Long-term effects of intrauterine growth restriction on cardiac metabolism and susceptibility to ischaemia/reperfusion

Christian F. Rueda-Clausen, Jude S. Morton, Gary D. Lopaschuk, and Sandra T. Davidge

Department of Physiology, University of Alberta, Edmonton, Canada; Women and Children’s Health Research Institute (WCHRI), University of Alberta, Edmonton, Canada; Cardiovascular Research Centre, University of Alberta, Edmonton, Canada; Mazankowski Alberta Heart Institute, University of Alberta, Edmonton, Canada; and Department of Obstetrics and Gynecology, University of Alberta, 220 HMRC, Edmonton, AB, Canada T6G 2S2

Aims
Adult offspring who are born intrauterine growth restricted (IUGR) are at risk of developing cardiovascular diseases during adulthood. Additionally, several cardiac diseases are associated with changes in myocardial energy metabolism. However, the potential long-term effects of being born IUGR on cardiac energetics are unknown. The aim of this study was to assess the long-term effect of IUGR on cardiac performance and energy metabolism under aerobic conditions and after ischaemia/reperfusion (IR) injury.

Methods and results
To induce IUGR, pregnant Sprague-Dawley rats were randomly assigned to hypoxic (11.5% O₂) or control (21% O₂) environments from day 15 to 21 of pregnancy. Cardiac susceptibility to IR was evaluated in male and female offspring at 4 (young-adult) or 12 (ageing) months of age using isolated working hearts. Cardiac production of energy was evaluated using radiolabelled substrates. Both male and female IUGR offspring exhibited an increased susceptibility to IR injury compared with controls (P < 0.05) as well as an increased post-ischaemic production of protons (P < 0.001) secondary to a mismatch between myocardial glycolysis and glucose oxidation rates. Moreover, offspring born IUGR exhibited an increased myocardial production of acetyl-CoA during reperfusion. The mismatch between energy production and cardiac performance indicates that in IUGR offspring, cardiac efficiency during reperfusion was decreased relative to controls.

Conclusion
Our results suggest that hypoxia-induced IUGR has long-term effects on cardiac susceptibility to IR injury that are independent of sex and age. Moreover, we identified a mismatch in glucose metabolism, leading to proton accumulation in the post-ischaemic myocardium of offspring born IUGR as a potential mechanism involved.

Keywords
Foetal programming, Cardiac metabolism, Ischaemia, Long-term effects

1. Introduction
Many pregnancy complications lead to intrauterine growth restriction (IUGR) and consequently to low birth weight. This constitutes the most common pathological condition diagnosed during pregnancy, affecting over 15% of all pregnancies in the USA and up to 32% of pregnancies in some developing countries. Beyond the well-described association between low birth weight and higher perinatal morbidity and mortality, several epidemiological studies suggest that babies born small are more susceptible to develop cardiovascular disease later in life. This interesting association is supported by a growing body of evidence and constitutes the foundation for the ‘foetal programming’ theory, which postulates that foetal exposure to suboptimal environmental conditions can cause permanent changes in the structure and function of key organs predisposing the development of chronic conditions later in life.

Pregnancy complications leading to IUGR have a number of aetiologies. However, in most instances, foetal growth is ultimately limited by a reduction of oxygen and nutrient delivery. Foetuses have alternative mechanisms to compensate for an acute nutritional
and may outweigh the benefits of the ATP produced from glycolysis. Using an animal model of hypoxia-induced IUGR, we have previously shown (ex vivo) that young-adult IUGR offspring exhibit changes in cardiac structure and function from early adulthood; including an increased expression of collagen type I, altered β/α myosin heavy chain ratio (β/αMHC), a decreased expression of matrix metalloproteinase 2, and an increased susceptibility to myocardial ischaemia/reperfusion (IR) injury.

