TRANSENDOCARDIAL AND TRANSEPICARDIAL INTRAMYOCARDIAL FIBROBLAST GROWTH FACTOR-2 ADMINISTRATION: MYOCARDIAL AND TISSUE DISTRIBUTION

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ABSTRACT:

Effective local delivery to the heart remains an obstacle to successful therapeutic application of a number of drugs and biological agents. This study was designed to study and optimize the delivery characteristics of transendocardial intramyocardial (IM) administration, determine myocardial deposition and retention over time, and compare it to transepicardial IM injection. Thirty-nine pigs were used for the study (15 for catheter optimization, 15 for transendocardial IM delivery, and 9 for transepicardial IM delivery). 125I-Fibroblast growth factor-2 (FGF2) (25 μCi) was used as the prototype molecule. Tissue and myocardial distribution was determined at 1 and 24 h and 7 days. Using 1-h 125I-FGF2 myocardial deposition as a parameter for delivery efficiency, the optimal needle length and delivery volume for transendocardial based delivery were determined to be 6 mm and 0.1 ml, respectively. Using these parameters for endocardial delivery, 125I-FGF2 cardiac activity was 18.01 ± 3.84% of delivered activity at 1 h, 11.65 ± 5.17% at 24 h, and 2.32 ± 0.87% at 7 days in ischemic animals. Studies in non-ischemic animals produced similar results. For transepicardial delivery, 125I-FGF2 cardiac-specific activity was 23.14 ± 12.67% for the 6-mm needle, declining to 12.32 ± 8.50% at 24 h, and did not significantly differ from values obtained following transendocardial delivery. Thus, optimized transendocardial intramyocardial delivery using Biosense guidance results in efficient delivery of FGF2 to the target myocardium that is comparable with transepicardial delivery, both providing markedly higher myocardial deposition and retention and lower systemic recirculation of FGF2 than intracoronary, intrapericardial, or intravenous delivery. However, myocardial distribution is limited to injection sites.

Effective local delivery to the heart remains the major obstacle to successful therapeutic application of a number of drugs and biological agents, including angiogenic growth factors such as vascular endothelial growth factor and basic fibroblast growth factor (bFGF or FGF2) (Laham et al., 1999a,b, 2000a; Simons and Laham, 1999). Although numerous preclinical studies have demonstrated the ability of these proteins to induce functionally significant angiogenesis in animal models of myocardial and limb ischemia (Harada et al., 1994; Hariawala et al., 1996; Lopez et al., 1998; Laham et al., 2000a), clinical studies to date have been substantially less promising (Laham et al., 1999c, 2000b; Simons et al., 2002; Henry et al., 2003). This, in part, stems from limitations of intracoronary, intravenous, and transepicardial delivery (Aiello et al., 1994; Ferrara, 1995; Bagheri-Yarmand et al., 1998; Laham et al., 2003). We have previously reported that intracoronary and intravenous delivery are relatively ineffective, resulting in myocardial deposition and retention of 0.88% of total dose 1 h after single bolus intracoronary and 0.26% 1 h after intravenous delivery with most of the delivered agent ending up in the liver (Laham et al., 1999b). The myocardial retention decreased 24 h postdelivery to 0.05% of total dose for intracoronary and 0.04% for intravenous administration (Laham et al., 1999b). This underscores the need for a delivery strategy that would result in enhanced myocardial deposition and retention and reduced systemic recirculation of these growth factors.

Transepicardial intramyocardial delivery (open thoracotomy) has been used in several angiogenesis studies; however, its invasive nature limits its use in patients, and its myocardial distribution and retention has not been studied (Losordo et al., 1998; Laham et al., 1999c; Symes et al., 1999). The availability of various catheter-based intramyocardial endocardial injection systems, such as the Myostar catheter available for use with Biosense guidance (Biosense Webster, Diamond Bar, CA), provides a delivery modality that may circumvent the need for surgery (Kornowski et al., 2000). This study was designed to optimize the delivery characteristics of transendocardial intramyocardial administration, determine the myocardial deposition and retention of a prototype molecule (FGF2) in normal and ischemic myocardium, and compare it to transepicardial intramyocardial injection. Such data would help to ascertain the actual amounts of therapeutic agent delivered to the myocardium, provide information regarding their persistence and stability, and measure their systemic recirculation.

