OBJECTIVES
We compared the effects of intrapericardial and intracoronary nitroglycerin on coronary cross-sectional area as assessed by intravascular ultrasound and demonstrated the feasibility of local cardiac drug delivery by a newly developed method to access the normal pericardial space through the right atrial appendage.

BACKGROUND
Studies of nitric oxide (NO) donors have suggested that their antiarrhythmic and antiproliferative properties are more effective when administered by the intrapericardial rather than intravascular route. We postulated that NO donors delivered intrapericardially would also cause sustained coronary vasodilation without significant systemic hypotension.

METHODS
Intrapericardial nitroglycerin (200 μg) was administered in five Yorkshire pigs. Coronary cross-sectional luminal area was measured with intravascular ultrasound at various time intervals. The effects of intracoronary nitroglycerin on coronary luminal area were used for comparison.

RESULTS
Transatrial pericardial access required 1 to 3 min in all animals. Intrapericardial nitroglycerin was associated with a mean 31.7% increase in luminal area at 5 min (p < 0.001). Vasodilation peaked between 5 and 10 min and persisted for 15 min. In contrast, intracoronary nitroglycerin was associated with a smaller mean increase in luminal area (20.3% at 5 min, p < 0.01) that disappeared by 10 min. Significant systemic hypotension was observed at 3 min with intracoronary but not with intrapericardial nitroglycerin.

CONCLUSIONS
Sustained coronary vasodilation can be achieved with intrapericardial delivery of nitroglycerin without systemic hypotension. Nitric oxide donors with longer half-lives could prove beneficial in the treatment of myocardial ischemic syndromes when administered through this route. Transatrial pericardial access offers a novel route for local cardiac drug delivery. (J Am Coll Cardiol 1999;33:2073–7) © 1999 by the American College of Cardiology

Studies of nitric oxide (NO) donors administered into the pericardial space have demonstrated that this group of vasodilators can decrease cyclic flow variations in endothelium-injured coronaries (1) and decrease the proliferative coronary vascular response after balloon injury (2) in animals. It has been postulated that these agents are more effective and are hemodynamically safer when administered via this route (1), because the pericardium acts as a natural barrier that minimizes systemic absorption and side effects and provides a low rate turnover reservoir in which delivery of a pharmacologic agent can achieve high concentrations around the epicardium and epicardial vessels (3). Despite these data supporting NO penetration to the coronary media from the adventitial surface, there is no information on whether NO donors or any other vasodilator delivered in the pericardial space has an effect on epicardial coronary reactivity.

We postulated that NO donors delivered intrapericardially would exert coronary vasodilation comparable to that observed after intracoronary injection but would have the added advantage of avoiding significant systemic hypotension. To test this hypothesis, we used a newly developed nonsurgical technique for intrapericardial drug delivery through the right atrial appendage. The effects of intrapericardial and intracoronary administration of nitroglycerin, a prototype NO donor, on coronary cross-sectional area as assessed by intravascular ultrasound were compared.
METHODS

The study was conducted according to National Institutes of Health standards and conformed to the “Position of the American Heart Association on Research Animal Use.” Protocols were approved by the Harvard Medical Area Standing Committee on Animal Use. The studies were conducted in seven Yorkshire pigs of either gender weighing 25 to 35 kg. The animals were preanesthetized with intravenous ketamine (15 mg/kg), xylazine (2.2 mg/kg) and atropine (0.04 mg/kg), and anesthetized with alpha-chloralose (100 mg/kg IV). Tracheostomy and endotracheal intubation were performed in all animals. Arterial PO2, PCO2 and pH were maintained at physiologic range with a volume ventilator and supplemental oxygen as required. Heart rate was monitored from a surface electrocardiogram. Both left and right femoral artery and vein were cannulated with 8-F introducer sheaths using standard percutaneous technique. Blood pressure was continuously monitored through one of the femoral arterial sheaths.

Transatrial technique for accessing the pericardial space.

The technique for transatrial access into the pericardial space was performed as previously described (4,5). An 8-F multipurpose guide was positioned under fluoroscopic guidance in the right atrial appendage (Fig. 1A). A custom-fabricated 4-F catheter with a 21-ga needle mounted at the tip was advanced through the guide, and a small perforation was made in the right atrial appendage (Fig. 1B). A soft 0.014-in. (0.036 cm) guide wire was advanced through the needle catheter and into the normal pericardial space (Fig. 1C). The guide wire confirms position in the pericardial space by conforming to the contour of the heart, secures the point of entry and allows over-the-wire exchanges of other catheters. The needle catheter was withdrawn over the wire and exchanged for a 4-F catheter with multiple side holes at its distal end, which was positioned and left in the pericardial space (Fig. 1D) for delivery of drugs. Radiopaque markers at the tip of all catheters improved visualization during fluoroscopy.

