

# Catheter-based delivery of cells to the heart

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## SUMMARY

Clinical trials have begun to assess the feasibility, safety, and efficacy of administering progenitor cells to the heart in order to repair or perhaps reverse the effects of myocardial ischemia and injury. In contrast to surgical-based injections, which are often coupled with coronary bypass surgery, catheter-based injections are less invasive and make it possible to evaluate cell products used as sole interventions. The two methods that have been tested in humans are injecting cells directly into the ventricular wall with catheter systems dedicated to that purpose and infusing cells into coronary arteries with standard balloon angioplasty catheters. The catheters described in this article have been shown in both animal and clinical studies to be effective in cell delivery and to be safe. They are well-designed and user-friendly devices, but require further investigation to identify means for optimizing cell retention and to address other limitations. Randomized, placebo-controlled trials utilizing catheters for cell implantation are under way, and others are soon to follow. The results of these studies will help to shape the direction of future investigations, both clinical and basic. The spectrum of cardiac diseases, the variety of catheters for cell delivery, and the wide array of progenitor cell types open up this young field to creative discoveries.

**KEYWORDS** catheters, cell delivery, intramyocardial, intracoronary, progenitor cells

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## INTRODUCTION

An unfortunate characteristic of the adult mammalian heart is its ineffective use of programs for repair and regeneration, especially after acute coronary occlusion and ST-elevation myocardial infarction (STEMI). Experimental studies have explored ways to overcome this limitation by introducing progenitor cells into the myocardium.<sup>1</sup> The choice of cells and of methods for isolating them are described in other papers in this issue of *Nature Clinical Practice Cardiovascular Medicine*.<sup>2–10</sup> The administration of progenitor cells to humans with cardiac disease has been recently described.<sup>11–16</sup> This article reviews methods for cell delivery that utilize percutaneous catheter technology.

Because the field of cardiac cell-based therapy is at a very early stage, many questions remain unanswered, including those relating to our basic understanding of the biologic effects of such therapy. Similarly, aspects of cell delivery, such as effective dose and timing of administration, are still largely undefined. Therefore, what follows is a synopsis of an evolving field, intended to provide a basic understanding of catheter-delivery systems and their functional capabilities.

## CURRENT DELIVERY METHODS

Percutaneous transplantation of progenitor cells into the heart, performed as a sole therapy, allows the evaluation of the cells' effects independently of revascularization or other interventions.<sup>17</sup> Furthermore, multiple administrations over time would be more easily justified with a low-risk percutaneous procedure. Two catheter-based methods have been used in clinical trials to deliver cells to the heart: direct intramyocardial injection and intracoronary infusion. Though substantially different techniques, they share the common goal of seeding progenitor cells into specific histoanatomic locations, specifically into the perivascular, interstitial space surrounding injured or ischemic myocardium. In doing so,

**Table 1** Devices for intramyocardial delivery of cells.

Device	Core needle			Support			Notes
	OD (mm)	Length (cm)	Composition; configuration	Size (Fr <sup>a</sup> )	Length (cm)	Configuration	
Helix™, <sup>39</sup>	0.51	124	Stainless steel; helical	8	110	Deflectable guide catheter	Guide catheter (Morph™) is FDA approved
MyoCath™, <sup>b</sup>	0.51	122	Stainless steel; straight	8	115	Integrated; multiple curves	
Myostar™, <sup>24</sup>	0.41	123	Nitinol; straight	8	115	Integrated; multiple curves	NOGA-guided; <sup>c</sup> CE marked
Stiletto™, <sup>35,36</sup>	0.46	133	Nitinol; straight; spring loaded	9, 7	100, 125	Two guide catheters	
TransAccess Delivery System™, <sup>25</sup>	0.41	177	Nitinol; curved; injection catheter	6.2, 10	125, 80	Guide catheter; transvenous	IVUS-guided; Peripheral device (Pioneer™) FDA and CE approved

<sup>a</sup>French size. <sup>b</sup>Sherman W *et al.* Results of the MYOHEART study, a phase I skeletal myoblast study for congestive heart failure. Presented at the 2005 scientific sessions of Transcatheter Cardiovascular Therapeutics, Washington DC, USA, October, 2005. <sup>c</sup>NOGA, an electromagnetic mapping system (Biologics Delivery Systems, Diamond Bar, CA, USA). CE, European Community (European Union); IVUS, intravascular ultrasound; OD, outer diameter.

it is hoped that cells so placed will find conditions suitable for their survival and retention, thereby giving them their best chance to effect repair or regeneration.