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ABBREVIATIONS: IM, intramyocardial; bFGF, basic fibroblast growth factor; FGF2, fibroblast growth factor-2; LCX, left circumflex artery; ANOVA, analysis of variance.
into the left ventricle using position tracking via the on-line Biosense navigation system within the "ischemic" zone (red) of the lateral wall. Ten intramyocardial injections were performed using Biosense-guidance (black dots) in the "ischemic" zone (red) of the lateral wall. Myostar injection catheter with a deflectable tip and a retractable needle with a tip sensor that allows localization within the left ventricle.

**Materials and Methods**

**Supplies and Reagents.** For delivery studies, 25 μCi of 125I-labeled FGF2 [specific activity 4050 kBq/μg (110 μCi/μg); New England Nuclear, Inc., Boston, MA] was combined with 30 μg of cold recombinant human FGF2 protein (Chiron Corp., Emeryville, CA) and 3 mg of heparin (Wyeth Laboratories, Marietta, PA). This represented the total dose used per animal and was divided equally among multiple injections and volumes. Over 95% of the label was precipitated with cold trichloroacetic acid and was bound to FGF2 at the time of administration as determined by thin-layer chromatography.

**Catheter Optimization Study.** The catheter optimization study was carried out in 15 normal Yorkshire pigs of either sex weighing 45 to 55 kg. Animals were anesthetized with intramuscular ketamine (10 mg/kg) and isoflurane inhalation anesthesia. A right femoral cut down was performed to introduce an 8-Fr arterial sheath. A Biosense NOGA map was performed using electromagnetic triangulation, which allows accurate on-line localization of the mapping catheter tip within the left ventricle (Ben-Haim et al., 1996; Kornowski et al., 1998) relative to three location pads positioned under the animal’s back, emitting ulrallow (10⁻⁸-10⁻⁵ Tesla) magnetic fields. The intensity of the three magnetic fields is detected by miniature antennae within the tip of the deflectable-tip mapping catheter, providing precise spatial localization after triangulation within a Silicon Graphics workstation (SGI, Mountain View, CA). As the catheter is placed sequentially against the left ventricular endocardial surface at a series of points, the local unipolar electrogram and tip motion during the cardiac cycle are recorded. This allows calculation of unipolar voltage and local wall shortening at each such point. A three-dimensional map of each parameter can be displayed and rotated freely in space to inspect all left ventricular walls (Fig. 1A) (Ben-Haim et al., 1996; Kornowski et al., 1998; Laham et al., 2002).

Following diagnostic mapping, a second catheter (Myostar; Biosense Webster; Fig. 1B) with the same tip sensor and a retractable 27-gauge needle was used for all endocardial intramyocardial injections. The catheter was advanced into the left ventricle using position tracking via the on-line Biosense navigation system. Perpendicular catheter position in relation to the left ventricular wall and contact with the wall were determined using Biosense guidance and confirmed using fluoroscopy. Catheter tip stability was suggested by a loop stability (catheter motion with cardiac cycle) of less than 2 mm. The needle was protruded, and penetration into the left ventricular wall was confirmed using fluoroscopy. Catheter tip stability was suggested by a loop stability (catheter motion with cardiac cycle) of less than 2 mm. The needle was protruded, and penetration into the left ventricular wall was confirmed using fluoroscopy. Catheter tip stability was suggested by a loop stability (catheter motion with cardiac cycle) of less than 2 mm. The needle was protruded, and penetration into the left ventricular wall was confirmed using fluoroscopy.

