma, tobacco use, alcohol use, antenatal steroid use), birth and postnatal characteristics (including but not limited to: gestational age, anthropometric data, delivery type, and data regarding neonatal comorbidities such as bronchopulmonary dysplasia, intracardiac shunts, sepsis, respiratory failure, nutrition), and childhood characteristics (including but not limited to: anthropometric data, history of early wheezing, cigarette exposure, treatment for respiratory illnesses such as bronchopulmonary dysplasia and asthma, and serial pulmonary function testing).

Compensation:

\$100 for completion of study visit. Parking validation and travel expenses (ie mileage) will be provided for research subjects. Compensation may be prorated at \$20/hr if a subject is unable to complete the visit.

Risks:

Hypoxia exposure: Hypoxia exposure carries the risk of chest discomfort, shortness of breath, arrhythmia (irregular heartbeat), nausea, headache and fatigue. Symptoms, if present, are typically mild with the degree of hypoxia used in this study (similar to traveling to an altitude of 14,000 feet, or Pikes Peak), and resolve after return to normal oxygen conditions. If for any reason, subjects feel they are unable to complete the hypoxia exposure, they will be instructed to notify a study team member.

Lidocaine Administration: Risk associated with the administration of lidocaine when used as a local anesthetic is a local allergic reaction.

Venipuncture: Risks associated with venipuncture are limited to slight pain, bleeding, bruising, and swelling at the puncture site. Some subjects may feel lightheaded during the procedure.

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IV catheter placement: may cause pain, bruising, fainting or infection.

Fasting: Risks associated with an overnight fast (minimum 8 hour) fast are minimal. Subjects may feel weak, lightheaded, or lethargic. Those accustomed to drinking caffeinated beverages may experience a headache during this time frame. Subjects will be encouraged to drink plenty of water during this time and, if for any reason, they feel they are unable to complete the fast, they will be instructed to stop and contact a study team member.

MRI: The standard risks associated MRI involve persons with certain metallic implants and devices (eg. pacemakers), and claustrophobia. Those patients eligible for study participation will be screened for contraindicated metallic foreign bodies and claustrophobia using standard clinical exclusionary procedures on our MRI safety screening form. No gadolinium will be administered, which eliminates the concern of contrast induced reactions.

PET: Risks associated with PET imaging result primarily from the radiation dose from the radiopharmaceutical. For this research study, approximately 10 mCi of 18F-FDG will be administered intravenously which is also the standard dose used for clinical studies. This dose corresponds to a whole-body effective dose equivalent of 10 mSv. For context, the average person in the United States receives an estimated effective dose of about 3 mSv per year from naturally occurring radioactive materials, such as radon and radiation from outer space, and the federally-regulated annual occupational dose limit for an adult, non-pregnant radiation worker is 50 mSv.

Pulmonary function testing: Risks associated with the pulmonary function testing include shortness of breath, dizziness, and cough. If they occur, they are expected to resolve after completion of testing.

EKG: Risks associated with EKG include discomfort or contact dermatitis from the adhesive used to adhere the leads.

Questionnaires: Risks associated with questionnaires include subject fatigue and feeling uncomfortable.

Rare but serious risks:

With placement of the IV catheter for FDG injection, there is a rare risk (less than 1 out of 100 people) of bleeding, or infection associated with placement of the plastic tube in the vein.

High levels of radiation exposure may cause secondary cancers.

Electronic implants, such as cardiac pacemakers, may be susceptible to interference from the magnetic and RF fields produced by the MR system. This interference may destroy or negatively affect operation of these devices.

The magnetic field of the MR system exerts a force on ferromagnetic objects within the field. This force can cause a ferromagnetic implant, such as an aneurysm clip, surgical clip, or prosthesis, to move or be displaced and cause injury or death. If the implant is large, sufficient currents can be induced in the metal by the magnetic field (eddy currents are induced by pulsed gradient fields) to cause heating of the implant.

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It is possible that subtle genetic or molecular changes could be caused by the magnetic fields produced by the MR system. To date, however, no harmful biological effects have been demonstrated at the magnetic field strengths and exposure times utilized by the MR system. At the present time, the likelihood of any significant biomagnetic effect is considered to be very low.

The magnetic field near the MR system is strong enough to attract ferromagnetic objects with great force. Near the magnet this force can be strong enough to pull objects in and cause them to fly down the axis of the magnet. Such objects become projectiles that can cause injury or death.

FDG: Hypersensitivity reactions with pruritus, edema and rash have been reported in the post-marketing setting.

