Embedded medical devices: Pressure volume loops in rodents

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Man has been instrumenting the human body with electrical devices since the early 1800s. McWilliam built an electrical stimulator of the heart in 1889. In the 1930s, Hyman built and patented multiple versions of an artificial pacemaker. The first one was operated by a hand crank and spring motor to generate and supply the electricity. Around 1960, battery-powered pacemakers arrived on the scene. There are five companies that currently provide pacemakers: Biotronik, Boston Scientific, Medtronic, St. Jude Medical, and Sorin. Hearing aids, glucose monitors, artificial joints and limbs, and biopotentials monitors are additional devices that can be implanted.

In addition to human applications, embedded devices are also developed for use in animals undergoing medical research. There are many devices available for larger animals but very few for rats and mice. One such device is made by Data Sciences International in St. Paul, Minnesota. The DSI PhysioTel transmitters are designed to measure biopotential, temperature, activity, and blood pressure, but not in the same device at the same time. Transonic Systems Inc. produces a full range of embedded devices for larger animals. Millar Instruments also markets a telemetric blood pressure (BP) monitor that similarly measures biopotentials but limits the system's use to animals weighing more than 200 g.

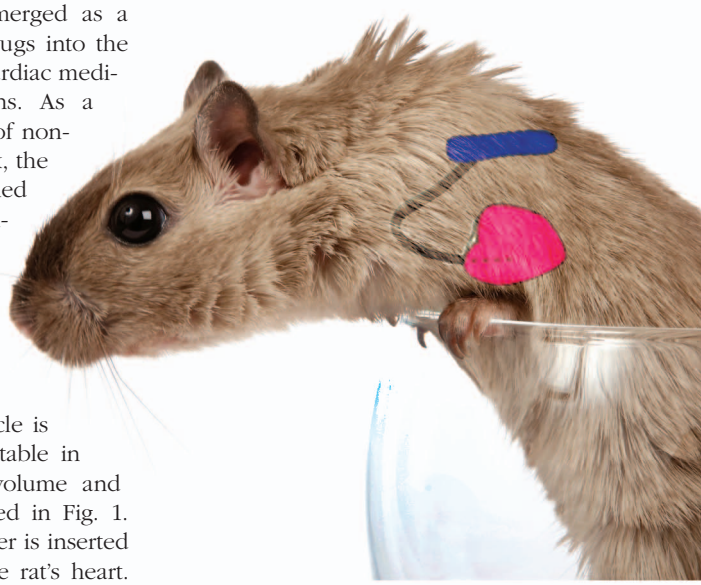
New drugs are commonly tested using transgenic models of heart disease. As a result, it has become important to accurately and thoroughly evaluate cardiac function in rodents (mice and rats). Rodent hearts are extremely sensitive to sedation and yield very different results when conscious studies are compared to those using anesthesia. Therefore, it is of paramount importance that a complete assessment of cardiac function is carried out in freely roaming, unanaesthetized rodents. In order to accomplish this goal, we must turn to wireless devices that utilize miniature, lightweight implants to transmit data to a nearby base station. Left ventricular pressure-volume (LV PV) measurements would be ideal for medical research involving the basic understanding of normal and diseased hearts, but more importantly in developing and testing new treatments of heart disease. An embedded device that can be implanted in conscious, ambulatory rodents will provide a complete hemodynamic profile to the academic scientist and for drug discovery and safety studies by large pharmaceutical companies. Additionally, miniaturization along with the low-power optimization of the circuitry is required for these devices to be practical.

Further support to develop a telemetric device comes from the identification of drug side effects that occur in patients pre- and post-U.S. Food and Drug Administration (FDA) approval. Safe cardiac pharmacology has emerged as a barrier for entry of new drugs into the marketplace, not only for cardiac medications but all medications. As a result of the restricted use of non-cardiac drugs such as Vioxx, the FDA has further strengthened its requirements for screening all new compounds for potential toxic cardiovascular effects, requirements that rodent studies can satisfy effectively and economically.

The purpose of this article is to discuss a device implantable in rats that measures heart volume and blood pressure, as illustrated in Fig. 1. The pressure-volume catheter is inserted into the left ventricle of the rat's heart. The left ventricle is the high-pressure pumping chamber of the heart. The pressure-volume catheter includes four ring electrodes, which are used to measure volume, and a pressure sensor. The embedded device is placed under the skin on the back where the rat cannot reach it. The device measures left ventricular pressure and volume and transmits the data to a base station via a wireless link. The base station records and plots pressure-volume loops.