Animals were sacrificed under general anesthesia 1 h after intramyocardial injection. The heart was excised and washed with saline. The left ventricle was cut into slices along the short axis. An ultraviolet light source was used to identify the injection sites (Fig. 2); individual injection sites were reassembled along adjoining slices if they spanned more than one slice. The injection site, along with surrounding tissue (1 cm from injection site, adjoining sites), was collected. The samples were then weighed and counted in an LKB gamma counter (Fremont, CA). In addition, a duplicate sample equal to the amount injected per site was counted to measure total activity. The treatment of animals was done according to the National Institutes of Health guidelines and the protocol was approved by the Institutional Animal Care and Utilization Committee of the Beth Israel Deaconess Medical Center.

**Tissue and Myocardial Distribution of Endocardial Intramyocardial 125I-FGF2.** Tissue and myocardial distribution of 125I-FGF2 was determined in normal animals (n = 6) and in animals with chronic myocardial ischemia (n = 9). Chronic myocardial ischemia was achieved using the ameroid con-
strictor model described previously (Harada et al., 1994; Lopez et al., 1998; Laham et al., 2000a). Chronically ischemic animals (3 weeks after ameroid placement) and normal animals were anesthetized with intramuscular ketamine (10 mg/kg) and isoflurane inhalation anesthesia. A right femoral cut down was performed to introduce an 8-Fr arterial sheath. Coronary angiography was then performed in multiple views using a 7 French JR4 diagnostic catheter (Cordis, Lawrenceville, NJ) to confirm LCX occlusion in ischemic animals and to assess coronary anatomy. Biosense NOGA mapping was then performed as described above. Electromechanical maps were then analyzed for areas of reduced local unipolar voltage and reduced local shortening to assess scar and ischemic tissue (Ben-Haim et al., 1996; Kornowski et al., 1998). Then, 10 intramyocardial injections using Biosense and fluoroscopic guidance with the optimal parameters determined in the first set of experiments were performed in each animal. Fluorescent microspheres were not used to avoid their potential effect on myocardial retention of FGF2 due to nonspecific binding to the growth factor. Injections were localized to the lateral wall (LCX distribution), targeting the area of reduced linear local shortening, but preserved voltage in ischemic animals and lateral wall in normal animals (Fig. 1). Areas of reduced unipolar voltage (scar) were avoided. All injections were performed only after confirming catheter tip stability (loop stability less than 2 mm), perpendicular contact with left ventricular wall (using Biosense guidance and fluoroscopy), and ventricular ectopy with needle protrusion.

Animals were sacrificed 1 h (n = 6, three normal and three ischemic animals), 24 h (n = 6, three normal and three ischemic animals), and 7 days (n = 3, ischemic animals) after 125I-FGF2 administration. The heart, liver, right lung, and right kidneys were excised and weighed. Duplicate blood (10 ml), urine (spot samples of 10 ml), and tissue samples from the liver, lung, and kidney were obtained. Tissues were washed in saline to avoid contribution of radioactivity in blood. A thin (1–2 mm) mid left ventricular transverse slice was obtained for organ level autoradiography and was exposed in a PhosphoImager (Amersham Biosciences Inc., Piscataway, NJ) for 24 h. The remainder of the left ventricle was divided into lateral (LCX distribution) and anterior-inferior walls. 125I-FGF2 activity was determined in a gamma counter (LKB). Following background subtraction, the amount of 125I-FGF2 deposited within a specific sample was calculated as a percentage of the total activity administered (determined by counting an aliquot from each administered dose). Total solid organ (liver, lung, and kidney) deposition was calculated by multiplying the percentage of injected activity per gram of tissue by the weight of the organ. Trichloroacetic acid precipitation was performed on selected samples to determine bound activity. Myocardial counts from the lateral wall and nonlateral walls were summed to determine total cardiac deposition in the LCX (occluded in ischemic animals) and non-LCX territories.