Potential benefits

There will be no personal benefit to the research subject. This study seeks to characterize the cardiac and metabolic function of young adults born preterm. Currently, the long-term risks following premature birth are poorly understood. An improved understanding at the molecular and substrate level could transform our understanding of cardiovascular disease after premature birth, from which preventive and therapeutic approaches can be devised.

Incidental Findings:

Testing that excludes a subject from study participation (i.e. fasting glucose consistent with diabetes diagnosis [126 or higher], positive pregnancy test) will be disclosed. EKG and pulmonary function testing will be reviewed by the study team, and any potentially clinically significant abnormal findings will be discussed with subjects by a qualified RN or MD on the study team.

Results from laboratory testing and PET/MR imaging will not be disclosed to subjects, as imaging will not be formally reviewed by a board-certified radiologist. Not all of the sample testing will be done by a CLIA approved clinical lab and those that will likely will not be available until after subjects have completed participation.

Privacy and Confidentiality

There is a risk of breach of confidentiality. In order to protect against this risk, all data will be stored on a secure, password protected network. All data will be identified using unique identification numbers, not names, date of birth, or other identifiable information. In files where identifiable information is linked to the unique ID number, only staff members who specifically use this information for contacting participants, etc. will have access. All PET/MR scans performed for research purposes only will be given a unique study number that cannot be linked to the patients' hospital medical records in any way. PET/MR research images will be stored on PACS (Picture Archiving and Communication System) under this study number only. Study data will be managed by the PI and co-investigators.

Data and Safety Monitoring Plan

The procedures administered for this research will be done in a manner that is consistent with clinical care. Therefore, an internal monitoring plan that includes the PI and all co-investigators will be implemented. Study team members will meet at least quarterly to discuss study progress including enrollment and data acquisition. Adverse events, if applicable, will be discussed at the

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time of occurrence. In the event any unanticipated problems occur during the course of this research, they will be reported to the IRB in accordance with posted policies.

Adverse Event Reporting

Ethical Considerations:

1. This study will be conducted in compliance with current Good Clinical Practice of the International Conference on Harmonization and the ethical principles of the Declaration of Helsinki. The study will begin only after the UW Health Sciences Institutional Review Board (IRB) has granted approval.
2. The UW IRB approved consent form will state that subjects may withdraw from this study at any time without any change in the quality of their medical care or loss of benefits.
3. Each subject is required to sign a HIPAA Research Authorization at the time of consent. This authorization clearly outlines who will have access to specified protected health information. The information obtained in these studies is not particularly sensitive. However, data will be coded by subject identification numbers and any key linking this code number to subject identifiers will have access limited to the investigator and key study personnel all of whom have had HIPAA training required by the University of Wisconsin. Data will be stored in files and a computer database, both in a locked location with access only by study personnel. Data obtained from the study may be published in scientific journals or presented in scientific meetings, but results will be coded so individuals are not identified. Records will be retained by the Principal Investigator in compliance with UW institutional policy.

Statistical Analysis and Power Calculations:

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The primary endpoints are (1) PET glucose uptake during normoxic rest and (2) the change in glucose uptake from normoxia to hypoxia, or substrate flexibility. Our prior pilot study (n=10) using the same PET/MRI rest-stress (hypoxia) protocol in swine demonstrated a myocardium to blood pool time activity curve slope of 0.0017 ± 0.0007 during normoxic rest, increasing to 0.0033 ± 0.0007 during hypoxia exposure. We assume similar values for control subjects and estimate at least a 30% increase in normoxic resting glucose utilization in young adults born premature. Thus, with a 2:1 enrollment strategy and an overall type I error of 0.05 and power of 0.8, we will need a study size of 44 preterm and 22 term subjects.

For the monocyte metabolism studies, oxidative stress has not previously been measured in a cohort of preterm born young adults, limiting the ability to conduct a true power analysis. However, studies of similar measures of bioenergetic health in cardiovascular disease, autism, Alzheimer's disease, and fibromyalgia have included 8-20 subjects per group.^{28,29} Since the proposed studies will be paired with PET-MRI imaging, we propose completing the mitochondrial

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analysis on all subjects enrolled for PET-MRI imaging with an interim assessment for true power calculations.

Pulmonary function, cardiac function, PET, and mitochondrial respiration measures will be summarized as means \pm standard error. A two-sample t test will be used to compare between control and preterm cohorts. For PET-MRI measures taken during both rest (normoxia) and stress (hypoxia), we will use a repeated measures model to analyze outcomes, examining differences between both groups and exposures. All p values will be two-sided, with $p < 0.05$ used to define statistical significance.

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