Fetoscopic Transesophageal Electrocardiography and Stimulation in Fetal Sheep

A Minimally Invasive Approach Aimed at Diagnosis and Termination of Therapy-Refractory Supraventricular Tachycardias in Human Fetuses

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Background—Therapy-refractory supraventricular tachycardia commonly results in hydrops and death in human fetuses. The purpose of this study in fetal sheep was to assess the feasibility of a minimally invasive fetoscopic approach for fetal transesophageal electrocardiography and stimulation aimed at diagnosis and termination of these tachycardias.

Methods and Results —We studied a total of 10 fetal sheep (87 to 103 days of gestation; term=145 days). We entered the amniotic cavity using a percutaneous fetoscopic approach and placed various electrophysiology catheters into the fetal esophagus. We recorded the number of animals in which fetoscopic transesophageal electrocardiography and stimulation were successful and assessed pacing success and thresholds for different catheters. In addition, we monitored for potential adverse effects from stimulation and for other complications of the operation. Recording of transesophageal electrocardiograms was successful in all fetal sheep. Capture during stimulation was successfully documented by additional fetal bipolar surface electrocardiograms in 7 fetuses. In fetuses in which fetal surface electrocardiograms were not recorded, pacing stimulus artifacts interfered with documentation of capture. Although stimulation thresholds were high, the maternal rhythm was not affected by fetal stimulation.

Conclusions—Fetoscopic fetal transesophageal electrocardiography and stimulation are feasible in fetal sheep. This minimally invasive approach might have the potential to improve diagnosis and management of therapy-refractory supraventricular tachycardias in human fetuses. **(*Circulation*. 1999;100:772-776.)**

Key Words: tachycardia ■ electrocardiography ■ electrophysiology ■ fetoscopy

Supraventricular tachycardia refractory to conventional therapy results in hydrops and death due to severe cardiac failure in >20% of affected human fetuses.[1] In survivors, an increased risk for brain damage has been observed.[1–3] If gestation is more advanced, premature delivery has been performed to salvage late gestation fetuses with therapy-refractory supraventricular tachycardias in cardiac failure. Premature delivery of these frail patients, however, results in additional morbidity and mortality.[4,5]

The poor prognosis of fetuses with therapy-refractory supraventricular tachycardia in cardiac failure has prompted interest in developing alternative treatment strategies to achieve tachycardia termination. Cryosurgical ablation of the atrioventricular node followed by long-term epicardial pacing through an open fetal operative approach has been performed in fetal sheep.[6] However, this approach is associated with high maternal and fetal morbidity because it requires maternal laparotomy and hysterotomy as well as fetal thoracotomy. Hysterotomy for open operative procedures, however, uniformly results in premature delivery in human fetuses.[7] In addition, cesarean section is obligatory after open fetal surgery for the treated as well as for any future child because of the risk of uterine rupture during normal delivery.[8] Of greater concern, significant decreases in fetoplacental blood flow have been observed in human fetuses after open fetal surgery for diaphragmatic hernia.[9] These flow changes may be particularly detrimental to a tachycardic fetus in cardiac failure. Furthermore, ablation of the atrioventricular node results in lifelong pacemaker dependency and associated problems. Because most tachycardia in the neonate/fetus is orthodromic reciprocating tachycardia with spontaneous resolution during the first year of life, the morbidity and mortality of atrioventricular nodal ablation seem excessive in the context of the natural history in these patients.[10,11]

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In contrast to open fetal surgery, fetoscopic surgery does not require maternal laparotomy and hysterotomy. As a result, no maternal mortality or significant morbidity has been reported in a large multicenter series of 3000 diagnostic procedures in human fetuses.[12] Recent studies in primates and sheep indicate that a minimally invasive fetoscopic approach also results in significantly less premature uterine contractions and less reduction in maternoplacental blood flow after the procedure.[13,14] A minimally invasive fetoscopic approach that permits recording of fetal transesophageal electrocardiograms and cardiac stimulation with low operative risks to mother and fetus may enhance our understanding of the underlying electrophysiological mechanisms of therapy-refractory fetal tachycardias and permit more appropriate drug selection. Transesophageal electrocardiography and stimulation might be of similar value in the fetus than it has been in postnatal patient populations to diagnose and terminate tachycardias of supraventricular origin.[15,16] Therefore, the purpose of our study in fetal sheep was to assess the feasibility of a minimally invasive fetoscopic approach for fetal transesophageal electrocardiography and stimulation.

