Glucose–Insulin Infusion Improves Cardiac Function During Fetal Tachycardia

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OBJECTIVES The aim of this work was to study the effects of substrate deficiency and supplementation on cardiac function during fetal tachycardia.

BACKGROUND Although sustained fetal tachycardia may lead to cardiac failure and intrauterine death, neonatal tachycardia is generally better tolerated. Fetal myocardial energy production relies almost solely on glucose as substrate. We hypothesized that increased substrate availability by glucose–insulin (GI) infusion would improve fetal myocardial responses to tachycardia.

METHODS We used three porcine models: 1) an isolated fetal heart model; 2) an in vivo fetal model; and 3) an in vivo closed-chest neonatal model. Each animal was randomized to control or GI treatment during tachycardia. In model 1, the controls were perfused with conventional Krebs-Henseleit solution containing a glucose concentration of 5.5 mmol/l; the GI hearts received double glucose concentration and added insulin. In models 2 and 3, the GI animals received insulin in a 20% glucose solution. All hearts were exposed to 90 min of pacing at 250 to 330 beats/min.

RESULTS The isolated fetal hearts in the GI group showed no decline in dP/dt max during pacing, while the controls declined. In the in vivo fetal hearts, dP/dt max remained unchanged in the GI group and decreased significantly in the control group. Myocardial glycogen content was higher in the GI group than in controls. Functional indexes remained unchanged among both neonatal groups despite a higher glycogen content in the GI group.

CONCLUSIONS Glucose–insulin infusion during fetal tachycardia has a beneficial effect on myocardial metabolism and cardiac function. These observations may have direct clinical relevance to the management of fetal arrhythmia. (J Am Coll Cardiol 2004;43:445–52) © 2004 by the American College of Cardiology Foundation

Although sustained fetal tachycardia may lead to cardiac failure, hydrops, and intrauterine death, neonatal tachycardia is generally better tolerated (1,2). Despite early diagnosis and transplacental antiarrhythmic drug exposure, fetal tachycardia has been associated with a mortality of up to 50% (1). The reasons for the rapid fetal demise in these situations are not completely understood.

Myocardial metabolism in the normal adult heart depends predominantly on fatty acid oxidation. In contrast, the fetal heart with fewer and less mature mitochondria has limited oxidative capacity for long chain fatty acids but a very high glycolytic capacity (3). Consequently, the fetus tolerates hypoxia relatively well, whereas prolonged periods with increased work demand (e.g., during tachycardia) are deleterious. The transition from predominantly carbohydrate-dependent to fatty-acid-dependent metabolism occurs during the first weeks of life (4–7).

In the fetal heart, glycogen represents an important energy source available during stressful events such as compromised placental blood flow or tachycardia. Insulin stimulates glycogenesis in the mature heart, but its metabolic effect on the fetal heart is poorly described. Furthermore, insulin has positive inotropic effects (8) independent of glucose metabolism (9) and has been suggested as a treatment for heart failure (HF) (10). Whereas insulin is known to improve neonatal cardiac function (11), the fetal heart has previously been considered resistant to insulin (5).

Based on these observations, we hypothesized that 1) fetal tachycardia depletes myocardial glycogen stores, which contributes to deteriorating ventricular function; 2) glucose–insulin (GI) administration prevents this depletion and thereby protects cardiac function during fetal tachycardia; and finally, 3) clinically relevant levels of tachycardia are better tolerated in terms of cardiac metabolism and function in the neonatal than the fetal heart.

To test these hypotheses, tachycardia-induced changes in myocardial function and glycogen stores were studied in fetal and neonatal pigs randomized to either GI or control infusions.

METHODS

Danish Landrace pigs were used in all experiments. The studies conformed to the guidelines of the American Heart Association on animal research. In all substudies, anesthesia was induced with midazolam (0.5 mg/kg intramuscularly) and azaperone (4 mg/kg intramuscularly) followed by etomidate (0.5 mg/kg intravenously). The pigs were intubated...
and ventilated (Servo 900, Siemens, Munich, Germany); anesthesia was maintained with isoflurane 1.5% in an O₂–NO₂ mixture. After completion of the experiments, the piglet/sow was euthanized with an overdose of pentobarbital.