#### Direct intramyocardial injection

As in the development of other biotherapeutics, early studies in cardiac cell therapy were conducted in animal models—in this case, open-chest models—in which techniques of controlled myocardial injury and administration of specific agents are well established. In large animals, surgical exposure of the beating heart permits myocardial injections, tagged for subsequent analysis, to be localized to segments diseased by coronary occlusion. With these techniques, the regenerative potential of many cell types has been studied.<sup>1,18</sup> Such studies became the foundation for the first injections of autologous skeletal myoblasts<sup>19</sup> and bone marrow-derived cells<sup>20</sup> in humans during coronary artery bypass surgery.

Catheter-based direct intramyocardial methods attempt to simulate surgical injection techniques,<sup>21</sup> by approaching the myocardium from either its epicardial or its endocardial surface. The demands of this task have led to the development of devices constructed of multiple components. One component (the core element) is dedicated solely to the transport of cells. It is small in caliber and terminates in a beveled injection needle distally. The

core catheter is advanced and retracted within the outer elements of the device. The other components (support catheters) are multifunctional, serving to protect the core and to direct it toward the region(s) of myocardium to be injected. However, while it is believed that the capacity to deliver cells by catheter-based methods is similar to that obtained with open surgical procedures, there are few data comparing the two delivery methods.<sup>22</sup> Moreover, certain aspects of the surgical technique described above are not feasible with current catheter systems.

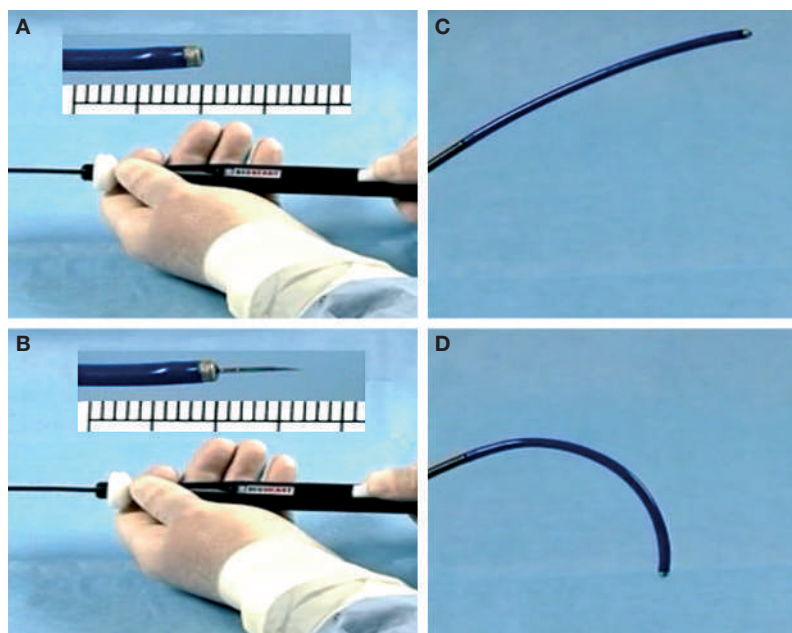
Five intramyocardial catheter-based delivery systems have been used in clinical trials (Table 1). All share the multicomponent design features just described. However, they differ in their anatomic approach to the myocardium, in specific design aspects and materials, and in ancillary imaging modalities.

