Pharmacokinetics and Consistency of Pencardial Delivery Directed to Coronary Arteries: Direct Comparison with Endoluminal Delivery

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Summary

Background and hypothesis: Pharmacologic modulation of the contents of the pericardial space has been shown to influence the response of coronary arteries to balloon injury. Endoluminal (EL) local delivery of various drugs into coronaries has been found to be limited by short residence time, as well as by highly variable deposited agent concentration. We hypothesized that compounds placed into the pericardial space (P) would penetrate into coronary tissue with greater consistency than seen after EL delivery and provide for prolonged coronary exposure to agents.

Methods and Results: ¹²⁵I-labeled basic fibroblast growth factor (bFGF), platelet-derived growth factor (PDGF), albumin, or ¹³¹I-labeled diazeniumdiolated albumin (NONO-albumin) were delivered as model/therapeutic proteins into the porcine pericardial space (n = 15 pigs) or into coronaries using an EL delivery catheter (n = 48 arteries). In subjects receiving ¹²⁵I-labeled proteins, the delivery target or mid-regions of the left anterior descending (LAD) and left circumflex (LCx) arteries were harvested at 1 h or 24 h for gamma-counting and autoradiography, and fractional intramural delivery (FID) or retention measured as percent agent in 100 mg artery/agent in infusate for both time points. In the animals receiving ¹³¹I-labeled NONO-albumin, serial gamma imaging was employed to evaluate the rate of redistribution in individual animals following either pericardial or endoluminal delivery. At 1 h, FID values ranged from 0.00064 to 0.0052% for P delivery (median 0.0022%), and from 0.00021 to 6.7 for EL delivery (median 0.27%). At 24 h, FID values ranged from 0.00011 to 0.003 for P delivery (median 0.0013), and from 0.0002 to 1.4 for EL delivery. The estimated T₁/₂ for bFGF redistribution from the vascular tissue was 22 h (P) and 7 h (EL), respectively, while the directly determined T₁/₂ values for NONO-albumin redistribution from the delivery region were 22.2 h (P) and 2.5 h (EL).

Conclusions: These data show that pericardial fluid contents can access coronary arteries with intramural concentrations which typically vary by 10–15-fold, while EL delivery results in a remarkably wide intramural concentration range with up to 33,000-fold variability. The apparent redistribution rate is more rapid following EL delivery, possibly due to sustained diffusive tissue loading from the pericardial space. Pericardial delivery appears to offer substantial advantages over EL administration with respect to residence time and reproducibility.

Key words: pericardium, coronary disease, local drug delivery, restenosis, angiogenesis

Introduction

Local drug delivery (LDD) within the cardiovascular system may offer a new therapeutic approach for focal vascular lesions by providing higher intramural concentrations and avoiding the side effects that accompany systemic administration. In particular, the prevention of coronary restenosis following catheter-based interventions appears to be a potential application for this approach. Another recent area of development in local delivery has involved attempts to facilitate collateral vessel development in ischemic tissues, both peripheral and coronary. The effectiveness of LDD for either of these applications will ultimately depend on several factors including the choice of the therapeutic agent, the mode of delivery, intramural retention, and the effects of delivery on vascular structural integrity.

A number of local delivery catheters (LDCs) has been designed and tested as means of endoluminal-based intramural delivery into coronary arteries. Comparative study of four devices employing pressure-driven convective transport of fluid
to achieve deposition of therapeutic agents has demonstrated substantial equivalence among these devices in the pattern and level of drug deposition achieved. However, endoluminal deliveries by these are routinely characterized by several limitations: (1) inconsistency in delivery, (2) low absolute efficiency of localization, and (3) relatively rapid washout of agent from the target vessel.

The recent advent of catheter-based approaches to pericardial access has made possible the evaluation of agent delivery directly into this space with the eventual goal of clinically useful therapies. We hypothesized that drug delivery into the pericardial sac would differ from endoluminal deliveries by (1) comparatively enhanced consistency, and (2) prolonged exposure of either coronary or myocardial tissues to drug as a result of a reservoir function of the pericardium.