The heart is an organ with high-energy requirements that depends on its ability to continuously produce large amounts of adenosine triphosphate (ATP) to guarantee its proper function and viability. Under aerobic conditions, the main pathways used by the heart to produce ATP include the oxidative phosphorylation of pyruvate, fatty acids, and lactate and, on a smaller scale, glycolysis. When oxygen availability is reduced, the oxidative phosphorylation capacity is limited and glycolysis takes over to maintain a modest production of ATP that partially compensates for the energy-depleted myocardium. However, a sustained increase in the glycolytic rate in the presence of a reduced pyruvate oxidation capacity (glucose metabolism uncoupling) results in the accumulation of other metabolites such as protons (H⁺), lactate, and sugar phosphates. The production of those by-products can adversely affect cardiac energetic efficiency and may outweigh the benefits of the ATP produced from glycolysis.

The pathways that govern energy substrate selection in the myocardium are known to be key elements, affecting glucose metabolism coupling, cardiac aerobic performance, and cardiac tolerance to IR injury. In fact, it has been demonstrated that interventions modulating cardiac selection of energy substrates can have a beneficial impact by improving cardiac function in a failing heart and cardiac function recovery after ischaemic challenges.

Interestingly, some conditions that have been previously described in our animal model of IUGR, such as ventricular hypertrophy and diastolic dysfunction, are known to be associated with changes in myocardial energy substrate selection. However, the potential long-term effects of IUGR on cardiac energy metabolism are not known. On the basis of these previous findings, we hypothesized that hypoxia-induced IUGR leads to long-term impairment of cardiac energy metabolism that prevents the effective recovery of the heart from IR injury.

In addition, our previous results also suggest that being born IUGR may accelerate the normal ageing process, in terms of cardiovascular function. Consequently, one of the secondary objectives of this study was to evaluate the interaction of these two factors (hypoxia-induced IUGR and ageing) in the development of an undesirable cardiac phenotype. Moreover, and despite well-described differences between males and females in the pathophysiology of chronic cardiovascular diseases, most studies of cardiac function in this field have been conducted only in male animals. Potential sex differences in this condition remain to be explored and, therefore, have been incorporated into our experimental design. Finally, clinical models of pregnancy at high altitude have previously described that a healthy placenta is capable of adapting when exposed to low oxygen concentrations and is able to ameliorate the effects on foetal development by increasing its functional capacity for gaseous exchange. Therefore, a question that has been raised regarding our model of IUGR, and one of the secondary objectives of this study, was to determine whether the maternal hypoxic insult that we are using does in fact limit oxygen availability to the foetuses.

2. Methods

2.1 IUGR animal model

Female Sprague–Dawley rats were obtained and mated within the Health Science Laboratory Animal Facility at the University of Alberta. On day 15 of pregnancy, rats were randomized to continue in either normal environmental conditions (Control; O₂ 21%; n = 11) or hypoxia (IUGR; O₂ 11.5%; n = 10) during the last 6 days of pregnancy (term 21d). At birth, litters were reduced to eight pups (four males and four females), and 3 weeks later, the offspring were weaned and housed under standard conditions in the animal facilities of the University of Alberta until experimental procedures were performed.

2.2 Assessment of foetal hypoxia and foetal growth restriction

To determine whether the maternal hypoxic insult that we used was compensated for by placental adaptation, we directly evaluated the hypoxic status of the foetuses. For this purpose, a separate set of dams was allocated to the hypoxia (n = 4) or control (n = 4) group as described above and treated with an intraperitoneal (ip) injection of either pimonidazole HCl (60 mg/kg) or an equivalent volume of vehicle 12 h before the estimated time of delivery. After injection, pimonidazole distributes to all tissues and adducts to thiol-containing proteins only in those cells that have an oxygen concentration <14 mmol/L (equivalent to a partial oxygen pressure pO₂ = 10 mmHg at 37°C). Six hours after injection, dams were euthanized and foetuses and placentas were weighed and tissue levels of pimonidazole were then determined by immunostaining.