Isolated fetal heart model (Langendorff). Three first-time late pregnant sows (100 ± 7 of 114 days of gestation, age 1 to 2 years, weight 140 to 185 kg) were used. From these, 14 fetuses were randomized to either GI or normal Krebs-Henseleit (control). The sows’ electrolytes, glucose, and arterial blood gases were checked hourly, and homeostasis was maintained accordingly. Particular attention was paid to keeping maternal blood glucose 3 to 7 mmol/l by 5% glucose infusion.

Each fetus was manipulated in utero through a 30-cm paramedian incision. The fetus was exposed through a 5-cm uterotomy. The fetal heart was excised, mounted via the aorta on the Langendorff system, and perfused with oxygenated Krebs-Henseleit solution. Left ventricular (LV) pressures were recorded continuously with a balloon-tipped catheter and stored on a personal computer. Left ventricular dP/dt max and dP/dt min were used as indexes of systolic and diastolic performance.

The protocol was followed in all experiments:

1) 5- to 10-min stabilization.
2) Baseline pressure was acquired for the unpaced basal rate and for the paced basal rate (150 beats/min).
3) To define the force–frequency relationship (FFR), pacing rate was increased incrementally from 150 to the occurrence of atrioventricular (AV) block. After 1 min of stabilization at each step, an LV pressure measurement was recorded. After completion of the FFR measurement, the fetuses stabilized for 1 min before starting continuous pacing at 250 beats/min.
4) After insertion of an intravenous line in the left foreleg, the fetuses were randomized to receive GI infusion or control (no) treatment. The GI fetuses received insulin in 20% glucose infused at 5 ml/h corresponding to 100 mU/kg/h (physiologic dose).
5) Pacing at 250 beats/min for 90 min. Pressures were recorded at 0, 30, 60, and 90 min.
6) Heart excised (within 10 s) and snap-frozen (within <2 s) in liquid nitrogen for analysis of glycogen content, and the fetuses were weighed.

Fetal in vivo model. One to four fetuses (weight, 825 ± 150 g) from each of 12 first-time pregnant sows (gestational age, weight, and age as above) were studied. The uterus was exposed through a paramedian 20- to 30-cm incision, and a fetus was manipulated in utero through the incision while the remaining fetuses (still in utero) were left intra-abdominally. Six hearts from random fetuses were removed immediately after uterotomy and frozen for analysis to establish a reference for myocardial basal glycogen content. For the hemodynamic experiments, each fetus was exter-
RA. The balloon was intermittently inflated to modify preload during measurement of LV elastance (Ees). A 5F thermodilution catheter was positioned into the pulmonary artery via the left internal jugular vein (Baxter Healthcare, Deerfield, Illinois) and connected to a dedicated cardiac output processing computer (Com2, Baxter Edwards). Finally, a size 5F bipolar pacing wire was positioned in the RA appendage via the right external jugular vein and connected to an external pacemaker (Medtronic, Minneapolis, Minnesota). Pressure and volume data were digitized at 1,000 Hz and stored on a personal computer with custom software.

The following protocol was conducted:

1) Baseline pressure-volume (including Ees) measurements were obtained at unpaced basal rate and paced at 150 beats/min.
2) To define the FFR: pacing rate was incremented in steps of 10 beats/min from 150 beats/min until occurrence of AV block. After 1-min stabilization at each step, the pressure traces were stored for dP/dtmax analysis. After completion of the FFR measurement, the neonates stabilized for 1 min at 150 beats/min before 90-min pacing.
3) Each animal was then randomized to GI or control treatment. If randomized to GI, infusion of insulin in 20% glucose at a rate of weight (in kg)*5 ml/h corresponding to 100 mU/kg/h.
4) Pacing for 90 min at 25 beats/min higher than the individual "critical heart rate" (the rate at which maximal force was developed measured from the FFR). Pressure-volume data were saved at 0, 30, 60, and 90 min.
5) The heart excised (within 30 s) and snap-frozen (within <2 s) for analysis for glycogen content.

