

Cellular Therapy for Chronic Myocardial Disease: Nonsurgical Approaches

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Abstract

The possibility for improving chronic ventricular dysfunction by the implantation of new regenerative cells has reached the level of Phase I Safety Trials. Early data from both surgical delivery studies are promising with regard to both safety and efficacy. While a number of catheter-based approaches to the myocardium are possible, currently investigated delivery techniques center around either needle injection or non-needle injection systems. Both types of delivery systems, including their merits and potential disadvantages, are reviewed in this article. Existing data, from both animal and human studies, are presented and indicate that catheter-based delivery of cells for the purpose of myocardial regeneration is feasible. This type of strategy for treating patients with heart failure has enormous clinical potential, but must await carefully conducted randomized trials.

Key words: autologous skeletal myoblasts, cardiomyoplasty, cellular therapy, intramyocardial delivery systems.

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As with other interventional techniques for cardiac disease, the development of catheter-based methods for cell implantation has followed initiatives of similar therapeutic intent occurring in the surgical arena. Other contributions to this series [1] of articles have addressed both the techniques and initial clinical results of surgical cell implantation for myocardial disease. This review will recount the status, within the growing field cellular therapy, of nonsurgical approaches, both as they have been tested in the research laboratory and as they have been initiated in clinical trials. More specifically, the focus of this article will pertain to the application of nonsurgical devices as cell delivery tools in the treatment of chronic myocardial disease. Data relating to the potential of cell therapy in the treatment of acute or subacute myocardial infarction, for which exciting data is emerging, will not be addressed in this article.

Conceptually, available pathways to cell implantation are transvascular (arterial or venous), transendocardial (endoventricular) and transepical. While the most attractive from the standpoint of common interventional practice would be the coronary arterial approach, animal studies [2], few as they may be, have uncovered important obstacles to such a technique if applied to humans with chronic myocardial disease. And while a percutaneous approach to the epicardium might allow simulation of the open chest surgical approach, little investigative energy is being applied in that direction at present.

Alternative methods to direct implantation, such as stimulating the migration of adult stem cells to the heart, from the bone marrow or other sites is at a very early stage of development [3].

The small number of catheters which have been used to deliver cells intramyocardially can be grouped into two design categories: needle injection and non-needle injection systems. With this in mind, several manufacturers have developed catheter systems for the purpose of delivering agents into the ventricular wall.

Injection Systems

Needle-based

Several needle-based catheter injection systems have undergone testing in preclinical and clinical studies. From the standpoint of general design, there are similarities between each in terms of their basic elements. All are coaxial devices, with outer shaft sizes in the 7 Fr to 9 Fr range. The key “therapeutic” element is the central injection lumen (“core lumen”), which runs the full length of the catheter and culminates distally in a stainless steel hypodermic needle. The core lumen is semi-rigid, enabling it both to be advanced and retracted independently of other catheter maneuvers, and to impart column strength sufficient to embed the needle tip into normal or fibrotic myocardium. At its proximal end, the core lumen begins with a standard luer lock connection, through which injections are accomplished

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manually. All needle-based catheter injection systems are designed to be introduced percutaneously into a peripheral (femoral) artery and to be placed within the left ventricle chamber with the aid of fluoroscopic imaging.

Other features are not shared by all devices and will now be described.

The Biosense-Webster Myostar™ (Diamond Bar, CA)(Figure 1a) was the first to be utilized in humans, initially as a delivery tool for gene fragments [4] in patients with refractory coronary ischemia, and later for the injection of bone marrow and other cell types [5]. It is composed of a 27 gauge needle, the core lumen of which is housed in a 8 French catheter. The primary imaging method (electromechanical mapping [NOGA™] system) requires that a specialized transmission probe be positioned at the distal tip of the catheter, with its cabling coursing through the 125 cm shaft back to the proximal aspect of the device. The tip can then be positioned throughout the ventricular chamber, its contact with the endocardium being detectable, all by non-fluoroscopic imaging. Controls for catheter tip deflection, needle advancement and needle lumen injection are all contained within the handle, as is the cable connection to the central imaging console.

