Transatrial Access to the Normal Pericardial Space
A Novel Approach for Diagnostic Sampling, Pericardiocentesis, and Therapeutic Interventions

Richard L. Verrier, PhD; Sergio Waxman, MD; Eric G. Lovett, PhD; Ricardo Moreno, BA

Background—A nonsurgical means to access the normal pericardial space could provide opportunities for diagnostic sampling and therapeutic interventions. Because there are currently no approved nonsurgical methods to accomplish this, we tested a new approach in large animals.

Methods and Results—A catheter system was employed in a percutaneous approach from a femoral vein to pierce the right atrial appendage. Pericardial access was confirmed by placement of a radiopaque guidewire visible under fluoroscopy (6 dogs, 13 pigs). In 7 of the pigs, pericardial tamponade, produced by injection of saline or heparinized blood into the pericardial space through this route, was confirmed by fluoroscopy and hemodynamic evidence. The feasibility and safety of this access route were tested with multiple repetitions in all 19 animals. At the end of each of the 17 acute experiments, direct inspection after thoracotomy revealed no hemopericardium, laceration, or bleeding on catheter withdrawal. In 24-hour survival studies performed in 2 of the 6 dogs, the animals exhibited no behavioral signs of discomfort or untoward consequences on recovery from anesthesia. Histology revealed only a small (≈1-mm) fibrinous plug at the site of puncture.

Conclusions—The percutaneous approach via the right atrial appendage provides a rapid, safe route to access the normal pericardial space for diagnostic sampling and to alleviate high-volume and low-volume (<200 mL) pericardial effusions. The access route is potentially useful for selective administration of therapeutic agents, growth factors, gene vectors, and cardioactive and vasoactive agents to the heart. (Circulation. 1998;98:2331–2333.)

Key Words: drugs ■ catheters/pericardium ■ diagnosis ■ angiogenesis

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nonsurgical, percutaneous approach that could permit rapid, safe access to the normal pericardial space has the potential for considerable diagnostic and therapeutic utility. The only approved nonsurgical means for entering the pericardial space are the subxiphoid and the ultrasound-guided apical and parasternal needle catheter techniques. These methods are indicated for drainage of moderate to large effusions and tamponade but carry significant risk of cardiac puncture and coronary laceration when the estimated volume of pericardial fluid is <200 mL or the depth is <5 mm anteriorly on the echocardiogram. Entry to the pericardial space with the available methodology necessitates relatively advanced progression of disease with significant accumulation of fluid.

Thus, it has not been possible to sample pericardial fluid for diagnostic purposes or to administer therapeutic agents in the absence of sizable effusion. The main goal of our study was to demonstrate the feasibility of a nonsurgical, percutaneous route for accessing the normal pericardial space for diagnostic or therapeutic purposes. This new approach uses a catheter system for percutaneous access into the undisturbed pericardial space through the right atrial appendage.

Methods

The study was conducted according to National Institutes of Health standards, and protocols were approved by the Harvard Medical Area Standing Committee on Animal Use. Six dogs of either sex weighing 15 to 25 kg and 13 Yorkshire pigs of either sex weighing 25 to 35 kg were used. The animals were preanesthetized with ketamine 5 mg/kg IV, xylazine 2.2 mg/kg IV, and atropine 0.04 mg/kg IV and anesthetized with isoflurane or α-chloralose 100 mg/kg IV. Fluoroscopic images were obtained with a clinical unit (OEC Diasonics, model OEC 902). Arterial blood pressure was recorded through a femoral or carotid arterial sheath. Precordial ECGs and arterial blood pressure were monitored with a Gould recorder.

An 8F femoral introducer sheath was placed via standard approach into the right or left femoral vein. A 6F or 8F guide catheter was positioned under fluoroscopic guidance in the right atrial appendage to provide support for the other components. A small perforation was made in the right atrial appendage with a custom-fabricated, 21-gauge, hollow, radiopaque needle mounted at the tip of a 4F catheter. A soft, 0.014-in guidewire with a second radiopaque marker was advanced through the needle catheter into the pericardial space to secure the point of entry, guide the application catheter, and confirm position in the pericardial space. In 7 pigs, the needle catheter was withdrawn and exchanged over the guidewire for a tapered-tip 4F aspiration catheter with withdrawal side ports and a radiopaque marker, which was advanced into the pericardial space to deliver and
alterations in mean heart rate and mean arterial blood pressure during tamponade were analyzed by 1-way ANOVA with the Newman-Keuls post hoc test. Blood pressure was calculated from 10 heartbeats during baseline, tamponade, and relief in each animal. Corresponding heart rates were obtained for a minimum of 10 seconds. Values are expressed as mean ± SEM.