The first four devices listed (the Helix™ [BioCardia Inc., South San Francisco, CA, USA], the MyoCath™ [Bioheart Inc., Sunrise, FL, USA], the Myostar™ [Biologics Delivery Systems, Diamond Bar, CA, USA], and the Stiletto™ [Boston Scientific, Natick, MA, USA]) approach the myocardium from within the left ventricular chamber (the 'transendocardial approach'), which is accessed crossing the aortic valve in a retrograde fashion, much as is done during routine left heart catheterizations.

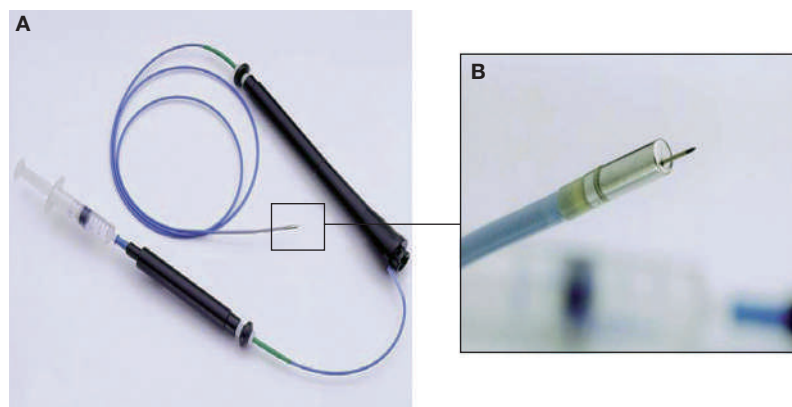
Two of these transcatheter devices—the MyoCath™ (Figure 1) and the Myostar™ (Figure 2)—are so-called integrated systems, in which the core and support catheters are joined to form a single unit. These two devices are manipulated through a combination of axial rotation and deflection of the distal aspect (the latter under a separate control mechanism capable of inducing up to 180° of flexion). With the tip of the device in contact with the endocardium, the core catheter is advanced, forcing a straight needle to a controlled intramyocardial depth (3–8 mm). The integrated design provides a relatively simple mechanism for navigation and repeated injections. However, there is no guide-wire lumen in either and they must be advanced from the femoral artery and across the aortic valve using the same navigation mechanisms that guide the device within the ventricular chamber.

The other two transcatheter devices—the Helix™ (Figure 3) and the Stiletto™ (Figure 4)—are not integrated: the core catheter is a physically separate device that can be inserted and removed in its full length separately from the support catheters. The latter are constructed, and approved, for use as vascular guiding catheters. The latter are constructed, and approved, for use as vascular guiding catheters. Directional control within the left ventricle is effected by manipulation of a single, deflectable catheter (the Helix™) or of two preshaped support catheters (the Stiletto™). Two features are unique to these two devices: the ability to insert the support catheters into the ventricle over a guide wire, and the configuration of the injection needles, which in one case is helical and in the other is spring loaded. The helical design, based on pacemaker lead technology, may be advantageous with regard to stability of the needle tip during injection. The spring-loaded needle of the Stiletto™ device is set to a fixed depth (3.5 mm) and may be more able to penetrate fibrotic tissue. As with integrated devices, the coordinated movement of support catheters and core elements enables multiple, topographically distinct injections throughout the left ventricle.

The fifth catheter listed in Table 1, the TransAccess Delivery System™ (Medtronic Vascular, Santa Rosa, CA, USA) (Figure 5) is unique among the intramyocardial devices in approaching the myocardium through the epicardial surface. To achieve this, a support catheter is positioned in specific branches of the cardiac venous system, by way of the

