CREATIVE CONCEPTS

Preclinical testing and optimization of a novel fetal micropacemaker

Yaniv Bar-Cohen, MD, FHRS,[*] Gerald E. Loeb, MD,[†] Jay D. Pruetz, MD,[*] Michael J. Silka, MD,[*] Catalina Guerra, DVM,[‡] Adriana N. Vest, BE,[†] Li Zhou, MS,[†] Ramen H. Chmait, MD[§]

From the [*]Division of Cardiology, Children's Hospital Los Angeles; and Keck School of Medicine, University of Southern California, Los Angeles, CA, [†]Department of Biomedical Engineering, University of Southern California, Los Angeles, California, [‡]C.W. Steers Biological Resources Center, Los Angeles Biomedical Research Institute, Harbor–University of California, Los Angeles, Torrance, California, and [§]Department of Obstetrics and Gynecology, Keck School of Medicine, University of Southern California, Los Angeles, California.

Introduction

Complete heart block (CHB) in the human fetus may result in progressive bradycardia with the development of hydrops fetalis in one-fourth of these pregnancies.[1,2] If hydrops fetalis occurs and the fetus cannot be delivered because of prematurity or other clinical concerns, fetal demise is nearly inevitable. Although the degree of myocardial dysfunction due to antibody-mediated damage in congenital CHB is variable, successful pacing of a fetus with CHB and hydrops fetalis theoretically could allow resolution of hydrops in several weeks and permit an otherwise normal gestation. However, historical attempts at pacing human fetuses have invariably failed, with no survivors reported to date.[3–6] To address this problem, we designed a single-chamber pacing system that is self-contained and can be percutaneously implanted in the fetus without exteriorized leads, thereby permitting subsequent fetal movement without risk of electrode dislodgment (Figure 1).

Previous preclinical animal studies in adult rabbits demonstrated the viability of our implantation scheme and allowed us to optimize the electronics of our pacing system.[7] We now report on implantation outcomes of functional micropacemakers in fetal sheep.

Materials and methods

Device design and function

In order to meet our rigorous requirements regarding device size, power consumption, and development cost, we used a simple relaxation oscillator based on a single transistor.[8] The device functions in a fixed-rate mode (ie, VOO) with a rate that predictably varies with battery voltage (generally 100–110 bpm). The output pulse exponentially decays with a total charge that is fixed by the electronic component values and is independent of electrode impedance.[7] In 6 of 7 experiments, the devices had a 3-μC output pulse (3-V peak, 250-μs time constant for fully charged battery). This corresponds approximately to a conventional 2 V over 0.4-ms square pulse. The 3-mAh lithium battery cell in the implants sustains pacing for approximately 6 days and can be recharged by inductive coupling of a 6.78-MHz electromagnetic field from a transmitting coil positioned outside the maternal body. With the 6th implantation, a higher-output device (7 μC, 3-day recharging interval) was used.

Device implantation

Implantation experiments were performed on pregnant sheep (*Ovis aries,* Rambouillet, and Columbia mix breed) at 112–128 days of gestation with only singleton pregnancies included. The protocol conformed to the Guide for the Care and Use of Laboratory Animals and was approved by the Institutional Animal Care and Use Committees at the University of Southern California and the Los Angeles Biomedical Research Institute. The ewes were anesthetized with ketamine and atropine, followed by isoflurane. Oxacillin and gentamicin were given preoperatively. Dissection down to the uterine wall was made via a midline abdominal incision, and the uterus was externalized. A pursestring suture was placed, and a uterine incision was made. The fetal thorax was exposed, and electrodes were placed in triangulated locations surrounding the fetal heart to allow fetal ECG evaluation.

In the first 3 animals, the fetal subxyphoid area was exposed via the uterine incision for insertion of the percutaneous implantation trocar and cannula (3.8-mm internal diameter, 4.5-mm external diameter; Richard Wolf Inc,

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ABBREVIATIONS CHB = complete heart block (Heart Rhythm 2015;0:-1–8)