This study was designed to provide a direct comparison of endoluminal with intrapericardial delivery for selected agents which could be evaluated following delivery by these approaches. For endoluminal deliveries we employed a microporous infusion catheter (MIC; Cordis Corp., Miami, Fla., USA) consisting of a flow-restricting inner balloon with multiple 25 μm holes and an outer balloon membrane with 0.8 μm pores, which provides a "weeping" convective transport of the infused drug during balloon inflation. For intrapericardial deliveries, we employed either a hollow, helical-tipped catheter designed for controlled penetration through the myocardium during fluoroscopic visualization, or a sheathed needle with a suction tip designed for grasping the pericardium and accessing the pericardial space using a transthoracic approach while avoiding myocardial puncture.

The substances chosen for this study were proteins with an anticipated potential for therapeutic effect following local delivery, as well as additional model proteins. These included (1) albumin diazeniumdiolate (NONO-albumin), a potentially anti-thrombotic agent; (2) basic fibroblast growth factor (bFGF), an agent currently under evaluation for its proangiogenic effects; and (3) albumin and (4) platelet-derived growth factor (PDGF)-BB, two model proteins with minimal and substantial receptor-binding affinities, respectively. These were delivered either using the endoluminal catheter, or by a pericardial delivery catheter as described below, and the consistency as well as rate of redistribution of delivered substance were noted.

Materials and Methods

Study Design

This study involved four experimental groups: (1) Endoluminal delivery of 125I-labeled bFGF, PDGF, or albumin followed by timed quantitation of agent placed; (2) pericardial delivery of 125I-labeled bFGF followed by timed quantitation; (3) endoluminal delivery of 131I-labeled NONO-albumin followed by serial gamma imaging of the cardiac region; and (4) pericardial delivery of 131I-labeled NONO-albumin also followed by serial gamma imaging. Two arteries were subjected to local delivery in each of 24 animals receiving endoluminal deliveries for acute (n = 24 arteries) or 24-h (n = 24 arteries) evaluation (Group 1); two arteries were also harvested and studied in each of 12 animals receiving pericardial delivery for acute (n = 12 arteries) or 24-h (n = 12 arteries) evaluation (Group 2); 1 animal was imaged serially after a single endoluminal delivery (Group 3); and 3 animals were imaged following pericardial delivery (Group 4). All experiments and animal care conformed to National Institutes of Health and American Heart Association guidelines for the care and use of animals, and were approved by the Animal Care and Use Committee of Indiana University.

Endoluminal Delivery Procedure

In all, 25 domestic swine (20–23 kg in weight) were premedicated with 375 mg oral aspirin on the day prior to the study. Animals were sedated with a combination of ketamine (20 mg/kg), acepromazine (1.1 mg), and atropine (0.6 mg/kg) by intramuscular injection. The animals were given pentobarbital sodium (300 mg) intravenously and were then intubated. They were ventilated mechanically with isoflurane 2% and oxygen 90% (2 l/min) using a respirator. The electrocardiogram (ECG) and intra-arterial blood pressure were monitored continuously throughout the procedure. Arterial access was made via surgical cutdown of a carotid artery or femoral artery, and an 8F introducer sheath was placed. Each animal received a single dose of heparin (5000 U) and bretylium tosylate (2.5 mg/kg). Under fluoroscopic guidance, an 8F guiding catheter was positioned in the left coronary ostium. After the intracoronary administration of nitroglycerin (100 μg), coronary angiography was performed in the anterior-posterior or 30° left anterior oblique (LAO) position. After review of the angiogram, a 3.0 mm diameter segment of each of two coronary arteries [left anterior descending (LAD) and left circumflex (LCx)] was selected so as to minimize side branches or tortuosity. In each case, measurements were performed using spot AP films and digital calipers. Coronary overstretch balloon injury at each selected site was performed by angioplasty twice for 15 s, each time using a noncompliant angioplasty balloon, 0.5 mm in diameter larger than the luminal diameter. Following balloon injury, a delivery balloon was selected to match the nominal diameter of the balloon used for the initial injury in each case, prepared as per the manufacturer’s directions, and placed at the midpoint of the injured segment. The agent to be delivered was infused in a volume of 2 ml, at a pressure of 3 atmospheres as measured at the operator end. The second target vessel then received percutaneous transluminal coronary angioplasty (PTCA) and local delivery in a similar fashion using a new catheter. These procedures were performed in 49 arteries (8 coronary arteries/agent × 2 time points in Group 1, and 1 LAD delivery in Group 3).