Metabolic analysis. Glycogen concentrations were analyzed as previously described (13) and expressed in nmol acid extractable free glycogen/mg wet weight biopsy.

Statistical analysis. Mean changes in peak force (dP/dtmax), contractility (Ees), diastolic performance (tau, dP/dtmin), and glycogen content during the 90 min of pacing were compared (control vs. GI) using the Student unpaired t test. Fetal and neonatal FFR data were compared using Student t test on summary measures (14). Glycogen content was related to survival time using linear regression. Values are described as mean ± SD unless otherwise stated.

RESULTS

Isolated fetal hearts. Total sow anesthesia time was approximately 5 h. All 14 hearts used (7 in each group) completed the protocol without AV block. Baseline LV dP/dtmax and dP/dtmin (obtained after 30 min of stabilization) were similar in both groups.

During 90 min of pacing at 250 beats/min, LV dP/dtmax decreased 16.9 ± 4.3% in the control group but increased 4.5 ± 12.4% in the GI group (p < 0.005) (Figs. 1 and 2).

Similarly, LV dP/dtmin increased 17.8 ± 3.8% in controls but remained unchanged (0.6 ± 14.9%) in the GI group (p < 0.05) (Figs. 1 and 2). Myocardial glycogen content after pacing was 40.4 ± 11.7 nmol/mg in the control group and 52.4 ± 14.8 nmol/mg in the GI group (NS, p = 0.11, respectively) (Fig. 3). There was no relationship between order of, or time from, removal of the fetal heart from the sow and heart function.

Fetal in vivo model. The stability of this model was tested on six fetuses that remained unpaced but thoracotomized and placed in the saline bath for 2 h while connected to the sow via the umbilical cord. They showed no changes in systolic or diastolic function during 2 h of monitoring (data not shown). Furthermore, the hearts had myocardial glycogen contents (37.9 ± 9.9 nmol/mg) similar to those excised immediately after uterotomy (see the subsequent text).

In the experimental part of the study, 10 fetuses died during preparation due to technical errors during the delicate surgical procedure. Four fetuses died during FFR measurements and were excluded. Whereas all of 13 fetuses included completed the initial FFR study, only one fetus in the control group and two fetuses in the GI group survived the prolonged pacing protocol. The remaining (5 in each group) died during pacing after development of AV block followed by rapid decrease in cardiac function. Mean survival time was 60 ± 23 min in controls and 78 ± 9 min in GI fetuses (NS, p = 0.10, respectively). In all cases, fetal demise (defined as LV pressure <10 mm Hg) occurred a few minutes after rapid development of advanced or complete AV block.

FFR. Peak LV dP/dtmax occurred at 189 ± 39 beats/min (Fig. 4). The increase in LV dP/dtmax was only 4.3 ± 4.8% from baseline (150 beats/min) to peak LV dP/dtmax (Fig. 5). Atioventricular block occurred at 362 ± 81 beats/min.

Prolonged pacing. Basal (unpaced) heart rate was 129 ± 26 beats/min in the control group and 126 ± 19 beats/min in the GI group (p = NS). Basal LV dP/dtmax was 793 ± 106 mm Hg/s in the control group and 827 ± 86 mm Hg/s in the GI group (p = NS). Basal tau was 25.0 ± 3.2 ms in the control group and 25.0 ± 5.2 ms in the GI group (p = NS).

Left ventricular dP/dtmax declined during up to 90 min of
pacing at 250 beats/min in the control group but remained stable in the GI group (Fig. 5). At 30 min, LV dP/dt max decreased 15.8 ± 21.8% in the control group (n = 6) but increased 12.3 ± 20.2% in the GI group (n = 7) (p < 0.05). At 60 min, there was a mean decline from 0 min of 24.9 ± 15.2% in the control group (n = 4) compared with an increase of 8.4 ± 22.3% in the GI group (n = 7) (p < 0.02).