**Epicardial Intramyocardial Delivery of 125I-FGF2.** Nine Yorkshire pigs weighing 45 to 55 kg were used to investigate transepicardial delivery. The animals were anesthetized as described previously. Left thoracotomy (5-cm incision) was performed through the 4th intercostal space during mechanical ventilation. The pericardium was opened, and the heart was exposed. Ten epicardial intramyocardial injections of 125I-FGF2-cold FGF2-heparin were performed under direct vision targeting the lateral wall (LCX distribution). The injectate volume was determined by the above described optimization (0.1 ml) study, and two needle lengths were used (3 and 6 mm, adjusted using electronic calipers). Injections were performed over 10 s, and the injection location was recorded. The pericardium and chest were closed. Animals were then sacrificed at 1 h (n = 6, 3- and 6-mm needle length) and 24 h (n = 3, 6-mm needle length). Heart and tissues were processed as described above to determine tissue and myocardial distribution of 125I-FGF2.

**Statistical Analysis.** Data are expressed as mean ± standard deviation. Continuous variables were compared by unpaired Student’s t test and ANOVA. All reported p values were two-tailed, and a p value ≤ 0.05 was considered statistically significant.

**Results**

**Intramyocardial FGF2 Administration—Immediate Results.** A total of 39 animals underwent transepicardial (n = 9) or transendocardial (n = 30) injections of 125I-FGF2-cold FGF2-heparin. All animals survived until sacrifice. Hemodynamic monitoring disclosed no acute hemodynamic effects, and injections did not produce sustained ventricular tachyarrhythmias. The average duration of Biosense NOGA mapping was 28 ± 8 min, and the average duration of transepicardial injections was 11 ± 4 min. The average duration of thoracotomy was 18 ± 4 min and the duration of transepicardial
injections was 6 ± 3 min. The average post-mortem wall thickness at the site of injections (lateral wall) was 8.9 ± 1.1 mm.

Catheter Optimization Studies. Fifteen normal Yorkshire pigs were used for catheter optimization studies assessing different injection volumes and needle lengths (five groups, three animals per group: 3 mm-0.1 ml, 4.5 mm-0.1 ml, 6 mm-0.05 ml, and 6 mm-0.2 ml). A total of 30 injections (10 injection per animal) were done per group. The percentage of recovered injections sites defined by localized fluorescence (of 10 per animal and 30 per group), ranged from 73 to 90% and was similar for all groups, except for a slightly lower recovery in the 0.05-ml group (Table 1). The “missing” sites probably represent injections into the left ventricular cavity.

Needle length optimization was performed first. The mean percentage of injected activity of ¹²⁵I-FGF2 recovered from the injection site 1 h after injection was the highest in the 6-mm needle length group (Fig. 3A, 3 mm, 25.2 ± 16.9% of administered dose; 4.5 mm, 26.9 ± 21.8%; and 6 mm, 36.5 ± 11.4%; ANOVA, p = 0.048). With the 6-mm needle length providing the best myocardial ¹²⁵I-FGF2 recovery, it was used to study the effect of varying injection volume. Injections using 0.05 and 0.1 ml resulted in significantly higher myocardial deposition of ¹²⁵I-bFGF than injections using 0.2 ml (Fig. 3B, 0.05 ml, 37.6 ± 18.4%; 0.1 ml, 36.5 ± 11.4%; and 0.2 ml, 17.8 ± 13.5%; ANOVA, p < 0.001).

To examine the intramyocardial diffusion of FGF2 following intramyocardial needle injection, we assayed ¹²⁵I-FGF2 percentage of injected activity in adjoining sites (1 cm from injection site). Compared with the activity at the injection sites, activity at these sites was markedly reduced for all injection volumes (3 mm-0.1 ml, 0.2 ± 0.2% of administered dose of ¹²⁵I-FGF2; 4.5 mm-0.1 ml, 0.2 ± 0.4%; 6 mm-0.1 ml, 0.1 ± 0.2%; 6 mm-0.05 ml, 0.2 ± 0.3%; and 6 mm-0.2 ml, 0.2 ± 0.3%).

