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Percutaneous cell delivery techniques: devices and issues

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Introduction

A steady rise in the prevalence of chronic cardiovascular diseases coupled with new insights into tissue healing has stimulated an interest in the potential of progenitor cell-mediated repair and regeneration. The administration of biologic agents via catheters has a long history and, in recent years, research and development teams have turned their attention to creating devices specifically for delivering cell products. Catheters used for cell delivery are varied in fundamental ways, and do not fall into a "one-size fits all" group. As evaluation of these devices continues[1], a clearer picture is emerging as to the capabilities and limitations of percutaneous cell delivery.

The goals of cell-based therapeutics are to promote tissue repair and regeneration. As depicted in Figure 1, the methods now used involve a series of steps, two of which (cell processing and delivery) themselves are multi-staged. Irrespective of the cell type or preparation being tested, or whether its desired effects occur through the release of intracellular mediators and/or the maturation and integration (engraftment) into specific tissue, maximising the retention of cells after administration is paramount to the procedure's success. Unfortunately, the ability of the heart to retain an injection of cells is poor and the literature is replete with discouraging data. Of the total administered dose of cells (or other similar material), no more than 35-40% are detectable at one hour[2] and 10% at one day[3]. Moreover, rates of retention appear similar and independent of type of cell, delivery technique or disease state[4], although variability by injection method exists for specific agents[5]. The mechanisms of cell attrition are very different in the environment of high interstitial flow (normal myocardium) versus that of ischaemic and fibrotic tissue. While individual steps in a specific method of cell administration may influence cell retention, all are dependent to a large degree on the effectiveness of the delivery technique.

Despite significant strides made during the past 2 years, the field of percutaneous cell delivery is at an early stage of development. To date, it has not developed measures of procedure success, depriving itself of a parameter valuable to intra- and inter-study comparisons. Nevertheless, even in its present form, it holds clear advantages over alternative delivery strategies: 1) higher efficiency of cell delivery compared peripheral intravenous injection, 2) lower

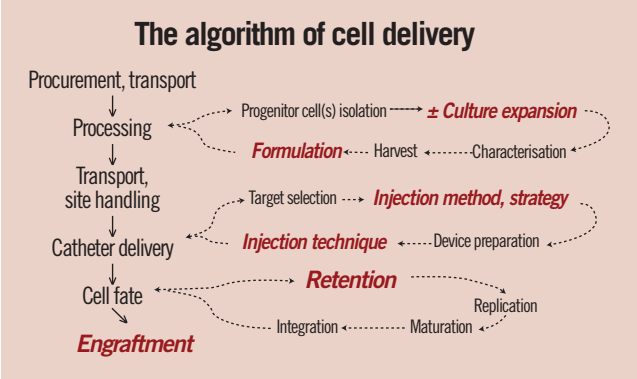

Figure 1. Algorithm of cell delivery. The flow diagram of a typical, stepwise process for procuring and administering cell products. Highlighted in red are those parts of the process which that may have a larger role in affecting cell retention and engraftment.

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procedure risk-profile compared to surgery, 3) high potential for integration into clinical practice, in that many techniques are modifications of current interventional methods, and 4) higher facility for repeat applications compared to surgery, which is still the benchmark for intramyocardial injections. Regarding the last point, it is assumed that catheter-based delivery will provide a level of efficiency equal to (or greater than) surgery, although data comparing the techniques are scarce, especially in diseased myocardium. From several studies the comparison appears to be favourable[6-9]. Hou et al[9], observed insignificant differences in the retention of radiolabelled mononuclear cells given by intramyocardial (surgical), intracoronary or retrograde venous approaches in a one week old porcine-MI model. Nevertheless, no study dedicated to the rigorous assessment of cell injections into advanced myocardial disease with these techniques has been reported; nor have clinical trials attempted to do so as yet.