The diastolic performance was significantly impaired in the control group (Fig. 6). At 30 and 60 min, tau increased 39.1 ± 50.7% and 30.9 ± 13.8% in the control group but decreased 5.4 ± 18.6% and 2.4 ± 23.6% in the GI group (p = 0.09 and p < 0.02).

Biochemistry and glycogen. Mean plasma potassium level at time of death was 3.6 ± 0.4 mmol/l in the control group and 3.5 ± 0.5 mmol/l in the GI group (p = NS). Blood glucose was significantly higher in the GI group (16.3 ± 8.9 vs. 4.6 ± 2.2 mmol/l, p < 0.01), and mean free myocardial glycogen was significantly lower in controls (13.6 ± 11.3 vs. 54.7 ± 12.9 nmol/mg, p < 0.005) (Fig. 3). For all animals, survival time correlated with myocardial glycogen (r = 0.86, p = 0.002 [r = 0.90, p = 0.0005 if the three fetuses euthanized after 90 min are left out]) (Fig. 6), although two fetuses in the GI group died prematurely despite preserved myocardial glycogen content (>30 nmol/mg).

The fetal hearts removed immediately after uterotomy had a mean free glycogen of 42.2 ± 10.3 nmol/mg.

Neonatal model. Of the 18 piglets included, six piglets in each group completed the whole protocol. Five died due to accidental perforation of the heart during manipulation of catheters, and one died during pacing due to sudden ventricular fibrillation. Basal (unpaced) heart rate was 124 ± 15 beats/min in the control group and 127 ± 9 beats/min in the GI group (p = NS). Basal LV dP/dt max was 1,242 ± 65 mm Hg/s in the control group and 1,166 ± 183 mm Hg/s.

Figure 2. Box (in quartile range) and whisker (10th to 90th percentile) plot of systolic and diastolic performance of the isolated hearts in the control (left) and glucose-insulin (right) groups during 90 min of atrial pacing at 250 beats/min. Circles = outliers. LV = left ventricular.

Figure 3. Comparison of free myocardial content of free glycogen (shown as nmol/mg wet weight biopsy) in control and glucose-insulin (GI) groups in the three lines of experiments. *p < 0.005; #p < 0.01. Solid bars = control; open bars = GI.

Figure 4. Correlation between survival time and mean free myocardial glycogen content.
Fetal Tachycardia—Effects of Glucose-Insulin

This study investigated cardiac function during tachycardia in the porcine fetus and neonate and the effect of glucose and insulin on myocardial metabolism and indexes of systolic and diastolic function. There were three main findings. First, treatment with insulin and glucose improves fetal cardiac function during tachycardia. Second, the myocardial metabolic derangement occurring during tachycardia in the fetus can be prevented by increasing substrate availability, and this relates to the improvement in cardiac function. Finally, the neonatal heart tolerates both acute and prolonged clinically relevant tachycardia better than the fetal heart.

**Cardiac function.** Despite major advances in our understanding of fetal cardiovascular physiology, our knowledge of fetal myocardial function is incomplete and mostly related to studies of flow (i.e., cardiac output). In human fetuses, assessment of cardiac performance has essentially relied upon information obtained with ultrasound techniques. Thus, to obtain more comprehensive information on cardiac function in the intrauterine environment, animal models are required. These are, for obvious reasons, not only complex and difficult to perform but also require the application of accurate measurement techniques adjusted for use in very small and fragile animals.

Because of the attractive size of the fetal sheep, most fetal studies have been performed in ewes with singleton pregnancies. In ex utero studies, the porcine model is perhaps more often used to study cardiovascular physiology. We therefore developed a porcine fetal in vivo model taking advantage of the multiple fetuses of the pregnant sow.