Challenges faced

Designing medical devices entails a long list of challenges. First and foremost, materials must be biocompatible. If you have ever left a splinter in your skin, you have experienced the body's normal reaction to foreign objects. It first attempts to isolate it, and then it attempts to dissolve or reject it. A second critical constraint is that of electrical safety. In our case, it is especially important because we have four metallic electrodes in the heart. Thresholds for safety are frequency dependent. At 60 Hz, we must limit current into the heart below 10 μA RMS. Our device operates at



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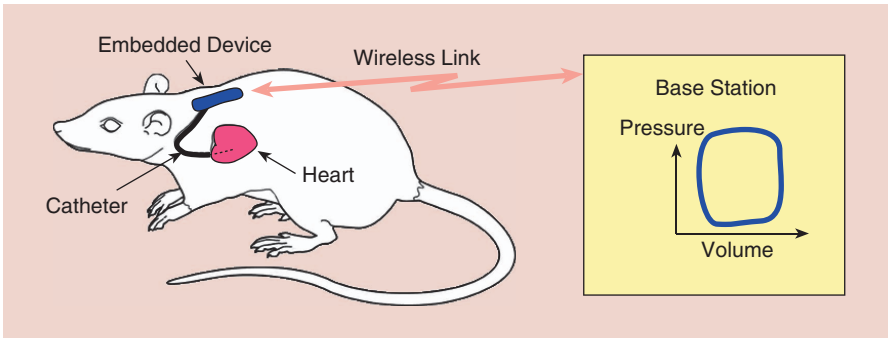

Fig. 1 Block diagram illustrating the components of the embedded device capable of measuring pressure and volume.

LEFT VENTRICULAR PRESSURE-VOLUME (LV PV) MEASUREMENTS WOULD BE IDEAL FOR MEDICAL RESEARCH INVOLVING BASIC UNDERSTANDING OF NORMAL AND DISEASED HEARTS, BUT MORE IMPORTANTLY IN DEVELOPING AND TESTING NEW TREATMENTS OF HEART DISEASE.

20 kHz, where it is safe to inject the 50 µA RMS needed to perform the volume measurement. Since the device will be embedded into a rodent, there will be size and weight constraints above which the animal cannot move around freely.

Transgenic animals are particularly susceptible to the effects of anesthesia and handling stress. Open-chest procedures in particular are known to be associated with unphysiologically low blood pressures. Furthermore, tethering can be problematic. The solution lies in the development of an instrument capable of being implanted internally, and providing accurate, reproducible, and instantaneous LV PV relations via telemetry in conscious freely roaming rodents.

Low power design

One of the obvious constraints is power. The power budget embodies this concept. Let E be the battery energy storage specification in amp-hours and t_{life} be the desired lifetime of the product. We can estimate the average current a system is allowed to draw as

$$\text{Average Current} \leq \frac{E}{t_{\text{life}}}.$$

For example, if we have a 130-mA-hr battery, we have to run at an average of 36 µA for the device to operate for five months. That is, 130 mA-hr * (1,000 µA/mA)(1 day/24 hrs) * (1 month/30 days)/5 months = 36 µA. There are many strategies that combine to make an effective low-power design. First, we must reduce the voltage as much as possible. This initial prototype runs at 3.6 V, but to make the device implantable in mice, we will need to run at 1.8 V. Second, we must run with a clock rate as slow as possible. In digital logic, transitions require power, so reducing the number of transitions will lower the power requirement. Third, we will not use circuits that traditionally require a lot of power. In general these high-power circuits have very fast slew rates. Therefore, we choose low-power components and limit the bandwidth as much as possible. Fourth, because we will have a base station monitoring system, we will move as many processing steps as we can from the implant to the base station. Fifth, we will follow the advice given to us by our grandmothers, "Turn off the lights when you leave the room." In particular, we need an effective way to disconnect power when not using a circuit.

Since our analog circuits are low power, it is possible to power them with a digital output pin of the microcontroller, as shown in Fig. 2. In order to run at very low power, the system could run directly off battery power without a voltage regulator. Many microcontrollers have built-in voltage references so precision measurements are still possible. To enter the "deep sleep" mode, the power to external circuits is first removed, and then the microcontroller is put to sleep.