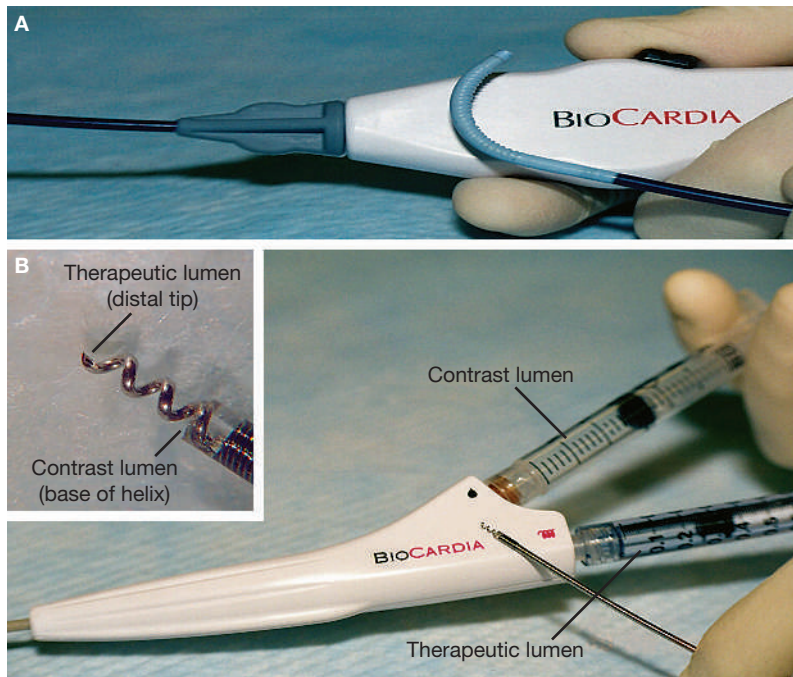


**Figure 1** MyoCath™ catheter for intramyocardial delivery of cells. An integrated-device with control mechanisms for needle movement from withdrawn (A) to extended (B) position, as well as for tip movement from straight (C) to deflected (D) position. Image courtesy of Bioheart Inc., Sunrise, FL, USA.

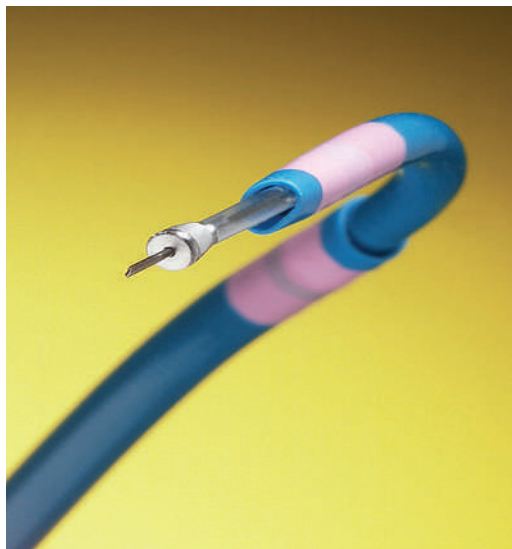


**Figure 2** Myostar™ catheter for intramyocardial delivery of cells. An integrated-device with similar control mechanisms (A) as noted in Figure 1, but with endocardial (NOGA) mapping capability. The sensor is contained within the distal tip of the catheter (B), through which the injection needle is extended. Image courtesy of Biologics Delivery Systems, Diamond Bar, CA, USA.

femoral vein. An intravascular ultrasound probe contained within the support catheter makes it possible to localize the adjacent coronary artery and pericardium. With these structures used as landmarks, the coronary vein is punctured with a small-caliber needle, and



**Figure 3** The Helix™ catheter for intramyocardial delivery of cells. A non-integrated system with an independent deflectable guide catheter (A) and removable helical-shaped-needle injection catheter (B). Image courtesy of BioCardia Inc., South San Francisco, CA, USA.



**Figure 4** The Stiletto™ catheter for intramyocardial delivery of cells. A nonintegrated system with two independently configured guide catheters and a removable spring-loaded needle. As shown here, the needle is extended beyond the flat surface of the core injection component. Image courtesy of Boston Scientific, Natick, MA, USA.

through this an injection catheter is passed into the ventricular wall through its epicardial surface. The injection catheter can be advanced for several centimetres along a trajectory within the wall. In this respect it more closely resembles surgical injection techniques than do other intramyocardial devices.