Pericardial Delivery Approaches

Pericardial deliveries were performed by either a percutaneous transventricular method, or a transthoracic approach. The transventricular method employed a hollow, helical-
tipped catheter designed for controlled penetration through the myocardium into the pericardial space during fluoroscopic visualization. Following placement of a 7F sheath into the right carotid artery, a catheter was placed through the sheath and advanced under fluoroscopic guidance into the left ventricle to the cardiac apex, with the catheter tip directed inferiorly. Upon firm contact with the myocardium, the catheter tip was advanced through the myocardium using a gentle turning motion. After advancement over several mm, hand infusion of a 1:1 meglumine/normal saline mixture was initiated and contrast location monitored fluoroscopically. Successful intrapericardial tip placement was identified by accumulation of contrast in the pericardium, at which point the catheter was fixed in position and flushed with 1 ml of saline prior to delivery of the desired agent in a volume of 10 ml. Following delivery, final catheter position was confirmed by fluoroscopic visualization of a bolus of air instilled into the pericardial space, after which the catheter was removed.

The transthoracic approach used in a subgroup of pericardial deliveries involved a sheathed needle with a suction tip designed for grasping the pericardium and accessing the pericardial space using a transthoracic approach while avoiding myocardial puncture. This device was placed from a subxiphoid position into the mediastinum under fluoroscopic guidance and positioned onto the anterior outer surface of the pericardial sac. The sac was then retracted under manual suction, entered by the needle, and a guidewire was placed through the needle lumen into the pericardial space. The wire was advanced several cm in order to identify a configuration which reflected intrapericardial position, after which the needle was removed and a 4F dilator catheter (Cook Inc., Bloomington, Ind.) inserted over the wire. Following removal of the wire, successful intrapericardial tip placement was confirmed by accumulation of infused contrast in the pericardium, at which point the desired agent was delivered in a volume of 10 ml and the catheter was finally removed.

Agents for Delivery

For endoluminal delivery, 125I-labeled bFGF, PDGF-BB, and albumin were obtained from DuPont/NEN (Wilmington, De.) and each was dissolved in a solution of bovine serum albumin (BSA) in order to minimize nonspecific binding to the catheter lumina. For pericardial delivery, 125I-labeled bFGF was dissolved in an excess of 200 μg cold bFGF either with or without the addition of 3 mg heparin. Bovine serum albumin was conjugated with nitric oxide-releasing diazeniumdiolate groups as described elsewhere (Hrabie et al., personal communication) and was labeled with 131I by Covance Laboratories, Inc. (Vienna, Va.), using the chloramine-T method; the sample was purified to radiochemical homogeneity by Sephadex chromatography and shipped to the Krannert Institute at a specific activity of 99 mCi/mg. This conjugated BSA (NONO-albumin) possessed approximately 30 moles NO/mole albumin and was used for both endoluminal and pericardial delivery. For gamma imaging studies, a dose of 20–25 μCi was coadministered either via the endoluminal or pericardial approaches, admixed with 40 mg of cold BSA-diazeneumdiolate dissolved in saline at a pH of 7.4.