2.3 Isolated working heart preparation

Both male and female offspring were studied at 4 or 12 months of age. Under general anaesthesia (pentobarbital 60 mg/kg, ip), hearts were rapidly excised and the aortas were fixed to a cannula and perfused for 10 min from a retrograde Langendorff mode against a constant perfusion pressure of 60 mmHg. Then, the hearts were trimmed of excess tissue and the right atrium was cannulated. After stabilization, hearts were perfused in an anterograde working mode by clamping the aortic inflow line from the Langendorff reservoir and opening the left atrial inflow line in a closed, recirculating system filled with 120 mL of modified Krebs–Henseleit solution. After 10 min of equilibration, hearts were paced at 300 b.p.m. (4-month old) or 260 b.p.m. (12-month old). Pacing rates were selected based on preliminary studies, showing that the hearts from 12-month-old animals do not tolerate pacing at the same rates as hearts from younger rats. Both cardiac output and aortic flow were measured using in-line flow sensors (Transonic Systems, NY, USA). Cardiac power was defined as ([(peak systolic pressure, mmHg – maximal preload, mmHg) × cardiac output, mL/min × 0.13]/dry weight, g) (joules/min/g dry wt) and calculated as described previously. Measurements of cardiac function were carried out every 10 min during an 80 min protocol that included a 30 min period of stabilization (pre-ischaemic), 10 min of no-flow ischaemia and 40 min of reperfusion (reperfusion). The duration of the no-flow ischaemia insult was based on pilot data from our laboratory, indicating that in order to have recovery in the aged, IUGR offspring, the ischaemic insult could not be longer than 10 min. After perfusion, hearts were placed in dry gauze, rapidly...
weighed, frozen by immersion in liquid nitrogen, and stored at $-80^\circ$C (see Supplementary Methods for a detailed description of this technique).

### 2.4 Cardiac energy metabolism

Myocardial production of acetyl-CoA and ATP were calculated using a previously described and validated technique. Glycolysis rates were determined by adding $0.1 \mu$Ci/mL of D-[5-3H(N)] glucose to the buffer and measuring the change in the levels of $^3$H$_2$O released into the buffer. Rates of glucose oxidation were simultaneously determined by adding $0.1 \mu$Ci/mL of D-[U$^{14}$C] glucose to the buffer and measuring the amount of $^{14}$CO$_2$ that was either released as gas in the oxygenation chamber and contained in a hyamine hydroxide trap, or diluted in the buffer as bicarbonate and extracted from the samples. If 1 mol of glucose passes through glycolysis to lactate without subsequent oxidation by the tricarboxylic acid (TCA) cycle, a net production of 2 mol of H$^+$ occurs. Therefore, rates of H$^+$ production derived from incomplete metabolism of glucose were determined by the difference in the rates of glycolysis and glucose oxidation at any given point and were calculated by the equation: H$^+$ production = 2 × (glycolysis rate – glucose oxidation rate) and reported as $\mu$mol/g/min. In a different set of

![Figure 1](image-url)

**Figure 1** Effect of prenatal exposure to hypoxia from day 15 to 20.75 of gestation on (A) foetal body weight, (B) placental weight, and (C) placental to foetal weight ratio. Data obtained from 69 pups from eight litters [four IUGR and four controls] at G20.75d. *A value of $P < 0.05$ for the respective sources of variation (sex or prenatal intervention) using two-way ANOVA. † $P < 0.05$ vs. controls of the same sex after a Bonferroni post hoc test. (D) A representative image of both control and IUGR male foetuses at G20.75d. In a different set of animals, dams were injected with hypoxia-reactive dye (pimonidazole). Sections of (E) liver, (F) heart, and (G) placenta were obtained from male pups and analysed by immunohistochemistry (hypoxic tissue labelled with pimonidazole in green and DAPI nuclei in blue; $n \geq 3$); scale bars represent 30 $\mu$m. Each panel presents summary figures and representative images of control and IUGR offspring. ‡ $P < 0.001$ when compared with controls using an unpaired t-test.
experiments, fatty acid and lactate oxidation rates were measured by adding both 0.1 μCi/mL of [9,10-3H(N)] palmitic acid and 0.1 μCi/mL [14C-U] lactic acid to the buffer and measuring the production of both \(^{3}\)H\(_{2}\)O and \(^{14}\)CO\(_{2}\) as described above.