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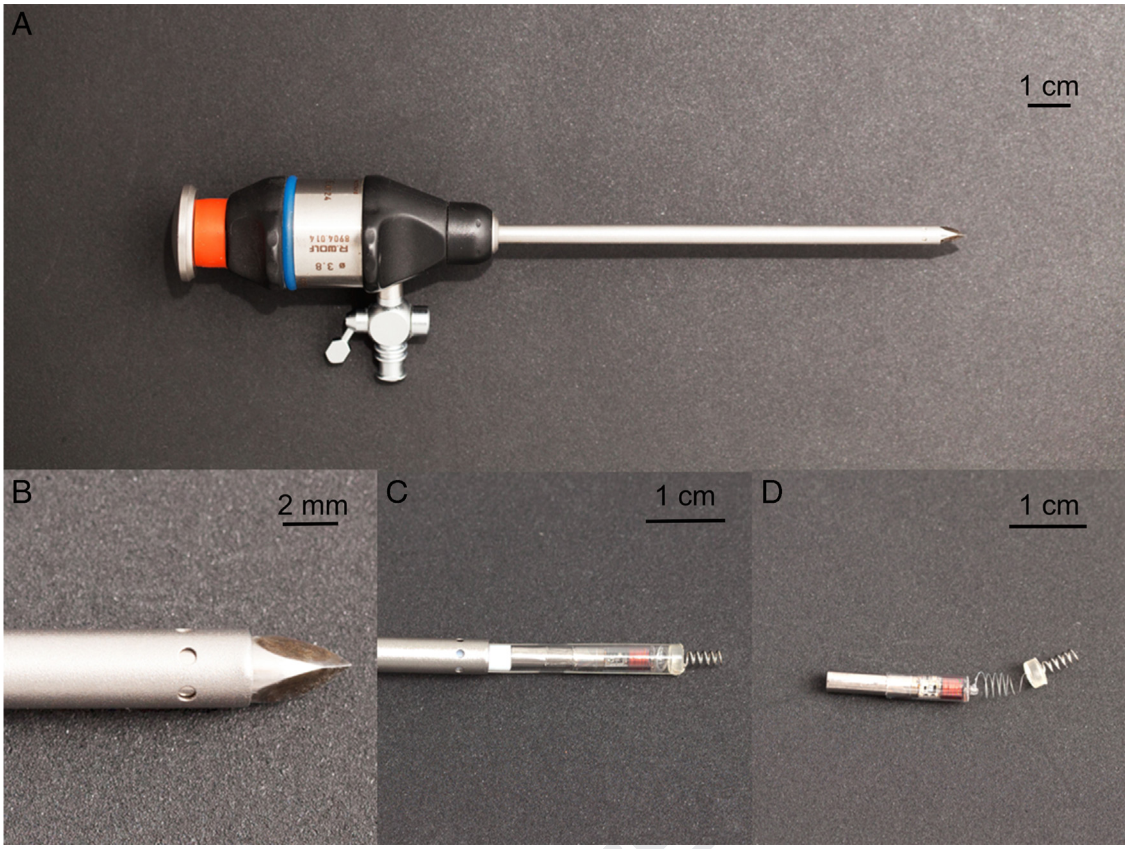

Figure 1 Implantation equipment. **A:** Implantation cannula with trocar inside. **B:** Sharp tip of trocar protruding from end of cannula. **C:** Micropacemaker inside its implantation sheath protruding through cannula. **D:** Micropacemaker device with distal electrode screw connected to the micropacemaker (3.475-mm diameter, 18 mm long) via a coiled flexible lead.

Vernon Hills, IL; Figure 1). In the latter 4 animals, the trocar and cannula were advanced percutaneously through an intact area of the uterine wall and into the fetus at the subxyphoid region. Under ultrasound guidance, the trocar and cannula were advanced through the fetal diaphragm and toward the ventricles. Once ultrasound imaging suggested that the cannula and trocar were against the epicardial surface, the trocar was removed and the pacemaker implantation system was advanced through the cannula. After the distal electrode screw reached the epicardium, the device was rotated clockwise into the myocardium. The device was then released by slowly withdrawing the cannula while keeping the device in place with a pushrod (Figure 2). In cases in which successful pacing could not be demonstrated with the initial device, a second and once a third device implantation attempt was performed in the same animal.

After initial experiments demonstrated difficulty in correctly positioning the implantation cannula at the epicardial surface, a pericardial effusion was created in the 4 latter experiments. This was performed in order to more closely replicate the clinical anatomy in a human fetus with hydrops fetalis. After the uterine wall was exposed and fetal electrodes were placed, a 17-cm, 21-gauge needle was advanced to the epicardial surface (Figure 3A). When the needle appeared to have entered the pericardium, saline was injected until ultrasound demonstrated the presence of a small pericardial effusion (Figure 3B). The cannula and trocar were then inserted as described earlier, with improved visualization of the epicardial surface.

After device deployment, the purse string uterine incision was closed, and the uterus was returned to the abdominal cavity. The fetal electrodes were delivered through a small incision in the maternal abdomen for postoperative access. Final ultrasound imaging of the fetus was performed to evaluate heart rate and rhythm, cardiac function, electrode and device position, and overall fetal well-being. The sheep was awakened from anesthesia, administered penicillin G, and returned to the animal housing.

Fetal sheep follow-up and device recharging

Repeat ultrasound evaluations were performed in the first 24–48 hours of follow-up and once to twice per week thereafter. In addition, the externalized fetal skin electrodes were used to obtain a fetal ECG during follow-up. In the last 4 animals, recharging of the fetal pacemaker was attempted using an external recharging ring that was specifically developed for the micropacemaker.[8] The design of the pacing circuit was modified to increase the pacing rate modestly (5–10 bpm) in proportion to the received strength of the radiofrequency magnetic field. By evaluating the pacing rates when the recharging ring was deactivated (ie, no