Communications

With embedded devices, communication is a crucial component of their functionality. Most devices implement two-way communication with a base station. Measurements are uploaded; commands and configurations are downloaded. However, in the future there will be a need for the embedded devices to communicate with each other. Our device uses an antenna and is configured to operate in the U.S. unlicensed Industrial, Scientific, and Medical (ISM) radio band between 902 and 928 MHz, with the center frequency at 915 MHz. Pacemakers communicate with their programmers using a low-frequency coil (typically about 6 cm in diameter), creating time-varying magnetic fields with frequencies in the 1–500 kHz range. Future embedded devices will use these types of waves for both communication and recharging the battery.

Volume and pressure measurements

The volume sensor consists of four electrodes, as shown in Fig. 3. A small 20 kHz current is applied to electrodes 1 and 4. The resulting 20 kHz potential difference is measured between electrodes 2 and 3. From this data, we calculate the complex electrical admittance (current/voltage), which is a function of both the blood properties (heart volume) and the muscle properties (unwanted signal).

Conductance is the real part of admittance and susceptance is the imaginary part. The muscle properties include

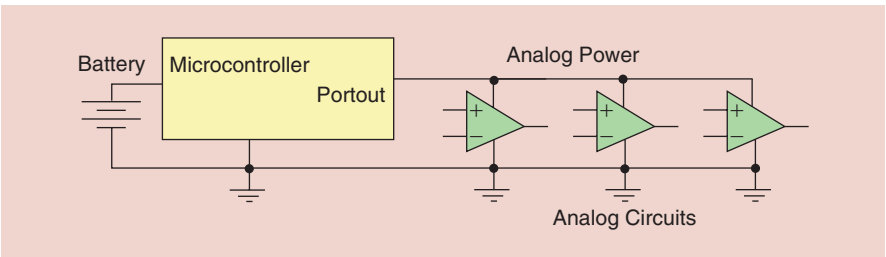

Fig. 2 The mixed-signal design includes software, digital hardware, and analog circuits.

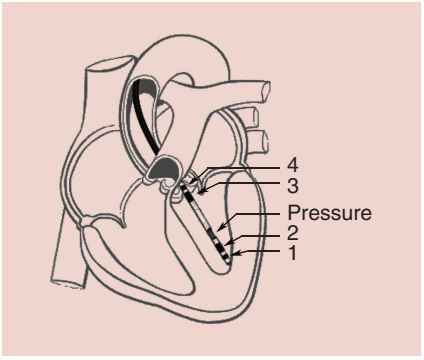

Fig. 3 A catheter with four impedance electrodes and a pressure sensor positioned in the left ventricle.

resistive (conductive) and capacitive (susceptive) components in tissues, while the blood is only resistive. Our measurement of the susceptance allows us to remove the contribution of the muscle, yielding a signal that is only dependent on the blood. Since the distance between electrodes 2 and 3 is fixed, our measurement of blood conductance varies monotonically with the volume of blood in the left ventricle. In this implementation, we calibrate the device with Two-dimensional (2-D) echocardiography when the device is implanted. Pressure is measured with a micromanometer cantilever beam pressure sensor, positioned in the left ventricle. The 1.9 F catheter has a diameter of 0.63 mm (0.025 in.).

Prototype of the embedded device

One approach to miniaturization is to design a mixed-signal, application-specific integrated circuit (ASIC). For designs with high production volume (like cell phones) or large markup (like pacemakers) this approach is economically feasible. For low-volume, low-cost products, we need to design from existing integrated circuits. Our first-generation embedded device was constructed from off-the-shelf low-power components. Fig. 4 shows the microcontroller, antenna, analog op amps, analog instrumentation amp, printed circuit board, and battery. Fig. 5 shows the implant coated with biocompatible silicone and with the catheter attached. This implant has a mass of 7.2 g and dimensions of 37 × 16 × 10 mm.