Results
After placement of the 6F or 8F guide catheter, accessing the normal pericardial space in experimental animals required 3 to 5 minutes and was confirmed fluoroscopically. Multiple repetitions of the access procedure were successfully performed in each of 19 large experimental animals (6 dogs and 13 pigs). In acute studies in 17 of the animals, direct inspection of the pericardial space after thoracotomy revealed no hemopericardium, laceration, or bleeding on catheter withdrawal. In 24-hour survival studies performed in 2 of the dogs, the animals exhibited no behavioral signs of discomfort or untoward consequences on recovery from anesthesia. Histology revealed only a small (≈1-mm) fibrinous plug at the site of puncture.

In 7 of the pigs, pericardial effusion was simulated by injection of 70 to 170 mL saline or 180 mL heparinized blood mixed with radiopaque dye and was evident in fluoroscopic images (Figure 1). Pulsus paradoxus was a frequent sign of hemodynamic compromise (Figure 2). During tamponade, there was marked elevation in heart rate (from 84 to 126 bpm), with pulsus paradoxus and reduction in arterial pressure. Tamponade was alleviated in 5 minutes with aspiration catheter, and ECG morphology and hemodynamics returned to baseline.

Discussion
The main objective of the present study was to demonstrate the feasibility of nonsurgical, percutaneous access to the normal pericardial space through the right atrial appendage. The intent was to examine whether potentially useful clinical interventions could be performed. The particular application tested was relief of pericardial effusion, because this is a medically indicated procedure for entering the pericardial space. Furthermore, successful demonstration of pericardiosentesis would carry the implication that the technique could be used for diagnostic fluid sampling and local cardiac drug delivery. We were able to access the normal pericardial space and instill up to 180 mL of saline or heparinized blood to produce sustained tamponade, indicating that leak-proof entry to the space had been achieved. The fluid could then be completely aspirated within 5 to 8 minutes, with alleviation of tamponade. Thus, the transatrial pericardial approach can be used for pericardiosentesis in incipient stages of effusion. This is a distinct advantage over the conventional subxiphoid approach, which requires a minimum of 200 mL or at least 5-mm depth anteriorly on the echocardiogram for safe introduction of the pericardiocentesis needle.12

Access was gained to the normal pericardial space, and endogenous fluid was withdrawn, demonstrating the utility of the access route for diagnostic sampling. The pericardial fluid reflects myocardial interstitial fluid and thus could aid in the early identification of myocardial and pericardial disease markers. To date, diagnostic sampling has been limited to cases with pericardial effusion for identification of infections, bacterial or fungal organisms, and malignancies.2 As a result of the present demonstration that the normal pericardial space can be accessed and with the advent of new analytical technologies to identify potential precursors of vascular and myocardial diseases,7 the applications of pericardial diagnostic sampling could increase.

Perhaps the most intriguing application of transatrial access to the pericardial space is local cardiac drug delivery, for which it may afford efficient, sustained delivery to perivascular and myocardial tissue while minimizing loss of agent into the circulation. The therapeutic opportunity is under-
scored by recent demonstrations of the efficacy of locally administered angiogenic, anti-ischemic, and antiarrhythmic agents and gene vectors. The main clinical approaches under current investigation for local drug delivery are injection of agents into perivascular or myocardial tissue during bypass surgery and fluoroscopically guided intracoronary injection. Transatlantal access provides a means for repeated, topical applications of agents without thoracotomy.

The transatlantal pericardial approach has important intrinsic advantages for administration of pharmacological agents. These include (1) access to perivascular tissue, (2) delivery into a low-turnover reservoir with minimum loss of agent into circulation, and (3) perfusion of atrial and ventricular epicardial tissue. Delivery of drugs and growth factors to the adventitial rather than the luminal surface of the vasculature may improve efficacy as a result of bypassing the endothelial layer and may reduce the risk of intimal hyperplasia, a complication of the intracoronary approach. Because of low clearance of compounds, intrapericardial delivery maximizes concentration and contact time of drugs with superior coronary and myocardial tissue deposition while minimizing potential for systemic toxicity and other side effects, particularly mitogenesis in the case of growth factors. Intrapericardially administered compounds have been proven capable of suppressing atrial and ventricular arrhythmias. A recent intriguing application is the use of intrapericardial cooling of the epicardial surface to reduce myocardial infarct size.

It remains to be demonstrated that the transatlantal approach can be implemented in human subjects. However, given the absence of complications during large numbers of interventions and the relative ease with which the procedure can be performed, it is reasonable to expect that this procedure can be implemented in humans. The safety of the access route needs to be explored further.

In summary, this study demonstrates the feasibility of percutaneous access to the normal pericardial space through the right atrial appendage. This route provides a new opportunity for identification of diagnostic markers in the pericardial fluid; for pericardiocentesis; and to administer therapeutic factors with angiogenic, myogenic, and antiarrhythmic potential.

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