Previous findings suggest that the fetal heart operates at near peak performance with limited compensatory mechanisms (15). This is supported by our observations, which clearly show that increasing heart rates result in declining cardiac function, thus obviating tachycardia as a compensatory response. The FFR curves show that fetal LV \( \frac{dP}{dt}_{\text{max}} \) is at a much lower level than in neonates, but, more importantly, that LV \( \frac{dP}{dt}_{\text{max}} \) increases only marginally during incremental pacing from 150 beats/min before falling. Furthermore, pacing at 250 beats/min was associated with deterioration in both systolic (\( \frac{dP}{dt}_{\text{max}} \)) and diastolic (\( \frac{dP}{dt}_{\text{min}} \) and tau) LV function in both isolated and in vivo fetal hearts. Loading conditions were unchanged in the isolated hearts during tachycardia, suggesting that the differences are likely to reflect true deterioration in myocardial contractility and relaxation.

In contrast to the flat response in the fetal hearts, the FFR curve in neonatal hearts showed a greater incremental response of \( \frac{dP}{dt} \) to increasing heart rates with overall higher absolute values. Indeed, the increase in \( \frac{dP}{dt}_{\text{max}} \) (14% vs. 4%, \( p < 0.05 \)) was higher, and the critical heart rate occurred at higher heart rate, at 120 ± 31 versus 60 ± 18 (\( p < 0.05 \)) above unpaced heart rate in the neonates and fetuses, respectively.

The increase in inotropic state during the transition from fetal to neonatal life and the positive FFR of the newborn have been observed previously (16), but the marked difference in basal LV \( \frac{dP}{dt}_{\text{max}} \) and FFR observed in this study was striking. Importantly, this maturation appears only to be beneficial to systolic function, as the neonatal indexes of diastolic performance were the same as, or inferior to, values in the GI group (\( p = \text{NS} \)). Basal tau was 32.8 ± 6.9 ms in the control group and 36.6 ± 4.8 ms in the GI group (\( p = \text{NS} \)).

**FFR.** Unlike the fetal hearts, neonatal FFR showed a more normal increment and decrement of developed force during pacing. The peak LV \( \frac{dP}{dt}_{\text{max}} \) occurred at 229 ± 30 beats/min and increased 13.8 ± 4.3% from baseline (150 beats/min) to the peak LV \( \frac{dP}{dt}_{\text{max}} \) (Fig. 4). Atrioventricular block occurred at 312 ± 60 beats/min.

**Prolonged pacing.** The hearts were paced at 262 ± 33 beats/min with no significant difference between the two groups. There was no significant change in systolic or diastolic performance during 90-min pacing and no significant differences in indexes of cardiac function between the two groups (Table 1, Fig. 5).

**Biochemistry and glycogen.** At time of heart excision, potassium was 2.9 ± 0.3 mmol/l in controls and 3.3 ± 0.9 mmol/l in the GI group (\( p = \text{NS} \)). Blood glucose was 6.3 ± 3.9 mmol/l in controls and 12.3 ± 10.3 mmol/l in the GI group (\( p = \text{NS} \)). Mean free myocardial glycogen was 25.8 ± 2.8 mmol/mg in the control group and 43.3 ± 5.5 mmol/mg in the GI group (\( p < 0.01 \)) (Fig. 3).

**Fetal versus neonatal FFR.** Basal (unpaced) LV \( \frac{dP}{dt}_{\text{max}} \) was lower in the fetuses (790 ± 90 mm Hg/s) than in the neonates (1,204 ± 137 mm Hg/s) (\( p < 0.0001 \)). Interestingly, basal tau too was lower in the fetuses (25.0 ± 4.2) than in the neonates (34.7 ± 5.9) (\( p = 0.0002 \)).

At a baseline rate of 150 beats/min, fetuses had a lower LV \( \frac{dP}{dt}_{\text{max}} \) than the neonates (787 ± 73 mm Hg/s vs. 1,319 ± 157 mm Hg/s, \( p < 0.001 \)) and lower contractile reserve with lower heart rate associated with peak LV \( \frac{dP}{dt}_{\text{max}} \) (\( p < 0.01 \)) and lower absolute and relative increase from baseline to peak LV \( \frac{dP}{dt}_{\text{max}} \) (both \( p < 0.001 \)).