Imaging and Computer Processing for Evaluation of Regional Nature of Delivery

A Pho-gamma LFOV scintillation camera 6413 with a medium-energy (300 keV) collimator (Searle Radiographics, Des Plaines, Ill.) that allowed visualization of the thoracic region of interest was used for imaging. The images were acquired into an ADAC 33000 computer using a 128 × 128 × 8 matrix. A known amount (about 10 μCi) of the 131I-labeled compound was put in a 13 × 100 mm tube, placed in a styrofoam at a distance from the γ camera that equaled the distance between the camera and the heart, and positioned adjacent to the animal during imaging. It acted as a control throughout the experiment. Background radiation was checked and recorded. Acquisition of serial 10 min anteroposterior planar images began immediately following infusion. After each static image, the pig was repositioned for a lateral 10 min image of the thorax. On each image, two or three areas of interest were drawn for separate quantitation: one around the external reference source, one restricted to the activity in the cardiac region, and one restricted to the most intense area of activity discerned in the mid-region of the heart, in the animal receiving endoluminal delivery into the mid-LAD. Counts were recorded from each area of interest and were corrected for decay.

The count rate was assessed, and the radioactivity/pixel was viewed in a matrix format with a pixel size of 0.19 mm/pixel. The total activity in each region of interest after correction for background and decay was plotted as a function of time to yield a local half-time of agent loss.

Preparation of Samples Containing 125I-Labeled Agents and Evaluation of Delivery Efficiency

Arteries infused by the endoluminal catheter (n = 48) with each 125I-labeled agent above, as well as those exposed to intrapericardial 125I-labeled bFGF with or without admixed heparin (n = 24) were obtained unfixed at either 1 h or 24 h following either delivery. The coronary artery segment region subjected to the endoluminal delivery (approximately 25–30 mm in length) was isolated from the underlying musculature or connective tissue, as were homologous segments in the case of intrapericardial delivery. These arterial samples were then subjected to well-counting for the amount of contained radioactivity. An aliquot of the infusion solution was measured as a control in each case. Results were corrected for background radioactivity, amount of injected radioactivity, and tissue weight. These results are expressed in terms of a fractional intramura delivery (FID) for each tissue, where FID = % (agent/100 mg artery)/agent in infusate, at an acute time point. A directly analogous value may be computed to express the relative amount of infused agent retained in the vessel at time points after delivery, in terms of a fractional intramura retention (FIR), where FIR = % (agent/100 mg artery)/agent in infusate at a particular time t after delivery.
Results

Feasibility of Catheter-Based Intrapericardial Delivery

In this study, a total of 15 animals received direct intrapericardial delivery using catheter techniques not requiring an open surgical approach. Entry into the pericardial sac was typically accomplished in less than 5 min following initial access, and no acute or subacute (24 h) complications of pericardial access were noted. Specifically, there was no evidence of progressive increase in intrapericardial fluid volume following the delivery, pericardial tamponade, or remarkable inflammation upon tissue harvest in any animal.

Reproducibility of Endoluminal versus Intrapericardial Delivery

The FID obtained from a determination of the activity present in each isolated target vessel acutely following delivery is shown in Figure 1A for both endoluminal and pericardial deliveries. The endoluminal approach is seen to be characterized by an extreme variability in FID, with an observed overall minimum of 0.0002% and maximum of 6.7%, resulting in a 33,000-fold range of variation, despite all experiments being conducted as consistently as possible with respect to catheter type, handling, sizing, infusion pressure, and tissue analysis. Wide variability was seen to be present for each of the three proteins infused. The pericardial instillation of bFGF showed a remarkably different profile, with a 10-fold range of FID. This comparatively tight clustering of data was present both for the bFGF/heparin and bFGF groups (the latter displayed less than 3-fold variability).