In this paper, we present an overview of percutaneous cell delivery techniques and devices, focusing on those devices in clinical or late-stage preclinical study. In doing so, we will present as comprehensive a picture as possible, by highlighting the features of individual devices, by identifying the issues they face and by discussing potential solutions to enhancing the effectiveness of these techniques.

Techniques and devices (Table 1)

The techniques for percutaneous cell injection fall broadly into 2 categories: "coronary vascular" or "intramyocardial". For the most part, the primary goal for these techniques is to provide access of injected cells to the microvasculature or extravascular space (interstitium), or both.

Coronary vascular techniques require that target tissue be served by angiographically identifiable vessels (even if only collateral channels), and that the desired effect(s) of the cell product occur through any combination of: 1) endothelial adhesion, 2) transvascular migration, 3) physical interruption of the endothelial barrier through hydrostatic or mechanical force, 4) cytokine release, 5) maturation and integration into diseased tissue (engraftment). The most commonly applied coronary vascular methods are antegrade arterial. In particular, sub-selective cell injections through the central lumen of an over-the-wire (OTW) angioplasty catheter, while either maintaining coronary flow or interrupting it with balloon occlusion (the so-called, "stop-flow" method). This technique is simple, utilises off-the-shelf devices and has been the method of choice for nearly all studies in patients with STEMI[10-16] in addition to other clinical conditions[17]. Diagnostic, guide and specialty catheters are suitable for nonselective cell infusion, given the calibre of their internal diameters (ID), although there is limited experience in their off-label use at this time[18]. Surprisingly, the kinetics of coronary arterial cell delivery have received little attention in preclinical studies[19]. Unlike the lead-in to the first clinical trials of IC gene products, the transition of cell-based studies from small animals[20] to humans[10] was rapid. Consequently, much of what is known regarding cell retention after IC administration has been learned from clinical studies[3,21].

The other category of vascular administration is retrograde venous. A solid body of data underlies this approach[9,22-24], and, in part, builds upon clinical experience in the administration of non-cellular agents. Directing cell products to the post-capillary vasculature circumvents several of the technical problems of arterial methods, especially those related to occlusive arterial disease. Theoretically, all vascular territories are accessible, although the full geometric breadth of this technique has not been reported.

Intramyocardial methods administer cell products by the insertion of small calibre needles directly into the ventricular wall. By necessity, devices capable of this are comprised of 2 or more components and are more aptly described as "catheter systems", especially in that several are coupled to dedicated imaging modalities. The two essential elements are the injection (core) lumen for biological delivery and the support catheter that enables directional positioning of needle tip. Other elements specific to individual devices permit redirection of the support catheter, transmission of image data, infusion/irrigation of lumina in addition to the core and passage of guidewires.

The intramyocardial catheter systems that have seen use in clinical trials are outlined in Table 2. The needle size (25-27ga) is comparable to all. Otherwise, they differ by virtue of access to the myocardium (transendocardial or transepicardial), of mechanisms of navigation (integrated "tip-deflectable" vs steerable guide vs transvenous-IVUS-directed) and of ventricular imaging. The integrated design provides a relatively simple mechanism for intra-cavitary navigation and repeated injections. However, without a guidewire lumen their passage from femoral artery to left ventricular chamber is dependent on those same navigation mechanisms or the use of long sheaths to facilitate access. Other differences between the five devices relate to needle composition (stainless steel or nitinol), configuration (straight, curved or helical) and activation (manual or spring loaded), and methods of catheter imaging.

All intramyocardial catheter systems in Table 2 use X-ray imaging for either a part or all of the procedure. Adjunctive imaging for catheter guidance is incorporated into the two systems. One (Myostar™25) utilises electromechanical sensing of the endocardium and is particularly well suited to delineating ischaemic and non-ischaemic tissue. The other (CrossPoint™), uses IVUS imaging to orient the needle on its initial trajectory from the coronary venous system into the myocardium. Passage of the injection catheter through the needle is then visualised by fluoroscopy. Other modalities have also been used, including integrated real-time MRI[2,26,27], 3D-echocardiography[28] and, more recently, a combination NOGA-imaging and automated catheter positioning system (Stereotaxis) has been piloted (E. Perin, P. Serruys, personal communication). MRI and 3D echo systems permit the visualisation of intramyocardial injections, although only the latter is readily available.