Transendocardial Intramyocardial FGF2 Delivery. Using the optimal delivery modality developed in the first part of this study, we then set out to evaluate the tissue and myocardial distribution and retention of ¹²⁵I-FGF2 administered into the lateral wall of the left ventricle in normal (n = 6) and ischemic animals (n = 9). Complete occlusion of the LCX coronary artery 3 weeks following ameroid surgery was demonstrated in all nine ischemic animals. Biosense NOGA electromechanical mapping showed an area of reduced linear shortening and preserved voltage in all nine animals, and small areas of reduced unipolar voltage indicating infarction in two of nine animals. Biosense NOGA maps were normal in all 21 nonischemic animals (including the 15 animals in the catheter optimization study). Biosense-guided injections into the LCX region were successful in all animals.

The amount of ¹²⁵I-FGF2 deposited within a specific sample and organ was indexed to the total activity administered. In ischemic animals, total ¹²⁵I-FGF2 cardiac percentage of injected activity was 18.01 ± 3.84% at 1 h, 11.65 ± 5.17% at 24 h, and 2.32 ± 0.87% at 7 days (Fig. 4). Importantly, ¹²⁵I-FGF2 was predominantly distributed in the target lateral wall (LCX distribution) with only 0.23 ± 0.31%,

![Image](https://via.placeholder.com/150)

**TABLE 1**
Injection recovery (percentage) with differing volumes and needle lengths

A total of 30 injections (10 injections per animal) were done per group.

<table>
<thead>
<tr>
<th>Injection Volume</th>
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<tr>
<td></td>
<td>3 mm</td>
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<td>0.05 ml</td>
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**FIG. 3.** Percentage of injected activity (¹²⁵I-bFGF activity in the sample indexed to the total ¹²⁵I-bFGF administered per injection) of injections with varying needle lengths (A) and injection volumes (B). The optimal delivery parameters are 6-mm needle length (ANOVA, p = 0.048) and injection volumes of 0.05 or 0.1 ml (ANOVA, p < 0.001). Data are displayed as mean ± standard deviation.

0.06 ± 0.1%, and 0.01 ± 0.02% of the administered dose recovered from the anterior and inferior walls combined at 1 h, 24 h, and 7 days, respectively. Left ventricular autoradiography confirmed significant retention of ¹²⁵I-FGF2 at the injection sites (Fig. 5). Studies in nonischemic animals were not statistically different (p = 0.34) from normal animals with total ¹²⁵I-FGF2 cardiac percentage of injected activity of 18.96 ± 8.23% at 1 h and 9.97 ± 4.00% at 24 h in the target area (Fig. 4). ¹²⁵I-FGF2 percentage of injected activity in the anterior and inferior walls was 0.9 ± 0.8% at 1 h and 0.21 ± 0.3% at 24 h.

Epicardial Intramyocardial FGF2 Delivery. The characteristics of Biosense-guided transendocardial intramyocardial FGF2 injections were then compared with open-chest direct vision transpericardial injections. As in the case of transendocardial injections, two needle lengths (6 and 3 mm) were used. Total ¹²⁵I-FGF2 cardiac percentage of injected activity was 23.14 ± 12.67% for the 6-mm needle and 20.86 ± 11.06% for the 3-mm needle at 1 h, declining to 12.32 ± 8.50% for the 6-mm needle at 24 h (Fig. 6), and were not statistically different (p = 0.52) from values obtained following transendocardial delivery. Sampling of the pericardial space for ¹²⁵I-FGF2 percentage of injected activity demonstrated that 1.23 ± 0.81% of the dose was present 1 h following injections with the 6-mm needle and 1.01 ± 0.92% with the 3-mm needle. Twenty-four hours later, 0.92 ± 0.77% of the dose (6-mm needle) was still present in the pericardial space.

