Maternal Hyperglycemia Improves Fetal Cardiac Function During Tachycardia-Induced Heart Failure in Pigs

M.R. Schmidt, MD, PhD; M. Smerup, MD; S.B. Kristiansen, MD; H.E. Bøtker, MD, PhD, DMSc; O. Schmitz, MD, DMSc; V.E. Hjortdal, MD, PhD, DMSc; K.E. Sørensen, MD; A.N. Redington, MD, FRCP

Background—Fetal tachycardia often leads to cardiac failure, which in experimental settings can be prevented by direct fetal glucose-insulin administration. In this study, we hypothesize that similar effects can be obtained indirectly by inducing maternal hyperglycemia.

Methods and Results—Systolic and diastolic indices (dP/dt max and τ) of left ventricular function were measured by use of high-fidelity catheters during 180 minutes of aggressive atrial pacing (≈300 bpm) in 12 preterm porcine fetuses. In 6 fetuses, maternal hyperglycemia (15 mmol/L) was induced for the last 120 minutes of pacing. The remaining fetuses served as controls. Glucose, insulin, and free fatty acid levels were determined, as was fetal myocardial glycogen content. Maternal glucose infusion led to significant fetal hyperglycemia and hyperinsulinemia but did not change the inherently low fetal levels of free fatty acids. There were no differences between groups with regard to dP/dt max (1025 ± 226 and 1037 ± 207 mm Hg, P = NS) and τ (20.6 ± 2.0 and 21.4 ± 1.6 ms, P = NS) at baseline (100%). During the 180 minutes of pacing, systolic function (dP/dt max) and diastolic function (τ) deteriorated more in the control group than in the hyperglycemic group (P < 0.001 for both). At 180 minutes, dP/dt max was 62 ± 18% of baseline in controls and 85 ± 11% in hyperglycemic fetuses (P = 0.03), and τ was 117 ± 12% and 98 ± 4%, respectively (P = 0.004).

Conclusions—Induced maternal hyperglycemia improves fetal cardiac function during fetal tachycardia and suggests a possible additional therapeutic option to improve the function of the failing fetal heart before or during antiarrhythmic therapy. The findings may be relevant in fetal heart failure in general. (Circulation. 2004;110:2627-2630.)

Key Words: heart failure • tachycardia • glucose

Despite early diagnosis and improved therapeutic algorithms, fetal tachyarrhythmias often lead to severe cardiac failure.1,2 Traditionally, treatment has been based on transplacental antiarrhythmic drugs, whereas little attention has been paid to metabolic support of the glucose-dependent fetal myocardium. In a porcine study, we have recently shown that direct fetal glucose-insulin infusion during tachycardia improves fetal cardiac function and metabolism.3

Because glucose passes almost freely across the placenta,4,5 fetal glucose levels follow those of the mother.6 Insulin transport, in contrast, is extensively blocked by the placenta,7 leaving fetal insulin levels much lower than maternal levels.8,9 During periods of maternal hyperglycemia, however, the associated fetal hyperglycemia leads to secondary fetal hyperinsulinemia.10–14 These mechanisms suggest that induction of maternal hyperglycemia would be a possible means of generating simultaneous fetal hyperglycemia and hyperinsulinemia and thus a stimulus qualitatively similar to what we previously obtained by direct fetal glucose-insulin infusion.3

In the present study, we test this approach as a potentially clinically relevant intervention on cardiac function and metabolism during fetal tachycardia.

Methods

One to 3 fetuses (weight, 840 ± 170 g) from each of 6 pregnant sows (Danish Landrace, 106 ± 2 of 114 days of gestation, age 1 to 2 years, weight 170 to 250 kg) were studied. Sows were anesthetized and ventilated and fetuses exposed as described previously.3

A 1.4F high-fidelity pressure catheter (Millar Instruments) was inserted into the fetal left ventricle (LV) via the exposed left carotid artery while a 1F bipolar pacing catheter (Numed) connected to an external pacemaker was advanced into the right atrium via the left external jugular vein.

LV pressures were acquired at 250 Hz and analyzed with dedicated software (Notocord). dP/dt max was used as an index of systolic function. Diastolic performance was assessed by τ (half-time of pressure in the end-diastolic phase) approximated by a monoexponential model with variable (nonzero) asymptote. dP/dt max and τ were calculated as means from beats recorded over a period of 15 seconds. Pressures were recorded continuously but specifically analyzed before pacing, during force-frequency (FFR) analysis, and during prolonged pacing with or without maternal hyperglycemia.