The FIR determined for each vessel 24 h following either endoluminal or pericardial delivery is shown in Figure 1B. The endoluminal approach is again characterized by remarkable variability, with the FIR displaying a 6,000-fold dynamic range again, despite every effort to optimize delivery consistency. Once again, the variability is present for each of the three proteins tested. The pericardial instillation of bFGF showed a persistent clustering of activity present both for the bFGF/heparin and bFGF groups, with a 30-fold range of FIR. Although computation of local pharmacokinetics and residence half-times is rather limited using such data sets that are obtained from measurements of unrelated samples with large in-group variability, an estimation may be made of the redistribution T1/2 of bFGF for the endoluminal and pericardial groups using the median values for FID (1 h) and FIR (24 h). This approach yields a value of 7 h for the endoluminal group and about 24 h for the pericardial group.

Geometry and Pharmacokinetics of Endoluminal versus Intrapericardial Delivery: NONO-Albumin

Each of three animals receiving intrapericardial delivery of 131I-labeled NONO-albumin was imaged acutely following the instillation, as well as at multiple time points subsequently. A representative pair of planar gamma images is depicted in Figure 2, showing both an anterior (A) and left lateral view (B) of the cardiac region obtained immediately after delivery. Such planar images reflect a sum of intrapericardial, intramyocardial, and blood pools of radioactive material. The activity is seen to be highly circumscribed, as expected for an agent predominantly localized to the region within the pericardium following initial deposition. This pattern was persistent during the subsequent imaging in each animal. A degree of heterogeneity of the activity/pixel was present, as is apparent in the pseudocolor image rendering, in which the intensity ranges from dark red (least activity) to bright yellow (most activity). The activity distribution tended to suggest a higher collection of agent laterally and inferopically, consistent

![Figure 1](image-url)  
**Fig. 1** (A) Fractional intramural delivery (FID) expressed as a percentage of each infused agent found in arterial tissue 1 h after delivery. The left panel shows one value for each coronary artery harvested after endoluminal delivery of the agents listed on the x-axis. The right panel shows one value for each coronary artery harvested following intrapericardial delivery of the indicated agents. It is apparent that endoluminal delivery results in greater degree of variation in FID by several orders of magnitude. (B) Fractional intramural retention (FIR) expressed as a percentage of each infused agent found in arterial tissue 24 h after delivery. As for (A), the left panel shows one value for each coronary artery harvested after endoluminal delivery of the agents listed on the x-axis. The right panel shows one value for each coronary artery harvested following intrapericardial delivery of the indicated agents. It is apparent that endoluminal delivery results in substantially greater degree of variation in FIR. bFGF = basic fibroblast growth factor, PDGF = platelet-derived growth factor.
with the intrapericardial distribution of radiographic contrast typically found to predominate after delivery of volumes in the order of 10 ml in the supine position. This distribution of liquid in the nondiseased pericardium presumably reflects the dynamic interaction of anatomic attachments, gravity as applied in the supine position, and myocardial contractile activity resulting in continuous mixing.

A typical sequence of images observed over a time course following endoluminal delivery of $^{131}I$-labeled NONO-albumin is shown in Figure 3A. The animal in this study received an infusion of 2 ml of solution into the mid-LAD, with the resultant image revealing a tightly restricted regional delivery of intensity surrounding this area. It is apparent from the series that the NONO-albumin, which possesses a molecular weight of about 72 kDa, is redistributed from the arterial region to a very significant degree within the first several hours after infusion. By contrast, the sequence of images observed following pericardial delivery of the same agent (Fig. 3B) shows a markedly prolonged redistribution time from this compartment. Furthermore, each of these images shows a larger projected area of activity associated with pericardial rather than periarterial localization.

A determination of fractional regional delivery (delivery efficiency) for each form of delivery could be obtained as a ratio of the activity detected in the region of interest immediately after delivery to the total activity infused. In the pericardial deliveries, this value was not appreciably different from 1.0 (100%), while for endoluminal delivery the initial activity was 8.7% of that infused.