Catheterization and imaging system protocol.

An 8-F guiding catheter was inserted through either left or right femoral arterial sheath and, under fluoroscopic guidance, advanced into the ascending aorta and was engaged in the ostium of the left main coronary artery. Heparin was administered intravenously at a dose of 1,000 U. A 3.5-F 30-MHz intravascular ultrasound catheter (SonCath, Mansfield Corp., Watertown, Massachusetts) was advanced into the proximal to mid-left anterior descending artery and left in place for the rest of each experiment. Transducer position was confirmed frequently by fluoroscopy, using the distance between the tip of the guide and the imaging catheter by fluoroscopy and the presence of side branches by ultrasound as reference points. Ultrasound images were displayed on a video monitor and recorded at 30 frames per second on high resolution super VHS videotape. The ultrasound was gated to the cardiac cycle, and for each measurement, a single frame depicting the lumen at the peak of the QRS wave, which corresponds to end diastole, was selected. Lumen cross-sectional area was calculated by computerized planimetry. Reproducibility of lumen area measurements was determined by blinded intraobserver repeated measures (r = 0.97).

Nitroglycerin protocol.

Arterial blood pressure, heart rate and intracoronary dimensions by intravascular ultrasound were recorded at baseline. Nitroglycerin (200 μg), administered as 0.5 ml of a 400-μg/cc solution followed by a 5-ml saline bolus, was injected into the left coronary artery through the guiding catheter in four pigs. This dose is commonly used in humans during coronary angioplasty procedures. Measurements were performed at 3, 5, 10, 15, 20, 25 and 30 min after injection. For intrapericardial injection of nitroglycerin, 200 μg was diluted in 5 ml of saline solution and injected through the 4-F intrapericardial catheter in five animals. Arterial pressure, heart rate and
intracoronary dimensions were also measured at baseline and at each of the time points mentioned above. Three of the animals received both intracoronary and intrapericardial nitroglycerin with ≥20-min waiting periods between each experiment.

**Statistical analysis.** Data for each group (intrapericardial or intracoronary) at the various time intervals were compared with baseline using repeated measures analysis of variance with Bonferroni post hoc test. Data were also analyzed as percent change from baseline. The mean values in each group were compared with each other to look for a difference in the overall response curve between groups using a two-way repeated measures analysis of variance. Coronary luminal area change in response to intracoronary versus intrapericardial nitroglycerin administration was also estimated as the area under the curve and calculated using the numerical integration method of the trapezoidal rule equation (6). This technique involves constructing adjoining trapezoidal panels and calculating and summing the areas of all trapezoids that are fit under the empirical curve of the luminal diameter versus time plot.

**RESULTS**

After percutaneous placement of the arterial and venous femoral sheaths, access into the normal pericardial space required 1 to 3 min. No hemodynamic or electrocardiographic changes resulted from transatrial pericardial access.

**Effects of nitroglycerin on coronary vasodilation.** Intracoronary nitroglycerin was associated with a mean 20.3% increase in luminal area at 5 min as compared with baseline (p < 0.01). The vasodilatory effect peaked at 3 to 5 min after injection (from 9.27 mm² ± 0.68 SEM at baseline to 10.83 mm² ± 0.54 SEM at 3 min, p < 0.05, and to 11.15 mm² ± 0.45 SEM at 5 min, p < 0.01) and disappeared by 10 min. In contrast, intrapericardial nitroglycerin was associated with a mean 31.7% increase in luminal area at 5 min as compared with baseline (p < 0.001). This greater increase in luminal area was also significantly more sustained than that observed with intracoronary administration, because it peaked between 5 and 10 min and persisted for more than 15 min (from 9.9 mm² ± 0.84 SEM at baseline to 12.84 mm² ± 1.48 SEM at 3 min to 13.04 mm² ± 1.42 SEM at 5 min, to 12.92 mm² ± 1.26 SEM at 10 min and to 12.52 mm² ± 1.30 SEM at 15 min, all comparisons with baseline, p < 0.001). Intrapericardial nitroglycerin produced a greater absolute luminal area dilation (p = 0.03) and percent area change (p < 0.005) than intracoronary administration (Fig. 2). The magnitude of the vasodilatory effect by trapezoidal analysis was 363.2 mm² × min for intrapericardial compared with 285.6 mm² × min for intracoronary nitroglycerin administration.

**DISCUSSION**

We demonstrated that nitroglycerin administered directly into the pericardial space has a coronary vasodilator effect which is more sustained and of greater magnitude than that observed with intracoronary injection. This effect is not associated with the hypotensive response that is usually seen with intravascular delivery. Our finding that coronary vasodilation, and therefore smooth muscle cell relaxation, can be induced by intrapericardial nitroglycerin administration supports this approach to targeting the coronary media and intima.