To calculate the amount of energy produced by the myocardium, it was assumed that each mol of glucose produces 2 mol of ATP when undergoing glycolysis, 1 mol of glucose undergoing glucose oxidation produced 2 mol of acetyl-CoA or 30.5 mol of ATP, one mol of palmitate undergoing oxidation produced 8 mol of acetyl-CoA or 105 mol of ATP, and 1 mol of lactate produced 1 mol acetyl-CoA or 15 mol of ATP.\(^{32}\) Cardiac efficiency was determined by dividing the amount of developed cardiac work by the estimated amount of acetyl-CoA produced at any given period of time and reported as joules/mmol/L of TCA acetyl-CoA × 10\(^{2}\).\(^{32}\)

2.5 Statistical analyses

Data are presented as mean ± standard error of the mean. Data obtained from male and female offspring were analysed separately. Differences between the two groups were tested using a t-test or Wilcoxon’s rank-sum test according to the data distribution. Two-way analysis of variance (ANOVA) and a Bonferroni post-test were then used when appropriate. A P value of <0.05 was considered statistically significant (see Supplementary Methods for a detailed description of statistical analyses).

3. Results

3.1 Effect of hypoxia on foetal growth

The weight and age of pregnant dams were comparable before the hypoxic insult (P = 0.8). There were also no differences in litter size (controls 17 ± 0.7 vs. IUGR 18 ± 0.7 pups, P = 0.7) or sex distribution (proportion of male offspring: controls 51% vs. IUGR 47%, P = 0.9) between the groups. As expected, foetal and placental weight were significantly smaller in both male and female IUGR pups compared with controls (Figure 1). Histological sections of placentas and foetal segments of the heart and liver prepared with pimonidazole demonstrated that pups born from dams exposed to hypoxia indeed resulted in a foetal hypoxic insult (Figure 1). Similar to our observations previously made in this model, the long-term effects of hypoxia-induced IUGR include decreased body weight and an

![Figure 2](image-url)

**Figure 2** Cardiac power development [(peak systolic pressure – max preload × cardiac output × 0.13)/dry weight] (joules/min/g dry wt) after stabilization (pre-ischaemia) and after 10 min of no-flow ischaemia (reperfusion) in (A) male and (B) female offspring from different experimental groups. (C and E) The average maximal cardiac power developed during the pre-ischaemia period by both male and female offspring, respectively. (D and F) The average maximal cardiac power developed during reperfusion by both male and female offspring, respectively. Values of n > 9 per group. *A value of P < 0.05 for the respective sources of variation (age or prenatal intervention) using two-way ANOVA. †P < 0.05 vs. controls of the same age after a Bonferroni post hoc test.
increase in the relative heart weight that was observed in male but not in female offspring (see Supplementary material online, Figure S1).

3.2 Long-term effects of hypoxia-induced IUGR on cardiac susceptibility to IR insult

During the initial pre-ischaemic period, hearts from all offspring developed comparable levels of cardiac power, independent of their sex, age, or in utero exposure to hypoxia. However, during reperfusion, both male and female offspring born IUGR exhibited a remarkable decrease in cardiac performance recovery when compared with age- and sex-matched controls (Figure 2). In male offspring (both IUGR and controls), ageing had an additional deleterious effect on cardiac susceptibility to IR injury (P for ageing effect in the two-way ANOVA < 0.0001). Interestingly, ageing had no additional effect on the susceptibility to IR injury in female offspring (P for ageing effect in the two-way ANOVA = 0.51) (Figure 2). Additional information regarding cardiac function experiments (including cardiac output, coronary flows, and left ventricle developed pressure) is presented in the Supplementary material online, Figure S2.