Results

In order to meet the power budget constraint, the device operates in four modes. Most of the time, the device is in deep low-power sleep mode, where the system current is around 5 µA. During data collection mode, the analog circuits

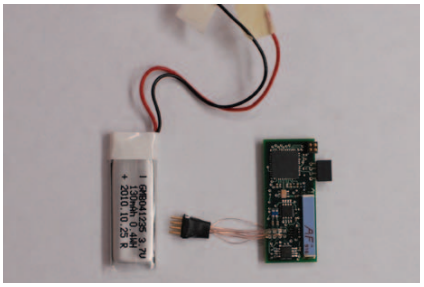

Fig. 4 The embedded device contains a microcontroller, wireless transmitter/receiver, antenna, analog circuits, and a battery.

are active and the microcontroller is running at full speed. As you can see from Fig. 6, it takes about 6 s to collect and send one epoch (380 points) of data at a sampling rate of 1,000 Hz. This translates to about two full PV loops. Fig. 6 shows the current profile during data collection and transmission. First, it takes 13.8 mA for 400 ms for the analog circuitry to make the 380-point measurement, then 30.6 mA for 680 ms for the radio to transmit this information to the base station. Then the radio switches to listening mode to download any setting changes specified by the user. In listening mode, the instantaneous current is 20.3 mA. Overall, the total current consumed for one 380-point epoch is 13.8 mA * 0.400 s + 30.6 mA * 0.680 s + 20.3 mA * 4.63 s = 120 mA-s. If the implant transmits once every two hours, and the sleep current is 5 µA, then the average current draw is

$$\frac{120\ mA-s}{\text{measurement}} * \frac{0.5\ \text{measurements}}{1\ \text{hr}} * \frac{1\ \text{hr}}{3{,}600\ s} + 5\ \mu\text{A} = 22\ \mu\text{A}.$$

This is within our current limit of 36 µA for five-month operation.

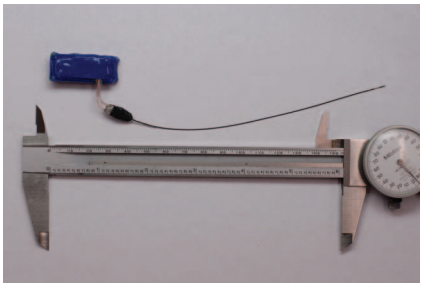

Fig. 5 The tip of the pressure-volume catheter includes four ring electrodes (used to measure volume) and a pressure sensor (Scisence Systems Inc. part #FTH-1912B-8018, a 1.9F PV sensor). The implant is coated with bio-compatible silicone.

One of the concerns of embedded devices is long-term drift. Fig. 7 shows measured pressure over 48 days. Since the sensor measures absolute pressure (nonvented), it is sensitive to changes in atmospheric pressure. However, these data suggest accurate measurements can be performed if the base station measures atmospheric pressure and performs an offset subtraction to adjust.

Figure 8 shows a real-time plot of the pressure versus impedance magnitude (|Z|) loop obtained in a freely roaming, unanaesthetized rat. To measure volume,

MICROCONTROLLERS AND ANALOG ELECTRONICS CURRENTLY AVAILABLE MAKE THE DESIGN AND IMPLEMENTATION OF EMBEDDED MEDICAL DEVICES POSSIBLE.

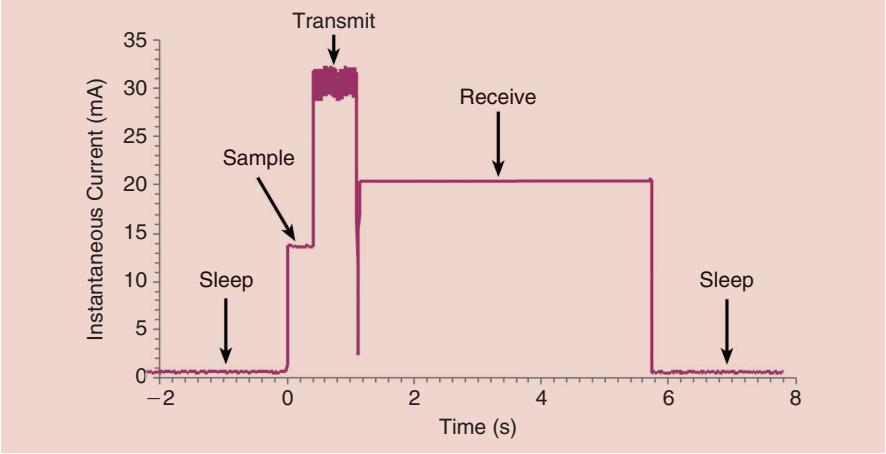

Fig. 6 Measurement of the supply current required to power the implant.

the imaginary part of the admittance is used to estimate the muscle component. The muscle component is then removed, leaving just the blood conductance. As the blood volume increases so does the conductance because there is more blood to conduct electricity (lowering the impedance). Because Fig. 8 plots impedance, the minimum volume is on the right and maximum volume is on the left.