**Previous studies with NO donors.** Nitric oxide donors have been utilized intravenously to minimize the response to ischemia/reperfusion injury, inhibit ischemic arrhythmias and limit infarct size (7–11). More recently, intrapericardial use of these compounds has been proposed as a route for optimizing their effects while minimizing side effects. Baek and associates (2) demonstrated that intrapericardial NO donors decrease the neointimal proliferative response after balloon coronary injury in pigs, suggesting penetration into smooth muscle and endothelial cells from the adventitial surface. Fei and colleagues (7) reported that intrapericardial delivery of L-arginine, the precursor of NO, reduced the
severity of ventricular arrhythmias during sympathetic stimulation in a canine model of acute coronary occlusion. In their study, NO overflow (NO concentration × blood flow) in the coronary sinus increased after intrapericardial L-arginine, suggesting increased activity of smooth muscle or endothelial cell NO-synthase even though the amino acid was administered on the epicardial surface. Moreover, Willerson and colleagues (1) reported that intrapericardial nitroprusside, an NO donor, decreases platelet aggregation in the coronary circulation and cyclic flow variation in endothelium-injured coronary arteries. These effects were more pronounced and the required doses were smaller with intrapericardial than with intravenous administration. They also demonstrated a smaller dose-dependent reduction in aortic pressure with intrapericardial than with intravenous nitroprusside. Similarly, in our study, the decrease in arterial pressure was much less pronounced with intrapericardial than with intracoronary nitroglycerin, suggesting that absorption into the peripheral circulation may be minimized by the barrier action of the pericardium.

**Studies of other intrapericardially delivered agents.** The sustained coronary vasodilator effect of intrapericardial delivery of nitroglycerin suggests that the drug is contained within the pericardial space, prolonging the time of action and exposure to perivascular tissue, and is not diffused rapidly into the systemic circulation. In contrast, intracoronary or intravenous administration of nitroglycerin is limited by a relatively short duration of action, with minimal or no organ selectivity, and is associated with systemic effects such as hypotension. These limitations may be particularly important when considering administration of vascular or myocardial growth factors, viral vectors or other proteins to induce angiogenesis or improve contractility, whose possible side effects include intimal hyperplasia, mitogenesis and systemic toxicity (12–15). For such agents, exposure to myocardial tissue needs to be maximized while minimizing availability to other organs. Lazarous and coworkers (16) demonstrated that intrapericardial administration of basic fibroblast growth factor (bFGF) via thoracotomy resulted in the highest myocardial uptake of bFGF as compared with intravascular delivery. Moreover, the lower systemic absorption from the pericardial space is further supported by their findings that after intrapericardial administration, a significantly smaller percentage of bFGF could be recovered in extra cardiac tissues (16). Further interest has been generated in attaining cardioselective pharmacologic action with intrapericardial delivery of diverse agents such as prostaglandins (17), autonomic blockers (18,19), bradykinin (20) and antiarrhythmic agents (21–23).

Until recently, the delivery of pharmacologic agents into the normal pericardial space has been limited by the inability to access this space without thoracotomy. Surgical pericardial window and needle pericardiocentesis are usually performed only in the setting of significant pericardial effusion. Our study demonstrates the feasibility of the percutaneous approach for transatrial access to the normal pericardial space. The method provides rapid access and is performed through femoral venous access such as in routine right heart catheterization. It has been previously employed for pericardiocentesis in animal models (4). Further studies will be required to test its feasibility and safety for human use.

**Study limitations.** It remains to be determined whether the epicardial vasodilatory effect of localized delivery of nitroglycerin can be exploited clinically. Its utility in the clinical setting of coronary obstruction or diffuse atherosclerotic disease is not established. Because flow was not measured, we cannot determine whether the observed changes in epicardial diameter are associated with increased flow. Given the lack of change in arterial blood pressure with concomitant increase in coronary diameter, a flow increase is postulated.

**Clinical implications.** We demonstrated that sustained and significant coronary vasodilation can be achieved by intrapericardial delivery of nitroglycerin, circumventing the hypotensive effect of this agent when administered by conventional routes. Intrapericardial delivery of NO donors or other vasodilators could prove beneficial in the treatment of refractory ischemic syndromes or severe, diffuse coronary artery disease. The ability to access the normal pericardial space with the transatrial method also offers a novel route for local delivery of antiarrhythmics, angiogenic factors, myocardial protection (24) and other agents designed to improve myocardial contractility or modulate the vessel wall response in atherosclerosis.

**Acknowledgment**

The authors thank Sandra S. Verrier for her editorial assistance.

**Reprint requests and correspondence:** Dr. Sergio Waxman, Beth Israel Deaconess Medical Center, West Campus, Cardiology Division, One Deaconess Road, Boston, Massachusetts 02215. E-mail: swaxman@caregroup.harvard.edu.

**REFERENCES**