Fitting of the quantitative data derived from these serial acquisitions demonstrated that the redistribution of NONO-albumin could be fit closely by a monoexponential decay function. This was true for both the endoluminal and the pericardial delivery conditions. Figure 4 shows the decrease in radioactivity within the regions of interest as a function of time for the pericardial deliveries averaged (A), and for the endoluminal delivery (B). The data displayed following the endoluminal delivery reflect the overall cardiac region (identical in

Fig. 2 Planar gamma images of cardiac region obtained immediately following intrapericardial delivery of $^{131}I$-labeled NONO-albumin. Images acquired from anterior of thorax (left) or left lateral (90°) view with animal supine, and rendered in pseudocolor with red as minimal intensity and white-yellow as maximal intensity.

Fig. 3 Redistribution following (A) local endoluminal and (B) local intrapericardial delivery of $^{131}I$-NONO-albumin. Planar gamma images of cardiac region obtained at multiple timepoints following either endoluminal (upper) or intrapericardial (lower) delivery of $^{131}I$-labeled NONO-albumin. All images acquired from anterior thorax with animal supine, and rendered in pseudocolor with red as minimal intensity and white-yellow as maximal intensity. Acquisition timepoints were 0, 0.66, 1, 2, 4, 5, and 26 h (A); and 0, 1, 2, 4, 6, and 27 h (B).

Fig. 4 Fraction of initial radioactivity remaining as a function of time following either intrapericardial (left) or endoluminal delivery into the LAD of $^{131}I$-labeled NONO-albumin. The left panel shows datapoints representing 3 studies. The right panel shows two sets of datapoints acquired from 1) the region of maximal intensity surrounding the LAD infusion area; and 2) the entire cardiac region of interest.
size/shape to that in the pericardial deliveries), as well as a local region of interest drawn immediately surrounding the site of maximal intensity in the mid-LAD region. The rate of decrease of agent over the local site of endoluminal delivery was best fit by an exponential function with a $T_{1/2}$ of 2.5 h. Similar fitting of the data acquired over the entire cardiac region of interest yielded a function with $T_{1/2}$ of 3.9 h. However, following intrapericardial delivery, the agent was washed out with an average $T_{1/2}$ of 22.2 h (range 14.3–27.3 h), or ninefold more slowly than following the endoluminal delivery.

Discussion

The prospect of using local delivery of bioactive agents to target their effect to a specific locus of disease in the context of the cardiovascular system has attracted much interest over the past several years, but only a few studies to date have validated the efficacy of particular locally applied drugs in large animal models of human vascular pathology. Several aspects of local drug delivery targeting the arterial wall have been identified as potential reasons for the difficulty in demonstrating such efficacy: low efficiency of localization, rapid agent washout in the absence of specific measures to prolong residence time, and poor reproducibility of local delivery. The development of delivery devices which are practical for nonsurgical clinical access to the pericardial space has set the stage for the evaluation of pericardial delivery as a possible approach to address these challenges. However, there have been few studies directed to careful characterization of the features of pericardial delivery, particularly as contrasted with the more traditional forms of endoluminal delivery. Moreover, there has been little analysis of the ability of material infused into the pericardial space to access the tissues of the coronary arteries. This study was thus designed to provide direct insight into the comparative features of pericardial and endoluminal delivery, specifically with respect to delivery consistency and pharmacokinetics.

The most striking finding of this study is the extreme variability found in the quantitated amount of material deposited locally following endoluminal delivery using a highly standardized approach. This is not entirely unanticipated, considering the results of an earlier multicenter animal study which also demonstrated substantial variability in the intensity of deposition of a fluoresceinated oligonucleotide antisense to the c-myc oncogene. However, this study was only semiquantitative in nature, so that the degree of variability was not apparent. The explanation for such generalized lack of reproducibility in endoluminal delivery is not fully clear, but may involve at least 1) variations in catheter-artery apposition due to seemingly minor changes in geometry, branches, or sizing; 2) additional variations in apposition due to differences in arterial compliance/elasticity and tone, resulting in variability of the extent to which fluid may move longitudinally along the catheter/artery interface rather than penetrating the artery directly; and 3) variations in the extent and timing of injury in the target vessel. This last mechanism may prove to be of particular importance in light of the observation that the extent of arterial injury, and especially the presence of medial dissection, is a key determinant of the pattern of drug deposition with respect to access to the adventitial or retromedial tissues, and the establishment of a perivascular depot of a substantial mass of agent when approaching from the endoluminal surface. Such a dependence on arterial injury for intramural access has also been described for vector agents.