The functional differences among or between vascular and intramyocardial devices have not been fully explored, although comparative data is emerging[29].

The issues: a 3-component analysis

As can be surmised from Figure 1, problems within this complex algorithm can arise at any step, including during cell injection. Methods of cell processing and handling, variability in biologic effects of individual cell preparations (especially autologous products), the lack of simple potency assays and other issues affect all

Table 1. Percutaneous cell and other biologic delivery techniques. Examples of vascular and intramyocardial studies, subcategorised by type of catheter, model of disease and agent injected.

Method	Catheter type	Examples (Manufacturer)	Disease model	Injected cell or biologic	References Preclinical	References Clinical
VASCULAR						
Coronary arterial						
Nonocclusive	Diagnostic	5 Fr (NA)	Normal canine	Autol-BMD MSC	Vulliet	
		6 Fr (Cordis)	CMI	Autol-CD34		Boyle
	Specialty	Tracker™ (Boston Scientific)	STEMI	Autol-BMD MSC		Musialek
	Balloon	Maverick™ (Boston Scientific)	CMI	BMD CD133		Pompili
		NA	CMI	BMD CD133		Goussetis
Balloon occlusive	OTW	Concerto™(Occam)	STEMI	Autol-BMD MC		Wollert
		OpenSail™ (Gudant)	STEMI	Autol-BMD MC		Schachinger
			Chronic MI	Autol-BMD MC vs CPC		Assmus
		Maverick™ (Boston Scientific)	STEMI	BMD CD133		Bartunek
			CMI porcine	Autol-BMD MC	Bhakta	
		Ninja™ (Cordis)	CTO	CPCs		Erbs
Perivascular	Specialty	µSyringe™ (MercatorMed)	MI (1hr)	BMD MAPC	Ting	
Coronary venous						
Balloon occlusive	Single	Centurion™ (Bard)	Chronic MI	Autol-BMD MC		Tuma-Mubarak
		NA	STEMI (12d)	Autol-BMD MC		Murad-Netto
	Double	(Venomatrix)	MI (5-7d) porcine	hCPCs	Hou	
INTRAMYOCARDIAL						
Endoventricular	Needle					
X-ray guided		Myocath™ (Bioheart)	Chronic MI	Autol-SM		Smits
			Chronic MI	Autol-SM		Sherman
		Stiletto™ (Boston Scientific)	Porcine MI (14d)	Allo-MSC	Freyman	
		Helix™ (Biocardia)	CMI	Autol-BMD MC		De la Fuente
3-D NOGA guided:		Myostar™ (BDS)	CMI	Autol-BMD MC	Fuchs	Fuchs
			CMI	Autol-BMD MC		Perin
			CMI	Autol-CD34		Losordo
X-ray 3-D Echo guided		Myostar™ (BDS)	Normal porcine	Echo contrast	Baklanov	
3-D MRI-guided		Stiletto™ (Boston Scientific)	Normal porcine	Allo-MSC	Dick	
		Myocath™ (Bioheart)	Normal porcine	Gadoliunium	Corti	
X-ray 3-D-MRI guided		Stiletto™ (Boston Scientific)	Ovine MI (1-74d)	Allo-MSC	de Silva	
Epicardial	Needle					
X-ray-IVUS guided		Cross-Point™ (Medtronic)	Chronic MI	Autol-SM		Siminiak
			Normal swine	BMD MSC- hydrogel	Thompson	
			Ovine MI (14d)	Autol-SM	Brasselet	