Two-dimensional echocardiography is used to calibrate the device. Fig. 9 shows six of the resulting ultrasonic images. These images demonstrate the catheter is properly positioned in the left ventricle. Microcontrollers and analog electronics currently available make the design and implementation of embedded medical devices possible.

Into the future

As medical science evolves, the need for electrical/electronic devices to measure disease status and control treatment will also evolve. For this prototype we were able to utilize off-the-shelf microcontrollers, wireless communication, and analog circuits. However, to migrate this device into the mouse, we need to make four advancements. As mentioned previously, significant power savings can be made by reducing the operating voltage. Second, the wireless transmitter requires a significant fraction of the total battery capacity. Consequently, lower power communication channels will be needed. Third, embedded devices will need a mechanism to recharge their batteries. You can see from Fig. 4 that the battery contributes significantly to the size. Inductive coupling and converting the mechanical energy of vibration are two possible modalities to charge the battery. Finally, miniaturization can occur by integrating the analog and digital circuits into a single chip that integrates the functionality of many large circuit components.

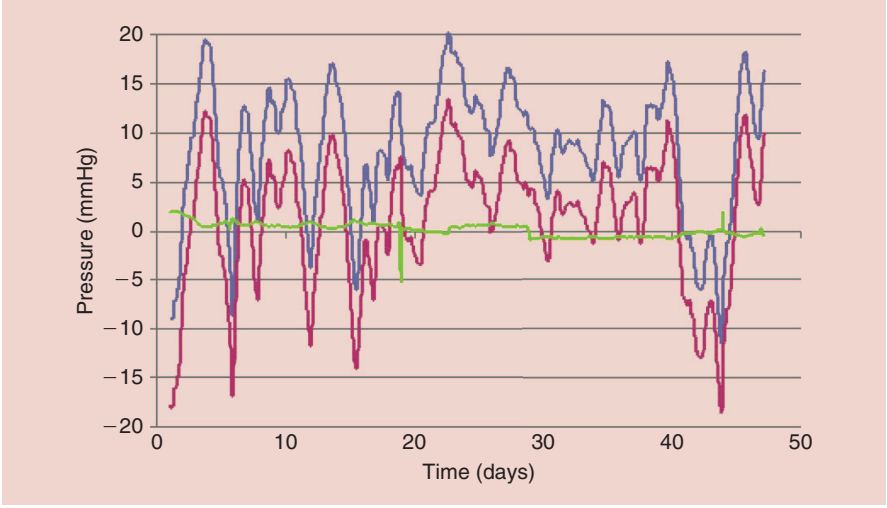

Fig. 7 Pressure drift measured over 48 days. The difference line (green) indicates that any drift over time is due to atmospheric pressure change. This correction will allow for a very stable, totally implanted, nonvented pressure measurement. (Data provided by Scisense Systems Inc., Ontario, Canada.)