Methods

We performed our studies in 10 time-bred fetal sheep (age range, 87 to 103 days of gestation; mean=94.5 days; term=145 to 150 days). Each ewe was positioned supine, intubated, and ventilated with 0.5% to 2% halothane in pure oxygen (Figure). Placental transfer of the anesthetic gas provided fetal anesthesia.

Operative Fetoscopic Approach

We placed three to four 5-mm trocars (M.E.M., Madison, Conn) into the amniotic cavity of each ewe by a percutaneous technique using T-fasteners (Ross Product Division-Abbot Laboratories, Columbus, Ohio).[17] Whereas the first trocar was placed by ultrasound guidance, subsequent trocars were placed under direct fetoscopic visualization following amniotic fluid removal and low-pressure (8 to 13 mm Hg) insufflation of the amniotic cavity. Using fetoscopic instrumentation (Karl Storz GmbH, Tuttlingen, Germany), we suspended the fetal head with a stay suture underneath the anterior uterine wall. In 7 sheep, we advanced an 8F standard catheter sheath into the fetal oropharynx. Head suspension and intraoral catheter sheath insertion were performed to facilitate introduction and exchange of various electrophysiological catheters (quadripolar monophasic action potential - pacing combination catheter, Boston Scientific Corporation; bipolar electrophysiology catheter, Arrow Technologies; decapolar electrophysiology catheter, BARD - Angiomed) (Table). We measured the distance between the fetal mouth and chest using laparoscopic instruments with length markings and advanced the electrophysiology catheter until a clear transesophageal ECG was recorded.

Recordings and Protocols

All electrophysiological signals were preamplified, digitized (1 kHz sampling rate; maximum amplitude voltage resolution <1%), and stored on optical disc for offline analysis using a 32-channel electrophysiology system (LAB System 2.57, BARD Electrophysiology). Transesophageal stimulation was attempted between the 2 electrodes recording the highest atrial signal amplitudes with a preselected impulse duration of 10 ms using a high output stimulator (Osypka Pace 500D, Sulzer Medica). Stimulus strengths varied between 10 and 150 mA. When stimulation was not successful, stimulation was attempted using other pairs of electrodes. Bipolar fetal surface electrocardiograms were recorded in the last 7 sheep by placing laparoscopic instruments (n=4) or suturing standard epicardial pacing wires (n=3) onto both fetal shoulders resembling Einthoven lead I. A standard 6-lead ECG was recorded from each ewe.

Study Variables and Statistical Analysis

We recorded the number of animals in which fetoscopic transesophageal electrocardiography and stimulation were successful. We assessed pacing success for different catheters and the threshold at high rate stimulation (300 bpm). We assessed adverse effects on fetal and maternal rhythm during and after stimulation and monitored for complications from the operation.

Following fetal electrocardiography and stimulation, we euthanized 5 ewes and their fetuses under deep anesthesia with potassium-chloride overdose. In these animals, fetal umbilical blood gases were taken. In the remaining 5 ewes, we filled the uterus with warmed saline containing antibiotics and closed the uterine trocar insertion sites by a percutaneous technique.[17] These ewes and their fetuses recovered from surgery. The newborn lambs were observed for injury and neurological damage from the procedure. At autopsy, in both the short- and long-term studies, we inspected the maternal abdomen for bleeding or injury to other organs from the procedure and assessed adverse fetal effects from percutaneous access and transesophageal stimulation. The study protocol was approved by the local committee on animal research and was performed according to institutional guidelines.