Methods: 3D - 3 dimensional, NOGA - , MRI - Magnetic resonance imaging, IVUS - intravascular ultrasound;
Catheter Type: OTW - over-the-wire;
Examples: NA - not available, Cordis - Cordis Corp., BSC - Boston Scientific Corp., Occam Corp., Mercator MedSystems, Inc., Bard Corp., Ventomatrix Corp., Bioheart Inc., Weston, FL, Biocardia, Inc., BDS - Biologics Delivery Systems, Medtronic Vascular Systems.
Disease model: CMI - chronic myocardial ischemia, STEMI - ST-elevation myocardial infarction (MI), CTO - chronic coronary occlusion;
Injected agent: Autol - autologous, Allo - allogeneic, h - human, BMD - bone marrow derived, MSC - mesenchymal cells, MC - mononuclear cells, CPC - circulating progenitor cells, CD - cell differentiation marker, MAPC - multipotent progenitor cells, skeletal myoblasts, Echo - echocardiographic.

Table 2. Intramyocardial delivery systems. The five intramyocardial delivery catheters, categorised by injection approach, support catheter and guidance system.

Device	Injection		Support Catheter(s)			Imaging and guidance system
	Myocardial access	Needle ID (ga)	Size (Fr)	Configuration	Guidewire lumen	
CrossPoint™ [15]	Transvenous, epicardial	27	6.2 10	IVUS-integrated Guide catheter	Y Y	X-ray and IVUS
Helix™ [29]	Transendocardial	25	8	Deflectable guide catheter	Y	X-ray
MyoCath™ [13]	Transendocardial	25	8	Integrated	N	X-ray
Myostar™ [30]	Transendocardial	27	8	Integrated	N	X-ray and NOGA
Stiletto™ [25]	Transendocardial	25	9, 7	Dual guide catheters	Y	X-ray

ID - internal dimension (gauge), Fr - French, IVUS - intravascular ultrasound, NOGA - 3D electromechanical mapping system (BDS).

cell delivery methods. The factors bearing on the immediate results of catheter delivery largely arise from interactions of the 3 components of the delivery process: cell product, cardiac tissue, delivery technique, and the magnitude of effect for each will vary variable, depending on the Table 3 lists the cell preparations in current use, or soon to be used in human studies. Clinical trials have been completed with bone marrow-derived mononuclear cells, mesenchymal stem cells and immunoselected populations (CD 34+, CD 133+, mesenchymal precursor). Multipotent adult progenitor cells (MAPCs), adipose-derived and cardiac-derived cells are in late-stage preclinical evaluations. In general, cell products are tested for viability (% cells, by methylene blue exclusion), purity (% cells of specific cell-type) and sterility (by gram stain) prior to administration; it is upon these three characteristics that "release criteria" are based and that determine a product's suitability for experimental use. Less often assayed is the "functionality" or "potency" of a cell preparation, i.e., those *in vitro* properties (maturation, migration, myotube formation), that may predict *in vivo* behaviour.

From the procedural perspective, an important feature of a cell product is its response to alterations in environment, such as passage into a syringe or through a delivery catheter, or release into the *in vivo* milieu. Such characteristics contribute to the early fate of cells after injection, and can be inferred from their *in vitro* expression of adhesion molecules. A framework for predicting cell behaviour upon initial contact with recipient tissue is presented in Table 3, in which cell size and surface molecule expression are denoted. The propensity for attachment to vascular- extravascular (interstitial matrix, collagen) bound ligands is appreciated from this table and is information that needs to be factored into the choice of the delivery method. Since cell products are often comprised of mixed populations, the presence of specific adhesion molecules is best defined as a% of cells. However, we have used >10% cell-expression as positive in Table 3, and cell diameter as a range. Variability is therefore inherent to this schema and it cannot account for changes in expression that may occur after implantation.

Nevertheless, the profiles of expressed adhesion molecules suggest that both bone marrow and adipose-derived cells will readily attach to vascular endothelium, less reliably to extracellular matrix tissues and with little affinity for myocardium. The muscle progenitors (skeletal myoblasts and cardiac-derived stem cells) express the most surface markers for adhesion to the intersitium and/or collagen, although mesenchymal-type cells demonstrate this capacity as well. Not included in the Table 3 are those factors that promote tissue growth, such as vasculogenesis or myogenesis, or those that facilitate migration. When such characteristics are combined with adhesion molecule expression, a more thorough profile of a cell product is created. From this, insight can be gained into its interaction with delivery catheters and recipient tissue, and a better estimation of cell retention.