3.3 Effects of hypoxia-induced IUGR on cardiac energy metabolism

During the pre-ischaemic period, the relative contribution of each metabolic substrate to the total myocardial ATP production was comparable among all groups, regardless of their sex, age, or prenatal intervention (Figure 3). However, during reperfusion, all groups exhibited a decrease in the relative proportion of ATP derived from fatty acid oxidation and a relative increase in the proportion of ATP derived from both the catabolism of carbohydrates and glycolysis (P < 0.05 for all groups; see Supplementary material online, Table S1). Interestingly, the proportion of energy derived from lactate oxidation remained unchanged in all groups of animals after IR injury. Moreover, during this reperfusion period, the proportional change in glycolysis rates relative to glucose oxidation rates (glucose metabolism coupling) was consistently higher in male IUGR offspring when compared with sex- and age-matched controls (Figure 3). IUGR offspring from both ages and sexes exhibited an increased production of H+ during reperfusion when compared with age- and sex-matched controls (Figure 4). Interestingly, in male but not female offspring, ageing was also associated with a higher degree of glucose metabolism uncoupling and H+ production during reperfusion independent of the prenatal history of IUGR.

Despite the observed changes in myocardial energy substrate selection, the overall energy production capacity of the hearts from IUGR offspring was not compromised. During the aerobic period, the myocardial production of acetyl-CoA was comparable among all experimental groups independent of sex, age, or prenatal exposure to hypoxia (Figure 5). As expected, during reperfusion, all groups of animals exhibited a decrease in myocardial energy production. However, during this period, offspring born IUGR exhibited an

![Figure 3](image-url) Relative contribution of each of the major myocardial energetic substrates in all experimental groups during aerobic and reperfusion periods. Values of n > 7 per group. *Significant differences in the proportion of glycolysis relative to controls in the same experimental group during reperfusion (detailed information provided in Supplementary material online, Table S1).
increased myocardial production of acetyl-CoA relative to sex- and age-matched controls (Figure 5). The mismatch between the post-ischaemic energy production and the amount of cardiac work developed indicates that in IUGR offspring, cardiac efficiency during reperfusion was notably decreased relative to their respective age-matched controls (Figure 6).

### 4. Discussion

Consistent with our previous results, we confirmed that the myocardium of IUGR offspring is more susceptible to IR injury. As a novel contribution, this study constitutes not only the first description of the cardiac metabolic profile in a foetal programming model, but also the first characterization of cardiac metabolism in both male and female offspring at different stages in life (early adulthood and ageing). Therefore, it provides valuable information for the understanding of potential interactions between ageing and sex in both the physiological changes in cardiac metabolism and the pathophysiology of the increased susceptibility to IR injury observed in adult offspring born IUGR.

Animal models of IUGR created by decreasing the foetal oxygen availability constitute an interesting tool that emulates conditions observed in many common obstetrical pathologies associated with IUGR (such as placental insufficiency, pre-eclampsia, placenta previa, placenta accreta, and maternal smoking, among others). Moreover, hypoxia is one of the most common prenatal insults as the foetus has no alternative sources to compensate for reduced oxygen supply. In the current study, we provide further validation of our hypoxia-induced model of IUGR by demonstrating not only a decrease in the birth weight of the pups born from dams exposed to prenatal hypoxia, but also a decrease in the absolute placental size. Both these findings have been previously described in the clinical presentation of IUGR and strongly relate to the development of cardiovascular events in adulthood.

One interesting characteristic of this foetal programming model is that cardiac performance during the pre-ischaemic period is

---

**Figure 4** Myocardial proton (H⁺) production derived from glucose metabolism uncoupling during both the pre-ischaemic period [male (A) and female (C) offspring] as well as during reperfusion after 10 min of no-flow ischaemia in male (B) and female (D) offspring. Values of \( n > 7 \) per group. *Values of \( p < 0.05 \) for the respective sources of variation (age or prenatal intervention) using two-way ANOVA. † \( p < 0.05 \) vs. controls of the same age after a Bonferroni post hoc test.
comparable among groups; which means that the long-term consequences of the prenatal hypoxic insult does not affect baseline cardiac function. However, after exposure to an IR challenge, adult offspring exposed to prenatal hypoxia demonstrated differences in the cardiac phenotype which were evident in both male and female offspring as early as 4 months of age.