**Extracardiac Deposition of ¹²⁵I-FGF2.** To assess systemic spill of ¹²⁵I-FGF2 following intramyocardial injection, we sampled liver, kidney, and lung tissues as well as blood and urine at various time points (Tables 2 and 3). Liver samples had the highest ¹²⁵I-FGF2 percentage of injected activity and were higher for transendocardial than transepicardial injections (3.22 ± 1.27% versus 0.89 ± 0.22% at
of clinical studies using sustained release growth factors or gene
Lopez et al., 1998; Laham et al., 2000a). However, with the exception
sions, or repeat injections (Harada et al., 1994; Unger et al., 1994;
modalities, including sustained release polymers, continuous infu-
angiogenesis have used sustained or repeated growth factor delivery
2002; Henry et al., 2003). Given the expected long time course of new
highlighted the need for alternative routes of growth factor delivery
of vascular endothelial growth factor and FGF2 in phase I and II trials
challenging task. Recent experience with intracoronary administration
of myocardium, these options are not feasible or practical for catheter-based approaches (Losordo et al., 1998; Schumacher et al., 1998; Laham et al., 1999c; Rosengart et al., 1999).
The drawbacks of systemic or intracoronary administration include poor myocardial uptake, retention, and distribution, as well as significant systemic recirculation and bystander organ deposition. For in-
epicardial delivery, poor myocardial penetration is a major limi-
tion added to lack of pericardial space post-CABG and poor
deposition and retention (Laham et al., 2003). Intramyocardial deliv-
transfer vectors via open surgical access to the myocardium, these
1 h and 2.95 ± 1.86% versus 0.08 ± 0.02% at 24 h, p < 0.05 for both
time points). The same pattern was seen for other organs and tissues
tested.

Discussion
Local delivery of drug and biological agents to the heart remains a
challenging task. Recent experience with intracoronary administration
of vascular endothelial growth factor and FGF2 in phase I and II trials
highlighted the need for alternative routes of growth factor delivery
(Laham et al., 1999b,c, 2000a,b, 2003; Ruel et al., 2002; Simons et al.,
2002; Henry et al., 2003). Given the expected long time course of new
collateral vessel formation, most preclinical attempts at therapeutic
angiogenesis have used sustained or repeated growth factor delivery
modalities, including sustained release polymers, continuous infu-
sions, or repeat injections (Harada et al., 1994; Unger et al., 1994;
Lopez et al., 1998; Laham et al., 2000a). However, with the exception
of clinical studies using sustained release growth factors or gene
Schumacher et al., 1998; Rosengart et al., 1999). The availability of several catheter-based transendocardial intramyocardial delivery systems may obviate the need for surgery but had not been adequately studied. One such system is the Biosense-guided Myostar catheter with an adjustable retractable needle. The theoretical advantages of this system include the ability to identify and map ischemic regions of the ventricle and ensure stable position of the needle prior to intramyocardial injection (Kornowski et al., 2000). However, the optimal delivery characteristics resulting in maximal myocardial uptake and retention of the delivered material have not been well defined, with different investigators using arbitrary injection volumes, infusion rates, and needle lengths.

This study, therefore, was carried out to systematically and comprehensively evaluate the delivery characteristics of transendocardial intramyocardial injections using the Biosense-guided Myostar catheter as a prototype catheter, to study the tissue and myocardial distribution and retention of 125-I-FGF2 as a prototype molecule in normal and chronically ischemic animals, and to compare catheter-based to epicardial delivery. We chose FGF2 as a prototype delivery agent because of the extensive preclinical and clinical experience with this growth factor and its stability in tissues (Yanagisawa-Miwa et al., 1992; Harada et al., 1994; Unger et al., 1994; Laham et al., 1999c, 2000a). FGF2 is a heparin-binding growth factor and this property may play an important role in its tissue retention (Faham et al., 1996; Schaper, 1996). Because tissue expression of FGF2-binding high-affinity receptors and cell surface heparan sulfates increases in ischemic tissues, we evaluated its myocardial uptake and retention both in normal and chronically ischemic hearts (Gabra et al., 1994; Faham et al., 1996). Although retention and washout of FGF2 may differ significantly from those of other proteins that may be used for intramyocardial delivery, its initial tissue deposition is likely to be similar to that of any other agent and be primarily determined by physical characteristics of the delivery system and not the biological properties of the agent.