Adjunctive imaging for catheter guidance is incorporated into the Myostar™ system.<sup>11</sup> Using electromechanical signal detection, a baseline 3-dimensional endocardial map (NOGA™, Biologics Delivery Systems) can be created; this map is color-coded to delineate regions of viable, ischemic myocardium (for an example of such a map, see Opie *et al.*<sup>23</sup> in this issue). Target areas can be precisely identified and electronically marked with each injection. Extensive experience with this system has been accumulated in both preclinical and clinical studies.<sup>24,25</sup>

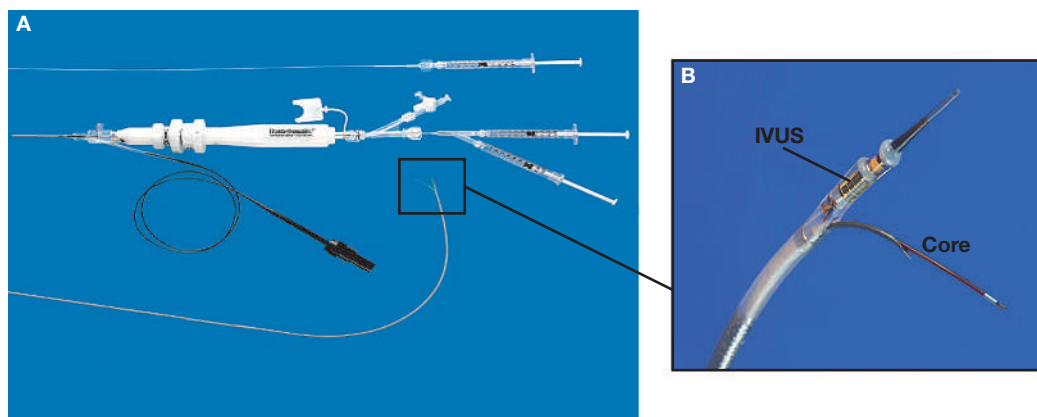
Other differences between the five devices relate to the needle composition (stainless steel or nitinol), and method of activation (i.e. manual or spring loaded). The relative merits of each design feature are not established.

Whether the ease of use of one-piece, integrated systems outweighs the versatility of independently controlled systems, whether the level of precision provided by devices with enhanced guidance mechanisms is necessary for effective delivery, and whether specific needle designs facilitate delivery and augment retention of cells are questions still open to debate. In the future, the selection of intramyocardial device may well be found to depend on the underlying myocardial disease. We are presently conducting studies to address this question.

In the US, all the devices listed in Table 1 are classified as having investigational status for intramyocardial injection; one (Myostar™) has CE marking (certifying conformity with the standards of the European Union and the European Free Trade Association) for this purpose. One of the guide catheters (Morph™, BioCardia) and a transvenous access catheter, similar to the TransAccess Delivery System™ but larger in caliber (Pioneer™, Medtronic Vascular, Santa Rosa, CA, USA) are approved by the FDA for use in treating peripheral vascular disease.

### Intracoronary infusion

The other method by which cells have been administered in clinical trials is intracoronary infusion. The underlying rationale is both



**Figure 5** TransAccess Delivery System™ catheter for intramyocardial delivery of cells. A nonintegrated system. **(A)** The full system with the proximal connection for the intravascular ultrasound component (IVUS, colored black). **(B)** The distal catheter tip, with the internal intravascular ultrasound imaging element (IVUS) and the extended needle and injection catheter (core). Image courtesy of Medtronic Vascular Systems, Santa Rosa, CA, USA.

biologic and pragmatic. The biologic goal is to amplify cell trafficking to ischemic myocardium, raising it above the levels known to occur after both acute and chronic coronary occlusion.