The same protocol was followed in each study. After basal (unpaced) values were obtained, the FFR was determined as dP/dt max at incrementing (10 bpm) pacing from 140 bpm to the occurrence of atrioventricular block. After the FFR-pacing sequence had been completed, fetuses were paced for 180 minutes at 50 bpm above the optimal heart rate (ie, the rate associated with the highest dP/dt max).
To avoid possible preconditioning effects of hyperglycemia, the first 1 to 2 fetuses in each sow were used as controls, and only the last were studied during maternal hyperglycemia.

In fetuses chosen for the hyperglycemic stimulus, maternal hyperglycemia was induced after 60 minutes of pacing. Blood glucose was adjusted to 14 to 16 mmol/L by controlled infusion of 20% glucose. Control sows received saline at a similar rate. Maternal blood glucose, electrolytes, and pH were measured every 20 minutes during glucose infusion and every 60 minutes during control periods. After 180 minutes of pacing, fetal blood samples were collected for measurements of blood glucose, insulin, and free fatty acids (FFAs). Finally, fetal hearts were excised and frozen in liquid nitrogen within 5 seconds for analysis of glycogen content. After completion of the experiments, the sows were euthanized with an overdose of pentobarbital.

**Metabolic Analysis**

Insulin levels were measured by ELISA with a 2-site immunoassay (Dako Diagnostics), FFAs by a colorimetric method (Wako Chemicals), and myocardial glycogen as described previously.15

**Statistical Analysis**

Blood glucose, serum lactate, serum insulin, and myocardial glycogen content were compared between groups by use of Student’s unpaired t test. FFR data were compared by use of Student’s t test on summary measures.16 Longitudinal changes in dP/dt\(_{\text{max}}\) and \(\tau\) from baseline to 180 minutes (measured at 0, 60, 75, 90, 120, and 180 minutes) were compared between groups by use of 2-way ANOVA (repeated measures). Cross-sectional differences in dP/dt\(_{\text{max}}\) and \(\tau\) between groups at 0, 60, and 180 minutes were compared by use of 1-way ANOVA. Values are described as mean±SD unless otherwise stated.

**Results**

Six control and 6 hyperglycemic fetuses survived the protocol and were included. Four fetuses were excluded, 1 because of premature death and 3 because of surgical shortcomings.

**Metabolic Indices**

Maternal potassium, pH, and lactate remained unchanged through the complete experiment. Maternal glucose was similar (4.3±1.6 mmol/L) during control settings and during the first 60 minutes of pacing before glucose administration. Maternal and fetal levels of glucose, insulin, and FFAs at study completion are shown in Figure 1. After 180 minutes of pacing, simultaneous blood sampling in the control fetuses and their mothers revealed similar glucose levels. In hyperglycemic fetuses, however, glucose levels were lower than maternal levels, albeit significantly higher than in control fetuses.

During the hyperglycemic challenge, maternal insulin concentrations were significantly raised, whereas FFA levels tended to be lower (Figure 1). Fetal insulin levels were also higher in hyperglycemic than control fetuses, whereas FFA levels were similar (Figure 1). Myocardial glycogen was significantly higher in the hyperglycemic fetuses than in controls (92.5±3.4 versus 74.1±10.6 mmol/mg, \(P<0.001\)).

**Cardiac Function**

Basal hemodynamics were similar in control fetuses and in those that subsequently underwent hyperglycemia (dP/dt\(_{\text{max}}\), 1008±187 and 997±214 mm Hg/s, \(P=\text{NS}\); \(\tau\), 21.7±2.4 and 23.5±1.6 ms, \(P=\text{NS}\); and heart rate, 149±33 and 158±33 bpm, \(P=\text{NS}\)). The optimal heart rate and peak dP/dt\(_{\text{max}}\) as defined from the FFR were similar in controls and fetuses subsequently exposed to hyperglycemia (251±53 and 260±29 bpm, \(P=\text{NS}\); and 991±211 and 946±210 mm Hg/s, \(P=\text{NS}\)). Pacing rate during prolonged pacing was 305±59 bpm in controls and 303±60 bpm in hyperglycemic fetuses (\(P=\text{NS}\)). There were no differences between groups with regard to dP/dt\(_{\text{max}}\) (1025±226 and 1037±207 mm Hg, \(P=\text{NS}\)) and \(\tau\) (20.6±2.0 and 21.4±1.6 ms, \(P=\text{NS}\)) at baseline (100%).