These findings have significant implications for the future of endoluminal delivery using catheter technologies that have been described as first- and second-generation (i.e., no specialized, nonhydraulic mechanisms to facilitate degree and consistency of intramural access). The extent of variability potentially found in local arterial dosing following endoluminal delivery may well explain the current difficulty in demonstrating any clinical utility for approaches employing endoluminal delivery based on the difficulty of placing a desired dose in the arterial wall in a treatment group. This may be the case unless a drug/exciipient is identified with either a very high wall affinity and rapid kinetic of partitioning into the wall that might reduce the dependence of delivery on apposition and injury parameters, or such a wide toxic:therapeutic ratio that it is feasible to attempt placement of doses several orders of magnitude in excess of those necessary to achieve the desired effects.

This is also the first report that directly documents the ability of any material to enter the arterial wall following infusion into the pericardial space. The relative consistency of intramural access by material delivered from the pericardial space is remarkable in light of the endoluminal findings and may, in part, be explained by the absence of dependence upon either specific catheter/artery appositional parameters, or upon the presence and extent of mural injury. Presumably, in the case of delivery from the adventitial side, mural access by agents is a predominant function of simple diffusion along the concentration gradient, which is maintained by an intrapericardial repository of agent for a time after the initial infusion. In marked contrast to the endoluminal findings, the reproducibility of local dosing from this approach might be expected to provide a basis for clinical success with the eventual use of intrapericardial delivery.

The results of the subacute experiments are in concert with the acute experiments, demonstrating improved reproducibility of tissue levels 24 h after intrapericardial delivery with respect to the data seen after endoluminal delivery. Evaluation of the levels from the two time points can provide at best a general estimate of the local tissue half-life as a result of the ranges found and the impossibility of assessing particular arteries twice. However, the data from the endoluminal deliveries for bFGF reveal an estimated $T_{1/2}$ of 7 h, while data from intrapericardial deliveries reveal an estimated $T_{1/2}$ of 24 h or more. It may be noted that this value is actually an apparent $T_{1/2}$, since ongoing loading of the arterial tissue from the pericardial fluid is expected to occur throughout the time of redistribution.

A more powerful approach to evaluating the comparative washout kinetics occurring after the endoluminal versus intrapericardial deliveries is provided by the serial gamma-imaging strategy, as has been described previously. These
data clearly demonstrate that the local rate of washout of NONO-albumin is significantly more rapid ($T_{1/2}$ of 2.5 h) following endoluminal delivery into the LAD than after delivery into the pericardial space ($T_{1/2}$ of 22 h). This may be due to the fact that the redistribution rate would be expected to depend directly on the local blood flow, so that the pericardial contents themselves would be rapidly washed out only after access to the myocardial tissues, while endoluminally delivered agents would be in a comparatively high-flow environment from the time of their initial deposition.

Conclusions

This study continues a series of reports focusing on intrapericardial delivery and adds to a growing literature establishing its feasibility using catheter-based, nonsurgical methods.21-24 The data presented here indicate that pericardial fluid contents can access coronary arteries with intramural concentrations which vary by 10-15-fold, while EL delivery results in an remarkably wide intramural concentration range with up to 33,000-fold variability. Also, the apparent redistribution rate is substantially more rapid following EL delivery, possibly due to sustained diffusive tissue loading from the pericardial space. Pericardial delivery thus appears to offer substantial advantages over EL administration with respect to both reproducibility and residence time.

As such, it is anticipated that clinical trials employing pericardially delivered agents directed to angiogenesis, restenosis, and perhaps other coronary and myocardial indications will emerge over the next several years.

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References