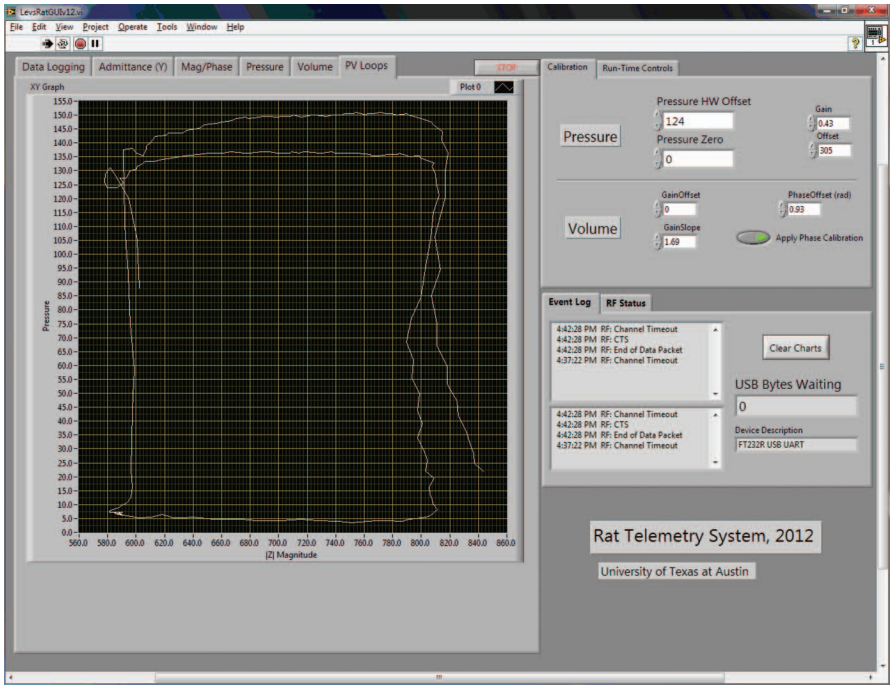

Fig. 8 Pressure volume loops being measured in real time on a fully conscious ambulatory rat. The left side of the |Z|-axis translates to a volume of about 500 µL and the right side translates to about 200 µL.

Acknowledgments

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The Institutional Animal Care and Use Committees at the University of Texas Health Science Center at San Antonio approved all experiments.

Read more about it

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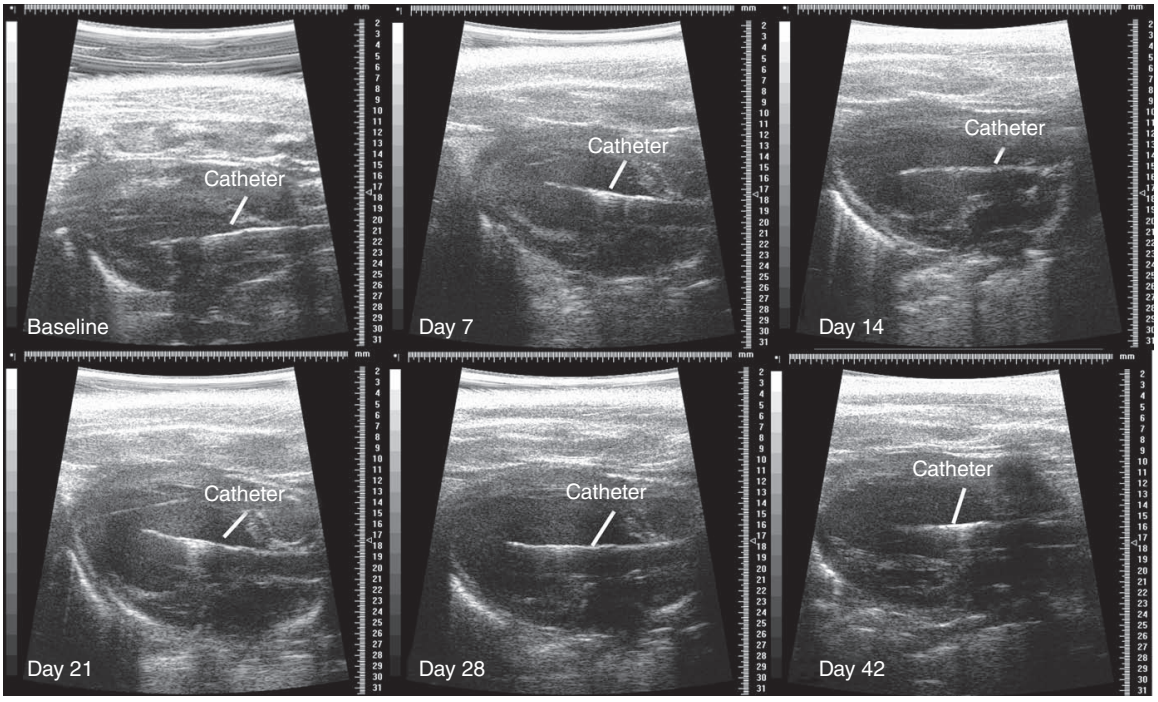

Fig. 9 Two-dimensional echo showing that the catheter position remains fixed over time. All figures captured at end diastole. At day 42, end diastolic volume is 517 µl; end systolic volume is 226 ml.

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