**DISCUSSION**

This study investigated cardiac function during tachycardia in the porcine fetus and neonate and the effect of glucose and insulin on myocardial metabolism and indexes of systolic and diastolic function. There were three main findings. First, treatment with insulin and glucose improves
recorded in the fetuses. The reasons for these differences cannot be provided by our study, and are probably multifactorial. However, the circulatory shift from fetal to neonatal conditions is associated with a rise in preload, which, in itself, would lead to higher LV dP/dt\textsubscript{max} (17), independent of any direct myocardial inotropic or neurohumoral effects. No matter the mechanism, the neonates seem better adapted to meet the challenges of increased heart rate, and the myocardial demands associated with it.

The mechanisms responsible for the differences in function of glucose-insulin-treated animals. Truncated curves illustrate premature death.

Figure 6. Individual fetal (in vivo) and neonatal systolic (dP/dt\textsubscript{max}) and diastolic (tau) function during 90 min of pacing in controls (left panels) and glucose-insulin-treated (right panels) animals. Truncated curves illustrate premature death.
pressure-volume relationship; GI /H11005

better tolerated both in terms of cellular metabolism and function. A similarly relevant tachycardia in the neonates is the fetal heart, and there is an associated decline in fetal (22). Nonetheless, it is clear that, at clinically relevant levels small amounts of adult isoforms (4 and II) in late gestation transition, but studies in rats have shown the presence of I to II, respectively. This is predominantly a postnatal shift in metabolism is also assumed to involve acquisition of myocardial insulin sensitivity when the glucose transporters and the hexokinase change isofrom from 1 to 4 and I to II, respectively. This is predominantly a postnatal transition, but studies in rats have shown the presence of small amounts of adult isoforms (4 and II) in late gestation (22). Nonetheless, it is clear that, at clinically relevant levels of tachycardia, rapid depletion of glycogen stores occurs in the fetal heart, and there is an associated decline in fetal function. A similarly relevant tachycardia in the neonates is better tolerated both in terms of cellular metabolism and heart function.

Our results can also be interpreted as demonstrating fetal cardiac sensitivity to insulin. The finding that cardiac function in the in vitro control hearts declined in the absence of changes in glycogen but remained stable in the GI group suggests that insulin not only improves function by replenishing the glycogen stores but may also have additional effects by stimulating the glycolytic flux or by direct positive inotropy independent of glucose metabolism (9).

Some of the fetuses that received GI in the in vivo model died during prolonged pacing despite preserved high myocardial glycogen content. The reason for this is not clear. Most fetuses died after sudden development of progressive AV block followed by a dramatic and irreversible decrease in cardiac function. Although we cannot exclude a direct myocardial effect, the mode of failure suggests that an electrophysiologic event may contribute. Little is known regarding the metabolism of fetal conductive tissue, but it is possible that this specialized myocardium behaves in different ways to that of the contractile myocardium.

Model considerations/limitations. The isolated fetal hearts generally were more resistant to the effects of tachycardia than the fetal hearts examined in vivo. This may be due to an inherent limitation of the Langendorff model because the hearts are perfused under constant pressure and with constant high oxygenation. Similarly, the effect of denervation is not known.

In the Langendorff model, pharmacologic doses of insulin were used to study whether it was at all possible to induce an insulin-stimulated effect on fetal cardiac function in a stress-response setting. Hence, no insulin was added to the Krebs-Henseleit solution in the control group, in order to avoid the potential confounding direct effects of insulin on contractile function. This study offers no direct evidence of the beneficial effect of insulin per se, and such proof could only be provided by a study of fetal cardiac function during euinsulinemic hyperglycemia.

The rationale for using physiologic doses in the in vivo models was to avoid hypokalemia, and to increase the potential clinical applicability of the findings. Diastolic performance in the isolated heart studies is described by dp/dtmin as this was the immediately available index for diastolic function. Tau is generally considered a less load-dependent index of diastolic function (12), but in the isolated heart model, this is of less significance, as loading conditions are constant. In the in vivo model, we used high-fidelity pressure catheters and software that allowed tau calculation.