To optimize the transendocardial catheter delivery, we first evaluated the effect of varying the injection volume (0.05–0.2 ml) and needle length (3–6 mm). Using a shorter needle length would result in more misses with the cardiac motion and using a longer needle length would increase risk of perforation. Injection site recovery ranged from 73.3 to 90%, indicating that 10 to 27.7% of injections may have missed the myocardium (intracavitary injection) or, less likely, may have been localized in a large vascular structure leading to rapid washout from the myocardium. Using 1-h 125-I-FGF2 myocardial deposition as a parameter for delivery efficiency, and testing the three needle lengths and three delivery volumes chosen, the optimal needle length in these animals with a wall thickness of 8.9 ± 1.1 mm was determined to be 6 mm and, using this needle length, the optimal injection volumes were determined to be 0.05 and 0.1 ml. In addition, these studies showed that the majority of delivered growth factor resides at the injection site with little lateral diffusion to adjoining sites, underscoring the potential need for spreading injections across the desired area.

Using these optimal parameters (6-mm needle length and 0.1-ml injection volume) for transendocardial intramyocardial delivery, we then evaluated distribution and retention of FGF2 in normal and ischemic myocardium. Transendocardial intramyocardial administration resulted in markedly enhanced efficiency (% of dose delivered) and myocardial retention compared with intravenous, intracoronary, and pericardial administration of the same amount of FGF2 previously reported by our laboratory at all studied time points (Laham et al., 1999b, 2003). In addition, the majority of myocardial distribution of FGF2 was localized to the targeted areas, emphasizing the accuracy of Biosense guidance, with myocardial levels in noninjected areas approaching the levels seen with intracoronary and intravenous delivery, likely resulting from systemic recirculation rather than intramyocardial diffusion. Finally, the presence of myocardial ischemia did not affect the efficiency of intramyocardial bFGF delivery or tissue retention at 1 and 24 h, as it did for intracoronary delivery, likely indicating saturation of the binding sites by high myocardial distribution (Laham et al., 1999b).

The amount of FGF2 successfully delivered to the myocardium using this transmyocardial approach was comparable with the amount delivered using direct vision open-chest transapical injection. Thus, the availability of transendocardial intramyocardial injection catheters may obviate the need for open-chest transapical injection.

With the few time points studied, endocardial delivery resulted in a slightly higher liver uptake than epicardial delivery, partially related to the 10 to 27% frequency of misses that presumably result in intracavitary injections. On the other hand, epicardial delivery resulted in significant distribution of the injected FGF2 to the pericardial sac, likely resulting from a combination of contamination at the time of injection and back-leak into the pericardial space. It should be noted, however, that this might represent an additional advantage for the transapical delivery, as pericardial administration has been shown to be an effective means of growth factor delivery (Laham et al., 2000a).

The time points studied may miss earlier events and are a limitation of this study, although the half-life of circulating FGF2 makes that rather unlikely (Edelman et al., 1993). The efficacy of intramyocardial injections for each agent needs to be studied, including optimizing the catheter to the agent, cells, or vectors used to maximize delivery to myocardium. Finally, the long-term effects of this mode of delivery are not well defined, with the potential of causing inflammation and fibrosis.

In conclusion, optimized transendocardial intramyocardial delivery using Biosense guidance results in a relatively efficient delivery of FGF2 to the target myocardium that is comparable with transapical delivery. Furthermore, intramyocardial delivery provides markedly higher myocardial deposition and retention and lower systemic recirculation of FGF2 than intracoronary, intravenous, or pericardial delivery. The practical relevance of this mode of growth factor delivery awaits testing in clinical trials of therapeutic angiogenesis.

References