Relative changes in cardiac function during prolonged pacing are shown in Figure 2. During the first 60 minutes of pacing, dP/dt\(_{\text{max}}\) decreased to 88±8.8% of baseline in control fetuses and to 89±3.7% in the subgroup to undergo the hyperglycemic stimulus (\(P=\text{NS}\)), whereas \(\tau\) increased to 105±5.5 and 106±2.6% of baseline (\(P=\text{NS}\)). During the following 120 minutes, systolic function (dP/dt\(_{\text{max}}\)) and diastolic function (\(\tau\)) deteriorated more in the control group than in the hyperglycemic group (\(P<0.001\) for both). At 180 minutes, dP/dt\(_{\text{max}}\) was 62±18% of baseline in controls and 85±11% in hyperglycemic fetuses (\(P=0.03\)), whereas \(\tau\) was 98±4% and 117±12%, respectively (\(P=0.004\)).
Discussion

This study shows that induction of moderate maternal hyperglycemia improves fetal cardiac function during tachycardia. It corroborates our previous finding that direct fetal administration of combined insulin and glucose prevents tachycardia-induced cardiac dysfunction and shows that a similar response can be achieved with a clinically relevant metabolic approach. It also confirms that maternal hyperglycemia leads to fetal hyperglycemia and hyperinsulinemia without changing fetal FFA levels, emphasizing the suppressed lipid metabolism in the predominantly carbohydrate-dependent fetal heart.

The metabolic strategy imposed reversed the linear decline in both systolic and diastolic function otherwise observed in fetuses undergoing aggressive pacing. Indeed, within the first 15 minutes of maternal hyperglycemia, dP/dt_max and τ returned to baseline.

Whereas the improvement in diastolic function could be maintained throughout the study period, a minor temporal decline in dP/dt_max was seen in the hyperglycemic fetuses. Nevertheless, a significant treatment benefit persisted throughout the study period. This gradual reduction in systolic improvement remains unexplained and raises questions about the possible duration of the protective effect of hyperglycemia. Although this can be explored only via new studies, existing data suggest that the hyperinsulinemic response attenuates over time and that long-term fetal hyperglycemia may depress myocardial function. To avoid the potential risk of fetal preconditioning, fetuses were not randomized to the control or hyperglycemia groups. Although this theoretically might have affected measurements unequally in the 2 groups, measured indices were not different before the hyperglycemic challenge.

The level of maternal hyperglycemia (~15 mmol/L) was chosen to ensure substantial fetal hyperglycemia and hyperinsulinemia. Actually, blood glucose and serum insulin increased by 3- and 30-fold, respectively. A glycemic level between 10 and 15 mmol/L is standard when conducting hyperglycemic clamp experiments in humans, because this elicits near-maximal glucose-stimulated insulin secretion. Thus, if this regimen turns out to be of clinical relevance, it would be feasible to perform the procedure for at least several hours.

Our data should not be interpreted as representing a possible alternative to antiarrhythmic therapy. Rather, if this intervention has a clinical role, it would be in the acute improvement in ventricular function before or coincident with maternal antiarrhythmic therapy.

With the protocol used, sufficient and lasting fetal hyperglycemia to keep fetal insulin levels substantially elevated may not have been achieved. Unfortunately, the limited fetal blood volume and the highly fragile umbilical cord made repeat blood sampling impossible. The observation that the fetal glucose levels in this porcine model did not fully reach the maternal levels during hyperglycemia is in contrast to previous studies in animals and humans. It should be noted that the present design did not allow us to tease out the relative importance of hyperglycemia and hyperinsulinemia per se on fetal cardiac function, because other factors may contribute, eg, the dynamics in electrolytes.

Finally, this model does not reflect the possible confounding issues introduced as a result of more chronic or intermittent arrhythmia. The hydropic fetoplacental unit clearly may exhibit different properties in terms of both glucose transport and insulin responses.

Conclusions

The present observations confirm that fetal cardiac function during tachycardia may be improved by indirect metabolic intervention and suggest a possible additional therapeutic option to temporarly improve the function of the failing fetal heart before or during antiarrhythmic therapy. Although the study focused on the effect of maternal hyperglycemia on tachycardia-induced heart failure, the findings may be relevant in fetal heart failure in general.

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References


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