Results

Fetal Electrocardiograms and Stimulation

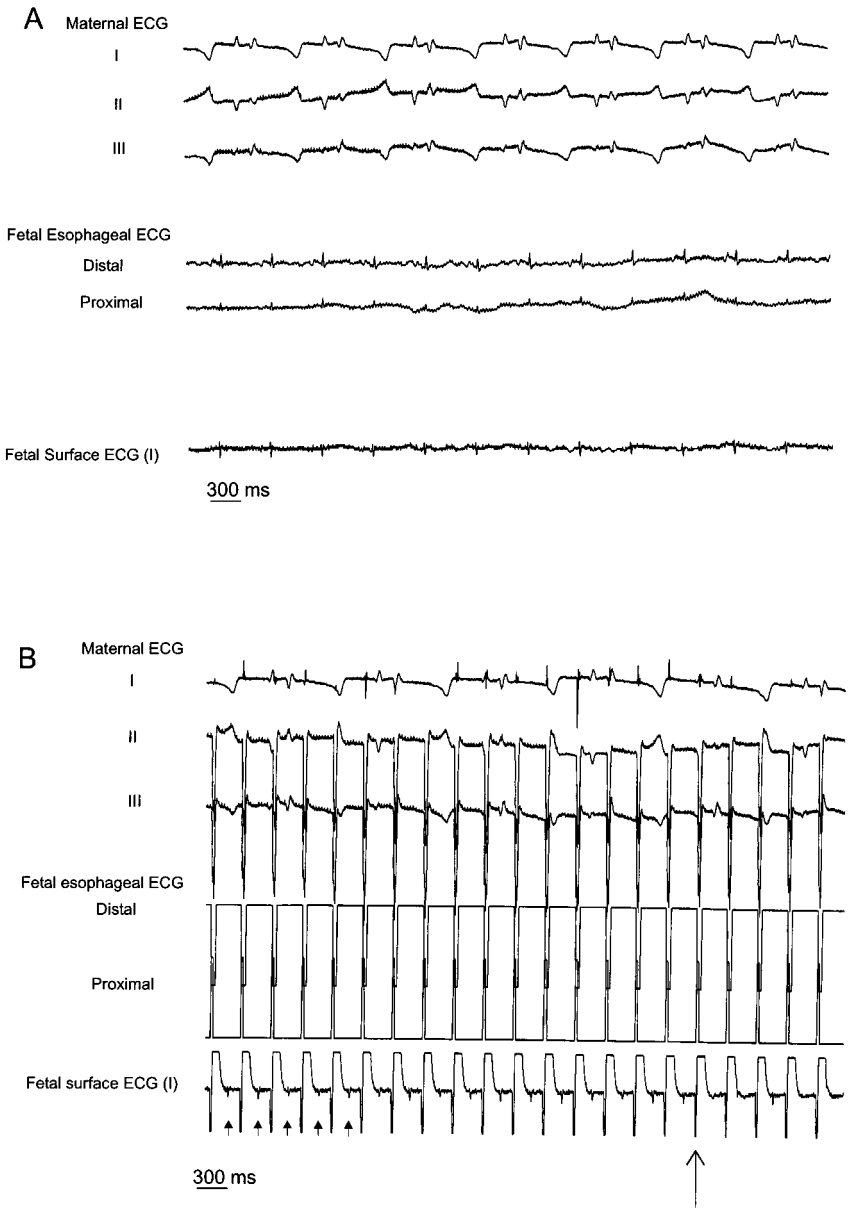
Bipolar transesophageal electrocardiograms were recorded in all fetal sheep. Transesophageal electrocardiograms allowed clear distinction between atrial and ventricular activation (Figure). In contrast, atrial signals, though probably present, were not distinguishable from noise signals by fetal surface electrocardiograms, with the exception of one sheep (in whom an atrial deflection could be identified by comparing atrial deflections in the transesophageal electrogram with the surface ECG).

Pacing artifacts in the transesophageal electrocardiograms were of high amplitude, thereby precluding verification of

Stimulation Success and Thresholds of Various Catheter Types in 7 Fetuses

Catheter Type	Catheter Diameter	Electrode Size and Morphology	Electrode Spacing	Stimulation Success	Stimulation Threshold (mA)
Quadripolar MAP catheter	7F	Round electrodes, 2 mm diameter	5 mm (MAP electrodes) 2 mm (pacing electrodes)	25% (1/4)	135
Bipolar catheter	2F	Circular electrodes, 2 mm length	5 mm	43% (3/7)	87±31
Decapolar catheter	6F	Circular electrodes, 2 mm length	3 mm	100% (7/7)	48±26

Using an impulse width of 10 ms. Successful stimulation at the lowest thresholds was most reliably achieved by the decapolar catheter. In the first 3 fetal sheep in which fetal surface electrocardiograms were not recorded, pacing artifacts interfered with documentation of capture during stimulation. These fetuses were not included in this table.