Acute coronary occlusion and STEMI lead to immediate, irreversible effects on myocardial function within the distribution of the infarct-related artery. Further deterioration of myocardial function can extend beyond the borders of the infarction, observed weeks or months after the acute event, in a process known as remodeling. The clinical consequences of remodeling are profound, leading to further deterioration of left ventricular function and congestive heart failure. Remodeling is believed to be due, in part, to 'demand' myocardial ischemia and myocyte apoptosis of the peri-infarction regions. Immediately after acute coronary occlusion, vascular progenitor cells are released from bone marrow, enter the peripheral circulation, and home to the site of myocardial injury,<sup>26</sup> where they promote the development of neovasculature and are incorporated into it. However, the scale of this process appears to be small in the clinical setting of STEMI.<sup>27</sup> Interventions that increase the level of neovascularization, such as through the administration of vascular progenitor cells, might mitigate the remodelling process.<sup>28</sup>

Patients with chronic coronary occlusions, myocardial ischemia, and refractory angina are also underserved by intrinsic levels of angiogenesis. They have been the focus of

numerous trials of gene therapy<sup>29</sup> and other novel therapies<sup>30</sup> and may benefit from increased levels of vascular progenitor cells in regions of chronic ischemia.<sup>29</sup>

There are also pragmatic reasons for intracoronary cell administration. Because diseased myocardial tissue retains a blood supply, irrespective of the nature or extent of disease, vascular pathways are identifiable by angiography. Cells injected into proximal coronary segments can be distributed to large regions of myocardium. Alternatively, infusion into specific branch vessels, such as infarct-related arteries, could utilize methods common to percutaneous coronary interventions (PCI) and familiar to interventional cardiologists.

From the preceding discussion, it follows that the efficacy of intracoronary administration depends on specific properties of the cell preparation and on coronary anatomy. Cells used for intracoronary infusion must be capable of transendothelial migration to perivascular spaces, as noted previously. Cell preparations that are viscous or in which the cell diameters are large may not be suitable for intracoronary infusion, due to the risk of microvascular obstruction and myocardial ischemia.<sup>31</sup> Additionally, myocardial targets must be supplied by well-defined vascular channels readily accessed by delivery catheters. While these requirements are ideally suited to patients with post-PCI STEMI, they may not be met in patients with chronic occlusive coronary

**Table 2** Some published clinical trials using over-the-wire balloon catheters.

Reference	Disease	Cells injected		Catheter (supplier)	Infusion regimen <sup>a</sup> (min)
		Number	Type		
Assmus <i>et al.</i> <sup>13</sup>	STEMI	2.4 × 10 <sup>8</sup> 10 × 10 <sup>6</sup>	BMMC, CPC	OpenSail™ (Guidant Corp., Indianapolis, IN, USA)	3 × 3
Wollert <i>et al.</i> <sup>14</sup>	STEMI	2.5 × 10 <sup>9</sup>	BMMC	Concerto™ (Occam International BV, Eindhoven, the Netherlands)	5 × 2.5–4
Bartunek <i>et al.</i> <sup>41</sup>	STEMI	12.4 × 10 <sup>6</sup>	BM-derived CD133 <sup>+</sup>	Maverick™ (Boston Scientific, Natick, MA, USA)	3 × 2–3
Janssens <i>et al.</i> <sup>b</sup>	STEMI	3 × 10 <sup>8</sup>	BMMC	Maverick™ (Boston Scientific)	3 × 2–3

<sup>a</sup>Number of infusions × duration of each infusion. <sup>b</sup>Janssens S *et al.* Intracoronary autologous bone marrow cell transfer after myocardial infarction: a double-blind, randomized, and placebo-controlled clinical trial. Presented at the 2005 Scientific Sessions of the American College of Cardiology 2005, Orlando, FL, USA, March, 2005. BM, bone marrow; BMMC, bone marrow mononuclear cells; CPC, circulating progenitor cells; STEMI, ST-elevation myocardial infarction.

disease, in whom ischemic areas are fed solely by collateral vessels, often arising from arteries afflicted with obstructive disease.