Clinical cardiac dysfunction develops slowly over hours or days in the human fetus with tachycardia. To avoid uncontrolled side effects of long periods of maternal anesthesia, however, we wanted a model that caused HF more rapidly. Pilot studies indicated that 90 min of pacing at 250 beats/min was a feasible protocol to achieve tachycardia-induced HF, and we believe that this stimulus is relevant and comparable to the clinical situation, although possibly not reflecting all aspects of human fetal tachycardia.

### Table 1. Relative Change in Systolic and Diastolic Indices of Cardiac Function in Neonatal Pigs

<table>
<thead>
<tr>
<th>Change 0–90 min in % (±SD)</th>
<th>Control (n = 6)</th>
<th>GI (n = 6)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>dp/dtmax (mm Hg/s)</td>
<td>–11.6 (±12.1)</td>
<td>4.0 (±13.5)</td>
<td>0.06</td>
</tr>
<tr>
<td>ESPVR (mm Hg/ml)</td>
<td>15.7 (±24.4)</td>
<td>32.7 (±41.8)</td>
<td>0.28</td>
</tr>
<tr>
<td>Ea (mm Hg/ml)</td>
<td>–17.0 (±32.7)</td>
<td>–2.8 (±18.5)</td>
<td>0.47</td>
</tr>
<tr>
<td>Tau (ms)</td>
<td>18.6 (±20.1)</td>
<td>–1.9 (±10.6)</td>
<td>0.06</td>
</tr>
<tr>
<td>dp/dtmin (mm Hg/s)</td>
<td>6.0 (±21.8)</td>
<td>–8.3 (±26.8)</td>
<td>0.34</td>
</tr>
<tr>
<td>EDPVR (mm Hg/ml)</td>
<td>–5.1 (±17.3)</td>
<td>–4.8 (±36.8)</td>
<td>0.98</td>
</tr>
</tbody>
</table>

EDPVR = end-diastolic pressure-volume relationship; ESPVR = end-systolic pressure-volume relationship; GI = glucose-insulin.
It is well known that neonatal tachycardia is well tolerated for many hours. Although pragmatically a fixed rate protocol could have been used, our aim was to induce a uniform stress. Thus, the neonatal protocol was derived to adjust to individual contractile reserve, and each animal was paced at 25 beats/min above the critical heart rate. Although this led to the use of different pacemaker rates, it resulted in a more homogenous myocardial response to pacing and less intragroup variation.

Clinical implications. Fetal supraventricular tachycardia is now the most common cause of fetal hydrops (severe HF), which may be associated with fetal demise if not appropriately treated. Although the optimal treatment of fetal tachycardia has not been established, the mainstay is transplacental drug therapy. However, the optimal treatment of fetal tachycardia remains to be clarified. Digoxin, flecainide (1), beta-blockers, and calcium antagonists (23) have all been used. However, because drugs are usually given to the mother and transferred to the fetus by transplacental passage, fetal drug concentrations are unpredictable, particularly in the hydropic fetoplacental unit. This study suggests that prenatal cardiac function may be improved by metabolic intervention, and although this clearly requires further investigation, our data suggest a possible additional therapeutic option. Maternal hyperglycemia (e.g., with gestational diabetes) is well known to induce fetal hyperinsulinism with increased myocardial glycogen deposition and secondary hypertrophy. It is interesting to speculate that imposed maternal hyperglycemia might lead to beneficial responses during tachycardia, before direct treatment of the tachycardia with antiarrhythmic agents.

Conclusions. Fetal tachycardia is associated with important systolic and diastolic dysfunction in association with reduced myocyte glycogen stores. Glucose-insulin infusion leads to improved glycogen stores during tachycardia and obviates this myocardial dysfunction. These findings may have therapeutic implications for the management of human fetal tachycardia associated with myocardial dysfunction.

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