The Bioheart MyoCath™ (Bioheart, Inc., Santa Rosa, CA) (Figure 1b) is an 8Fr system of similar design to the Myostar™, with the exceptions of containing a 25 gauge needle and of focusing on of radiographic imaging for guidance, and thus does not contain internal imaging elements. Therefore, the proximal handle possesses controls for tip deflection, needle advancement and injection.

The Stiletto™ (Boston Scientific SciMed, Inc., Natick, MA) (Figure 1c) system is fundamentally very

different in design from the previous two catheter designs. It contains three separate, independently moveable components: two steerable guiding catheters (9Fr and 7Fr), and an inner spring loaded needle component. Catheter tip orientation is accomplished by guiding catheter manipulation, and the spring loaded needle advancement mechanism theoretically allows the device to overcome tissue resistance to needle penetration.

Lastly, the Microheart, Inc. created a needle-based myocardial injection catheter. It had features similar to both the Bioheart and Biosense devices, in its method of tip deflection and fluoroscopic based imaging. Like the Stiletto, it had a spring loaded needle advancement mechanism. However, it is no longer in production or under active investigation.

As stated above, all three of the above devices are designed to be placed retrogradely into the left ventricular chamber. However, navigation within the ventricle is accomplished by either fluoroscopic (MyoCath™ and Stiletto™) or NOGA™ (Myostar™) guidance. The Stiletto™ is the only system that can be passed into the left ventricle over a guidewire; the other two catheter systems require manipulation using their deflection and rotation properties to be similarly positioned.

Non-needle-based

The TransAccess® MicroLume™ Delivery System (Transvascular, Menlo Park, CA) (Fig 1d) is a multi-component catheter designed to gain access to the extravascular space by way of the coronary venous system. Contained within this unique 6.2 Fr delivery system are an intravascular ultrasound (IVUS) probe, a preshaped 24 gauge needle and a 27 gauge catheter (Microlume™) for extension through and beyond the needle tip. For the purposes of intramyocardial injection, from the position of a coronary vein (adjacent to the myocardial region of interest) and with confirmation by IVUS, the needle is advanced the venous wall and into the myocardium. Through the needle and under fluoroscopic guidance, the Microlume™ catheter is advanced into the target myocardial segment. Through the Microlume™ catheter's central lumen, cells or other agents are injected.

Comparison of devices

From the standpoint of approaches to myocardial delivery, the needle and non-needle based systems have obvious, intrinsic differences. The parameters by which relevant comparisons between the two system types need to be made relate to 1) ease of use, 2) efficiency of delivery of injectate, 3) tissue retention of injectate, 4) safety. To date, head to head comparisons have not been made with respect to these parameters.

Preclinical Studies

Preclinical experience

Given the intended use of these devices in humans, preclinical studies have involved large animals. Proof of concept work has required demonstration of device in-

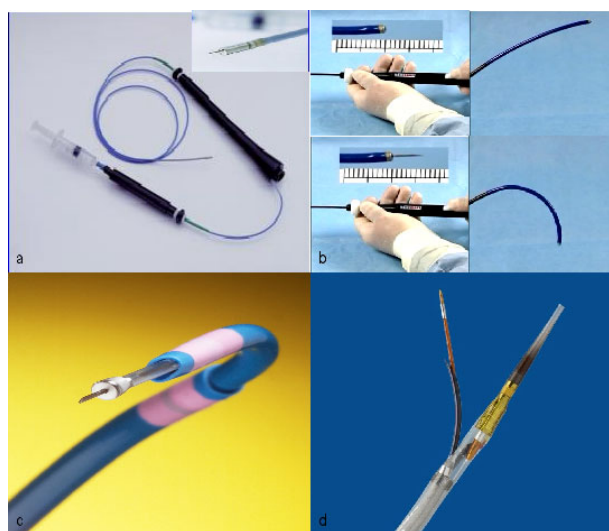


Figure 1. Four available catheter delivery systems for intramyocardial cell delivery. a) Myostar™ (Biosense-Webster, Inc.). b) Bioheart MyoCath™ (Bioheart, Inc.). c) Stiletto™ (Boston Scientific SciMed, Inc.). d) TransAccess® MicroLume™ Delivery System (Transvascular, Inc.).