Issues specific to catheter delivery are listed in Table 4 and grouped according to interactions of three major components: 1) the cell preparation; 2) the delivery system; and 3) the recipient tissue. A separate category identifies those issues that fall within the oper-

Table 3. Characteristics of cell preparations.

		Potential for:												
		Vascular adhesion			Matrix, Collagen, Muscle adhesion									
Cell preparation	Mean Cell	CD106	CD31	CD50,51,54	CD49	Integrins				CD61		M,N-	CD56	CD44
	Diameter(μ)	VCAM	PECAM	ICAM-1,3	a(α1)	B(α2)	C(α3)	d(α4)	e(α5)	f(α6)	(β3)	cadherins	CD167	H-CAM
Bone marrow-derived:														
Mononuclear	<10	–	+	+	–	–	–	+	–	–	–	–	–	–
CD 34+	<10	–	+	+	–	–	–	+	+	–	–	–	–	–
CD 133+	<10	–	+	+	–	–	–	+	–	–	+	–	–	–
MAPC	8–10	–	–	–, –, dim	–	+	–	–	+	–	–	–	–	–
Mesenchymal stem	20–30	+	–	+	+	+	+	–	+	+	+	–	–	–
Mesenchymal precursor	10–15	+	–	+	+	+	+	–	+	+	+	–	–	–
Circulating:														
EPCs	<10	+	+	+	–	–	–	–	–	–	–	–	–	–
Adipose–derived	15–20	+	–	+	–	+	–	+	+	–	–	–	–	–
Skeletal myoblasts	10	–	–	+	–	–	–	–	–	–	–	+	+	+
Cardiac stem cells	<10	–	+	–	–	–	–	–	–	–	–	?	?	?

Cell preparations used in human and animal studies. Propensity of adhesion to vascular endothelium or interstitial myocardium is denoted by expression of adhesion molecules. Cell diameters are range estimates, molecule expression "–", "+", "dim" or "?" if observed in <10%, >10%, =10% or unknown% of total cell population, respectively.
Methods: 3D - 3 dimensional, NOGA - , MRI - Magnetic resonance imaging, IVUS - intravascular ultrasound;
Catheter Type: OTW - over-the-wire;
Examples: NA - not available, Cordis - Cordis Corp., BSC - Boston Scientific Corp., Occam Corp., Mercator MedSystems, Inc., Bard Corp., Ventomatrix Corp., Bioheart Inc., Weston, FL, Biocardia, Inc., BDS - Biologics Delivery Systems, Medtronic Vascular Systems.
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μ - microns, VCAM - vascular cell adhesion molecule, PECAM - platelet/endothelial cell adhesion molecule, ICAM - intercellular adhesion molecule, HCAM - hyaluronate-receptor cell adhesion molecule