Clinical trials that have delivered cells by intracoronary infusion have done so through coronary balloon angioplasty catheters. Such catheters are well suited for this purpose, given the ease with which they can be positioned into selected coronary branches. The two features of balloon-dilating catheters that bear on their utility in delivering cells are the central (core) lumen and the expandable balloon. In 'over-the-wire' devices, unlike 'monorail' devices, the central wire extends the full length of the catheter. After positioning of the catheter, the guide wire can be withdrawn from the lumen, leaving it to function as a conduit for injection into the distal coronary bed. Furthermore, to prevent cell washout by antegrade blood flow and to increase the dwell time (the time during which the injected cells remain undisturbed by the resumption of blood flow), occlusive balloon inflation is initiated just before distal injection of the cell suspension and continued for up to 5 min or until the onset of clinically important ischemia. So far, catheters that lack the ability to obstruct coronary flow proximal to the site of cell injection have not been used in clinical trials.

Several commercially available over-the-wire balloons have been used in this way in clinical trials (Table 2). It is important to note that no balloon angioplasty catheter has received regulatory approval specifically for cell infusion, even though all are made of biologically inert materials and are unlikely to adversely affect cell survival or function.

### COMPARISON OF DELIVERY TECHNIQUES

The intramyocardial and intracoronary delivery techniques each have their own distinct advantages and limitations. Intracoronary procedures are performed extensively for the treatment of coronary artery disease, and any modifications specific to cell infusions would be easily integrated into such procedures. Intramyocardial procedures would require additional operational training, albeit with devices that are not complex. Moreover, the facility with which cells reach the extravascular compartment from an intracoronary injection may differ considerably from one cell population to another. Intramyocardial administration overcomes this problem by circumventing the vascular barrier.

Early studies have compared the two techniques, either directly or with surgically applied injections.<sup>32</sup> The retention of cells is poor by either route of administration,<sup>32,33</sup> with fewer than 10% of the injected cells detectable after 24 h. These studies were conducted in normal<sup>32,33</sup> or recently infarcted<sup>34</sup> myocardium, and their applicability to myocardium with chronic fibrosis is questionable. Retention of cellular or other biologic agents is low by every implantation method thus far tested, including surgical implantation. Solutions to this problem may be found in products that combine cells with agents more adhesive to resident tissue.<sup>35</sup>

### CONCLUSION

The field of cell-based therapy for cardiovascular disease is at an early stage. The catheters described in this article are well-designed, user-friendly devices that have demonstrated their

capability of delivering cells to the heart. In both animal and clinical studies, their safety profiles have been excellent—an especially noteworthy achievement for the intramyocardial devices, which are complex to construct and require needle puncture for access to the ventricular wall.

Important questions remain regarding catheter-based cell delivery; the catheter systems described here require further characterization. Balloon-dilating catheters were not designed (and have not been approved) for the administration of therapeutic agents. Though unlikely to pose significant problems to cell function and viability, each should undergo preclinical testing before use in clinical studies. Direct intramyocardial delivery catheters, on the other hand, were essentially developed in parallel with cell products<sup>36,37</sup> and consequently have had to undergo extensive biocompatibility testing. Despite the poor retention of cells injected by either route of administration, both compare favourably with the cell retention obtained by direct transepical implantation at surgery.

Standards have not been developed for testing and comparing the physical attributes of delivery catheters, or for their efficacy in delivering cells. We feel it important to conduct such evaluations in order to define their respective performance ranges. Our group is analyzing certain of these characteristics, as well as the physical properties of diseased myocardium, and believe the results will be pertinent to the design, conduct, and interpretation of future clinical studies.

Catheters used in clinical trials are sophisticated and, from the standpoint of cell delivery, early-generation devices. Whether by refining current designs, or by combining them in novel ways with other technologies,<sup>38</sup> or by developing techniques that pursue entirely new approaches,<sup>39,40</sup> significant advances in the efficacy of cell delivery will be made in the coming years.

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**Competing interests**

The authors declared they have no competing interests.

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