Simultaneous recordings of maternal surface ECG (upper 3 recordings), fetal transesophageal ECG (middle 2 recordings), and fetal surface ECG (Einthoven lead I, bottom recording). The vertical bar indicates a 300 ms reference. A, Recording during sinus rhythm of mother and fetus. Transesophageal electrocardiography allows distinction between atrial and ventricular activation. B, Recording during transesophageal stimulation of the fetal heart at 200 bpm. Small arrows at left portion of recording indicate atrial capture demonstrated by the fetal surface ECG. The larger arrow at right portion of recording indicates loss of capture after progressive reduction of stimulus strength. Note that despite high stimulation thresholds, the maternal rhythm remains unaffected by fetal stimulation.

local capture from this site. In the first 3 fetuses in which a surface ECG was not recorded, successful stimulation could not be documented. Successful transesophageal stimulation was documented in all fetuses in the 7 fetuses in which surface electrocardiograms were recorded (Figure).

Stimulation and the lowest stimulation thresholds (mean 48±26 mA) were most reliably achieved using the decapolar catheter (Table). Using the decapolar catheter, the 2 electrodes showing the highest amplitude in the transesophageal electrogram were used as stimulation electrodes. Because simulation success was rarely achieved and the MAP catheter was stiffer and larger than the other catheters, it was not used in the last 3 experiments. Despite good local electrocardiograms, the slim bipolar catheter allowed for successful stimulation in only 3 of 7 fetuses (Table).

Apart from pacing artifacts, the maternal rhythm was not affected by fetal cardiac stimulation. All fetal sheep survived fetoscopic transesophageal electrocardiography and stimulation and were alive at the end of the procedure. In 4 of the 5 ewes that were acutely terminated after the procedure, umbilical arterial blood gases were normal. One of the 5 ewes that continued gestation aborted 1 week after the procedure. The 4 other ewes continued gestation and delivered between 127 and 146 days of gestation (mean=137.5 days; term=145 days). At autopsy, no damage to the esophagus at the stimulation site was observed after the short-term studies. In all fetuses, fetal head suspension and intraoral catheter sheath placement was achieved with negligible injury.

Complications

In one ewe, the maternal stomach was perforated with one of the trocar tips and had to be repaired through a mini laparotomy. Another ewe became hypotensive and bradycardic during the procedure and her CO_2 elimination decreased. Hypotension was successfully treated by epinephrine administration and the operation could be completed. This

ewe delivered 2 lambs at 127 days of gestation; the lamb that had undergone transesophageal electrocardiography and stimulation had developed a membranelike form of esophageal atresia superior to the previous stimulation site and died from aspiration on the first day of life. In addition, bilateral cerebral hemorrhage was found in this lamb at autopsy. Histochemical staining revealed a fresh, peripartal hemorrhage unrelated to prior fetal electrocardiography and stimulation. Another lamb died in the first hours of life following a protracted delivery at 142 days of gestation.

Discussion

Our study demonstrates that percutaneous fetoscopic transesophageal electrocardiography and stimulation are feasible in fetal sheep. Importantly, despite high pacing thresholds, the maternal rhythm was not affected by fetal cardiac stimulation and maternal electrocardiograms at the end of the procedure were not different from baseline recordings.

Implications

Fetal transesophageal electrocardiograms allowing discrimination between atrial and ventricular activation can reliably and reproducibly be obtained by our minimally invasive fetoscopic technique. Similar to postnatal transesophageal electrocardiographic studies, the prenatal approach should permit assessment of the mechanism of tachycardia and characterization of conduction properties in the fetus.[15,16] On the basis of the tachycardia mechanism found, selection of specific drug treatment and drug testing by stimulation seem possible. Temporary placement of the intraesophageal electrophysiology catheter into the early postoperative period may permit repetitive termination of tachycardia relapses until the most effective drug therapy has been defined similar to previous experiments in adults.[18] Transesophageal electrocardiography and stimulation may, therefore, become useful diagnostic and therapeutic tools for definition and termination of therapy-refractory supraventricular tachycardias in fetuses.