Table 4. Pitfalls of percutaneous cell delivery

	Issue	Effects			Potential solutions
		Primary	Secondary	CR	
Interactions Device-cell product	Cell trauma 2° to: Bioincompatibility Shear	↓Viability, function	↓Functional cell dose	↓	Inert coating ↑Core lumen size
	Cell activation	Adhesion, aggregation Cytokine/mediator release	Core lumen obstruction ↑ Local, pulmonary and systemic effects	↓ ↓	↓Viscosity, cell concentration
Device-tissue	Coronary artery disease Multi-venous channels	Trauma Collateral-dependent flow Unreliable flow patterns	Acute ischaemia, MI Uneven tissue distribution Uneven tissue distribution ↑ Cell transit to pulmonary arteries	↓ ↓ ↓ ↓	Non-occlusive injection or low pressure balloon Double-balloon catheter Alternative injection method (intramyocardial)
	Myocardial disease: Recent infarction	Tissue friability Microvascular obstruct. Inconsistent delivery	Myocardial perforation	↓ ↓	Alternative injection method (venous, perivascular)
	Fibrosis Multiple pathologies	↓Needle penetration Reduced tissue distribution	Reflux via injection site ↑ Systemic appearance	↓ ↓	↓Needle calibre Reconfigured needle (side-holes, others) Alternative injection method Serial (months) injections
	Altered cardiac rhythm	Conduction trauma Electrical simulation	Fascicular block Ventricular tachyarrhythmias	— —	Prophylactic pacing Antiarrhythmics
Tissue-cell product	Vascular: Cell diameter < vessel	↑Transit to coronary venous system	↑ Pulmonary and systemic effects	↓	"Stop-flow" (arterial, venous), ↑adherent cells
	Cell diameter > vessel Cell aggregation	Microvascular obstruction	Myocardial ischaemia	↑	Alternative injection method (intramyocardial, perivascular)
	↑ Vascular AM	Epicardial vessel adhesion	Acute thrombosis, atherogenesis, restenosis	—	?Statins, DES
	Myocardial: ↑Interstitial flow rates	↑Transit to coronary lymphatic/ venous system	↑ Pulmonary and systemic appearance	↓	Adherent carrier (fibrin, hydrogel) Engineered cells (ligand-specific AM)
	Inflammation	Monocyte infiltration	Cell destruction	_	Delayed administration
	Fibrosis	Early reflux ↓Tissue vascularity	—— In-situ cell death	↓ ↓	Alternative needle and injection configurations Adherent carrier (fibrin, hydrogel) Engineered cells (VEGF, matrix AM)
Operator-related Cell product maintenance	Cell trauma from: Thermal changes Aspiration technique	↓Viability, function	↓Effective cell delivery	↓	Temperature control, large calibre aspiration needle
	Stasis	Cell layering Aggregation	Dilute cell concentration Device plugging ↑Shear, cell activation	↓ ↓	Frequent agitation of cell suspension
Device-user interface	Limited standardisation of techniques	Inter-operator variability	Inconsistent delivery	↓	Controlled injection mechanism (flow, volume)
	"Complex" devices	Shallow learning curve	Variable delivery ↑Cardiac trauma	↓ —	Programmable catheter control
	Poor target tissue delineation	Aberrant injection	↑ Pulmonary and systemic appearance	↓	Enhanced, multi-modality imaging
	Low spatial resolution, injection precision	Redundant injection	Poor cell distribution	↓	Programmable catheter control
	Limited intra-procedure assessment	Ineffective injection		↓	Radio-, echo-, MRI-contrast imaging

ator's direct control. Each component brings specific effects to the interaction and, unfortunately, most interactions negatively influence cell retention. Even though we have made no attempt to quantify the relative bearing of each component on cell retention, the nature of the underlying disease and the characteristics of the cell product are, in fact, primary, and will often precede the choice of delivery system in formulating a study design.

Interactions between delivery device and cell preparation may result in cell trauma (from shear effects or bio-incompatibility) and impairment of viability and function. The release of cytokines and other mediators may be hastened, leading to their early appearance locally and systemically. Cells may adhere to the device's lining or form aggregates, narrowing the core lumen diameter and changing the flow characteristics during delivery. Fortunately, most device-cell interactions are easily identified in bench-top testing, allowing for adjustments to be made in either component prior to *in vivo* use. Although methods for percutaneous catheter delivery have thus far been generally safe, risks from adverse device-tissue interactions exist. Coronary artery and myocardial trauma are the most worrisome[30,31]; disruption of normal cardiac rhythm[30] are largely temporary. Impairment of cell retention can result from unfavourable interrelationships between devices and tissues. In vascular delivery methods, obstructive coronary artery disease with inaccessible collateral channels or coronary venous anatomy with multiple communications both lead to shunting of cell injections away from target tissues[32]. Intramyocardial injection methods are plagued by myocardial fibrosis and tissue inhomogeneity, which can lead to inadequate needle penetration[33].