Experiments conducted to evaluate the sex differences in the cardiac response to IR injury are controversial. Several studies using the Langendorff perfusion technique have shown that due to the influence of hormones, hearts from female animals are more resistant to IR injury than males.35,36 In contrast, others have described no sex differences in the myocardial susceptibility to ischaemia.37,38 However, it has been shown that in the presence of pathophysiological conditions such as ventricular hypertrophy and hypercontractile states, sex differences can exacerbate the susceptibility to IR injuries.38 In our work, we described that in male but not female offspring, ageing was associated with a further increase in the susceptibility to IR injury. However, the deleterious effect of being born IUGR on the myocardial susceptibility to ischaemia was very similar in all offspring regardless of their sex or age.

In terms of cardiac energy metabolism, one of the major findings of this study was that relative to controls, IUGR offspring had a significant increase in the amount of glucose that underwent glycolysis relative to the amount of glucose that was oxidized during the reperfusion period. As previously proposed by Tani and Neely and coworkers,39 this uncoupling in myocardial glucose metabolism causes an increase in the amount of H\(^+\) in the cytoplasm, triggering a cascade of compensatory mechanisms to re-establish cellular ionic and acid/base homeostasis, which unfortunately causes an important increase in energy expenditure.40 To prevent cellular damage resulting from an H\(^+\) accumulation and the respective shift in pH, compensatory mechanisms such as Na\(^+\)/H\(^+\) exchangers are rapidly activated.41 These transporters reduce H\(^+\) without using energy, but cause an intracellular Na\(^+\) overload. To deal with this overload, the myocardium uses two major mechanisms; activation of ATP-dependent ion transporters such as Na/K ATPase, and activation of non-ATP-dependent exchangers like Na\(^+\)/Ca\(^{2+}\) (which reduce intracellular Na\(^+\) without depleting ATP but cause an increase in intracellular Ca\(^{2+}\)). Since an increase in Ca\(^{2+}\) levels constitutes a serious hazard for cardiac viability and is one of the major mediators
of IR injury, increased intracellular levels of this ion require the intervention of additional transporters such as the sarco/endoplasmic reticulum Ca\textsuperscript{2+}-ATPase (SERCA) to maintain cellular homeostasis at the expense of ATP depletion. Generally speaking, an increase in H\textsuperscript{+} production constitutes a major ionic imbalance that requires large amounts of energy to resolve. Therefore, the potential benefits of using the glycolytic pathway to produce energy under anaerobic conditions may be diminished by the increase in the energetic demands of ion homeostasis. One additional component that could be involved in the cardiac programming phenomenon that we have described is the activity of membrane transporters such as the Na/K ATPase pump, Na/H exchanger type 1, Na/Ca exchangers, and type 2A SERCA channels. These transporters are responsible for maintaining homeostasis in the cardiomyocyte and could be involved in both the increased susceptibility to IR injury as well as the increased post-ischaemic proton production observed in offspring born IUGR. Future experiments are required to evaluate the potential involvement of these particular homeostatic mechanisms in the development of the cardiac phenotype that we have described.

We also observed that despite recovering <50% of their initial cardiac work during the reperfusion period, control animals from all groups recovered ~70% of their basal energy production capacity. These results are consistent with previous reports showing that during reperfusion, the cardiac activity of the TCA cycle recovers rapidly and to a greater extent than the cardiac work. Interestingly, when compared with sex- and age-matched controls, IUGR offspring exhibited an increased capacity to produce energy during reperfusion. Therefore, this finding suggests that the post-ischaemic reduction in the developed cardiac work described in IUGR offspring cannot be attributed to a decreased ability of the myocardium to produce energy during the post-ischaemic period but rather to a higher expenditure of energy in non-contractile processes such as those required to maintain ion balance and cellular homeostasis.