In contrast, currently applied maternal transabdominal fetal echocardiography permits little differentiation among the various supraventricular tachycardias and, consequently, treatment has been empirical.[19–21] Postnatal electrophysiological studies of newborns with previously known fetal tachycardia are limited by their retrospective nature and selection bias.[22,23] Because the newborns analyzed in these studies belong to the group of survivors, the mechanisms of the most malignant tachycardias resulting in fetal demise might not be represented in these studies. Whereas tachycardia conversion is generally achieved in nonhydropic fetuses, fetuses with supraventricular tachycardia and hydrops respond less well to empirical antiarrhythmic therapy.[1,21–26] Premature delivery of this subgroup of patients results in additional complications.[4,5] Therefore, the mortality in this group has been considerable,[1] and accurate definition of the underlying mechanism by fetal transesophageal electrocardiography and stimulation may be helpful.

Fetal transesophageal electrocardiography may also help to identify potentially dangerous drug effects. Fetal demise within 24 hours of antiarrhythmic drug administration has raised concerns about a direct relationship between drug and demise.[1,27] Fetal monitoring by temporary fetal electrocardiograms may prove useful to recognize and counteract hazardous electrocardiographic changes indicating drug toxicity.

Technical Considerations

Percutaneous fetal access for intraesophageal catheter placement and fetal surgical manipulation can reliably be achieved by our previously described ultrasound and fetoscopic techniques.[17,28,29] Fetal head suspension combined with intraoral placement of a standard catheter sheath facilitates introduction and exchange of electrophysiology catheters. Recording of complimentary fetal surface electrocardiograms is necessary to confirm capture because pacing stimuli artifacts notably interfere with transesophageal electrocardiographic recordings. Although local transesophageal electrocardiograms could be recorded using all the catheters tested, stimulation was better achieved by using multipolar than bi- or quadripolar electrophysiology catheters (Table). Optimizing the stimulation technique in sheep fetuses may not apply to human fetuses because of differences in torso-heart-esophagus anatomy between both species. Despite these differences, transesophageal electrocardiography and stimulation of the fetal heart may provide useful information about the functional maturation of the cardiac conduction system.

Complications

In general, fetoscopic fetal electrocardiography and stimulation has been safe for the ewe and her fetus. Importantly, the maternal rhythm was not affected by the high fetal pacing thresholds. Nevertheless, some potentially serious maternal and fetal complications were encountered during our early studies. These complications can be partly explained by the step-by-step development of these experimental procedures.

In one ewe, the anterior stomach wall was perforated with one of the trocars during the fetal access procedure. In another ewe, marked hypotension was observed. Unattended, these complications can result in serious and intolerable maternal morbidity. Because maternal safety is paramount to any invasive fetal procedure, exclusion or treatment of any injury to maternal intra-abdominal contents by laparoscopy is important before the trocar insertion sites are closed. In addition, maternal monitoring during fetal procedures should follow established protocols.

All fetal sheep survived fetoscopic fetal transesophageal electrocardiography and stimulation and were alive at the end of the procedure. Normal umbilical blood gases obtained after 4 short-term studies provided the first evidence that, although time consuming, the minimally invasive fetoscopic approach does not result in serious compromises of maternoplacental and fetoplacental blood flows. Along with this finding, we did not observe any maternal or fetal neurological injuries attributable to the procedure. Bilateral cerebral bleeding in one fetus was clearly defined by histochemical staining as a peripartum event. Yet in one of our long-term studies, supracardiac esophageal atresia from intraesophageal catheter manipulation was observed at postnatal autopsy. This complication might have been due to mechanical trauma or thermal injury from stimulation. Therefore, immediate post-

partum assessment of esophageal passage will be mandatory in any human fetus subjected to this procedure.

Limitations

This study has been performed in healthy fetuses and acute fetal demise was not observed. In contrast, in tachycardic fetuses in severe cardiac failure, the operative mortality of the procedure may be higher. Nevertheless, we believe that the poor prognosis of this subgroup of fetuses may justify the application of our technique as a potential life-saving approach.

Conclusion

Our study demonstrates that fetoscopic fetal transesophageal electrocardiography and stimulation are feasible in fetal sheep. This minimally invasive approach has the potential to improve definition and management of therapy-refractory supraventricular tachycardias in hydropic human fetuses. Some potentially serious maternal and fetal complications encountered in our early studies can be explained by the experimental nature of these procedures and may be avoidable by enlarged operative experience.

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