Tissue-cell interactions. Ideally, injected cells will be retained in numbers sufficient to optimise their biologic effects. With coronary vascular delivery, the steps of adhesion and transvascular migration add to the challenge of cell retention. These processes involve paracrine signalling, and various adhesion molecules including integrins, Ig superfamily cell adhesion molecules (CAMs) and selectins. Among the highest rates of cell retention and engraftment comes with the cost of myocardial ischaemia and infarction[29]. By combining an understanding of surface marker expression and cell dimension, an acceptable balance between microvascular adhesion and obstruction can be achieved, especially with regard to arterial delivery. On a larger scale, interactions of cells with epicardial vessels may have acute and chronic implications[34,35]. The interactions between myocardial tissue and cell product also relate to surface marker profile and the underlying disease state, perhaps more so with the latter. The high interstitial flow rates of normal myocardium[36] lead to rapid clearance of most agents injected intramyocardially. A very different situation exists in chronic fibrosis, in which the loss of cells is related more to leakage through the injection track and to local ischaemia.

The operator controls the key aspects of percutaneous cell delivery. Maintenance of the cell product, by protecting it from injury (thermal or mechanical) or stasis prior to loading into the delivery system, is a simple and important task. By preventing cell layering, the chances of administering doses containing mostly media or cell aggregates are reduced. The latter, as noted above, may promote unfavourable device-cell interactions.

More positively challenging to the operator are the complex aspects of novel delivery systems and their imaging modalities. Intramyocardial injection catheters function within a different framework than the vascular devices and, while a fair body of experience exists with some[30,37-39], most have seen limited use in clinical trials to date. Even though none are overly demanding in concept or mechanics, the learning curves are still being charted for all of them, especially in states of advanced myocardial disease.

Excluded from Table 4 are two issues of particular importance to device and biotechnology companies: product adaptability and strategic partnering. Both are crucial for hypothesis testing and for discerning optimal pathways to product approval. As is now evident, delivery methods for cell-based tissue repair become increasingly complex when combined with the many variables of clinical diseases and cell characteristics. The design and conduct of preclinical and clinical studies often leave little room for error, and recovery from early misdirection can be challenging.

Summary

With its established successes in catheter-based therapies, the interventional community might expect the delivery of progenitor cells to the heart to be a straightforward task, since the coronaries, even if occluded, offer access to essentially all cardiac tissue and should therefore be effective conduits for cellular products. However, it has become clear that progenitor cell survival is poor after injection, irrespective of the sophistication of the delivery catheter or the expertise of the operator. Among the issues facing percutaneous delivery, including those pertaining to safety, cell retention is the foremost.

Together with underlying pathology and characteristics of specific cell preparations, percutaneous delivery techniques form the three major components of cell-based tissue repair. Interplay between them is variable and dependent on their unique properties: the nature (and stage) of disease, the immediate (and delayed) behaviour of the cell product, the ability of the catheter to effectively deliver cells with minimal trauma to cells or tissue. An understanding of the potential interactions is necessary in developing a study design. Unfortunately, since most interactions between the three components appear to reduce cell retention, the most we can expect is to minimise the losses.

Presently, there is no "preferred" technique for cell delivery, but, rather, a continued need to categorise existing and newer systems by their physical characteristics and capabilities. Multiple pathologies, tissue inhomogeneity and diversity of cell products have given rise to delivery methods that are more complex than their predecessors, or when compared to routine coronary interventions. The selection of a delivery method should be preceded by an assessment of the other two components in the decision matrix, rather than serving as the starting point. As the field evolves and as experience is gained, we will be better prepared to define a "successful injection" and the importance of integrating optimal delivery methods into pivotal studies. Then it will be possible to evaluate cell preparations and to interpret clinical trials results on the basis of the success, or failure, of the percutaneous catheter to deliver the study agent.

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