The fact that the aged male offspring born IUGR exhibit increased glucose metabolism uncoupling and increased H\textsuperscript{+} production is not completely unexpected, given that these animals are known to develop a certain degree of ventricular hypertrophy and similar metabolic alterations have previously been described in hypertrophic cardiomyopathy.
hearts. However, that fact that hearts from female offspring born IUGR exhibited similar metabolic changes in the absence of alterations in myocardial mass or function suggests that the changes in myocardial metabolism associated with being born IUGR are not necessarily linked to the development of ventricular hypertrophy. Therefore, these two conditions may have parallel and synergistic deleterious effects on cardiac metabolism leading to an increased susceptibility to IR insult later in life.

One of the limitations of the technique used to evaluate cardiac metabolism in this study was that it only determines the amount of glucose, lactate, and fatty acids converted to acetyl-CoA. However, not necessarily all of the acetyl-CoA generated in a cell is used to produce ATP. In fact, there are multiple mechanisms by which the proton gradient generated in the membrane of mitochondria can be consumed without producing ATP (a phenomenon that is known as proton leak) which could compromise the cardiac efficiency in post-ischaemic states. Some authors have suggested that ischemic insults could compromise membrane permeability and increase proton leak in the mitochondria. We chose to use a 10 min ischemic insult based on preliminary results showing that the hearts from aged rats do not recover when exposed to longer ischemic periods. The ischemic insult used in our studies was significantly shorter than the insults commonly used in other studies (up to 45 min) and may not be enough to cause a significant proton leak in the mitochondria. Moreover, there was a remarkable consistency between the changes in cardiac efficiency and the increase in proton production. Together, these results suggest that extra-mitochondrial proton production (and not mitochondrial proton overproduction and accumulation in the myocardium that requires significant amounts of energy to compensate for). Our findings could have several clinical implications. First, it suggests that identifying the population with a higher risk of myocardial ischemia who are undergoing a myocardial ischemic episode.

In conclusion, our results suggest that a prenatal hypoxic insult causing IUGR has long-term effects on cardiac susceptibility to IR injury by causing glucose metabolism uncoupling. These changes lead to a post-ischaemic H+ overproduction and accumulation in the myocardium that requires significant amounts of energy to compensate for. Our findings could have several clinical implications. First, it suggests that identifying the population with a history of IUGR or other pregnancy complications leading to foetal hypoxia may be useful for the screening of subjects more susceptible to myocardial ischaemic events. Moreover, our results suggest that therapeutic approaches aimed at improving glucose oxidation and decreasing intracellular H+ accumulation during reperfusion could be particularly beneficial in the management of adults born IUGR who are undergoing a myocardial ischaemic episode.

Supplementary material
Supplementary material is available at Cardiovascular Research online.

Acknowledgements
The authors would like to thank Yanyan Jiang and Ms Donna Beker for their technical support.

Conflict of interest: none declared.

Funding
This work was supported by a research grant from the Canadian Institutes of Health Research (CIHR) and Pfizer Canada (protocol NRA2580076). C.F.R.-C. was a fellow of the Tomorrow’s Research Cardiovascular Health Professionals (TORCH), C.F.R.-C. and J.S.M. are supported by the Heart and Stroke Foundation of Canada (HSFC) and the Alberta Heritage Foundation for Medical Research (AHFMR). G.D.L. is an AHFMR Scientist. S.T.D. is an AHFMR Scientist and a Canada Research Chair (Tier 1) in Women’s Cardiovascular Health.

References

et al


42. Borutaite V, Mildziene V, Brown GC, Brand MD. Control and kinetic analysis of ischemia-damaged heart mitochondria: which parts of the oxidative phosphorylation system are affected by ischemia? Biochim Biophys Acta 1995;1272:154–158.