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tegrity, of its compatibility with the therapeutic agents under proposal for injection, of its ability to successfully penetrate target tissue and to inject cells or other agents into target tissue with a high degree of safety.

For the Bioheart device, extensive work in collaboration with investigators at Columbia University (Daniel Bukhoff, MD, PhD and colleagues) and at the American Cardiovascular Research Institute (Keith Robinson, PhD, Nic Chronos, MD and colleagues) has substantiated proof of concept when injecting a variety of tissue marking substances as well as with autologous skeletal myoblasts. Using a porcine model, safety and precision of injection have been adequately demonstrated (Fig 2). With myocardial dysfunction secondary to coronary artery micro-embolization in a canine model of congestive heart failure, preliminary efficacy data following injection of autologous skeletal myoblasts are strongly suggestive of a clinical effect (D. Burkhoff, personal communication).

Numerous animal data exist for the Boston Scientific, the Biosense and the TransVascular devices with respect to non-cellular requirements. However, data examining the effects of cell injections on myocardial function are lacking.

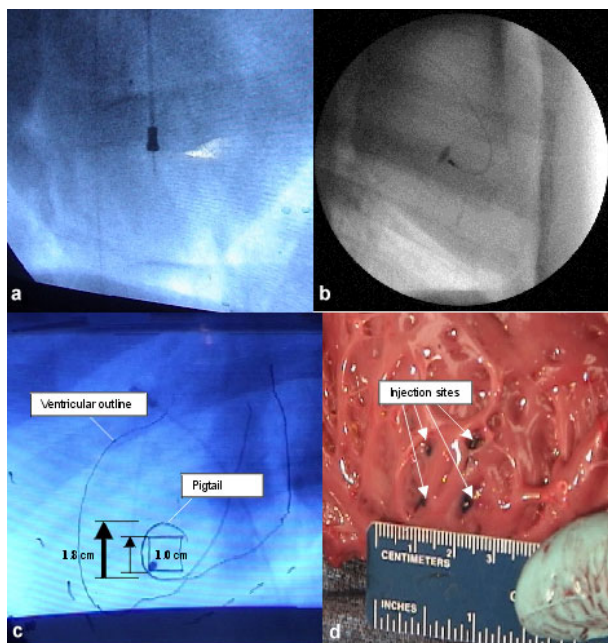


Figure 2. Injection technique in a normal porcine heart using MyoCath™. a) Fluoroscopic image of catheter tip with extended needle. b) Radiocontrast injection. c) Calibration of injection using pigtail catheter as internal reference (1.8 cm loop diameter), creating a 1cm x 1cm target drawn on fluoroscopy monitor. d) Gross pathologic specimen following single injections (radiocontrast and India ink) at all four corners of target in c), demonstrating precision of injection technique.

Alternative imaging strategies

Despite the strength of the accumulated data described above, the devices discussed thus far have an important limitation: none of the imaging techniques utilized for positioning the catheters is able to confirm that injectate has entered the myocardial wall. Given the likelihood that the TransVascular catheter will maintain an intramural position throughout its extravascular course, a high degree of confidence of injectate delivery is associated with this device. However, even with this confidence, the physical appearance of the injection is not possible. This leads to the logical question as to whether alternative imaging modalities would enable such a process to occur.

In this regard, we and others [6] have developed catheter that is magnetic resonance compatible. Ours, which is a modification of the Bioheart device, is able to fulfill the requirements of catheter tip tracking as well as the ability to demonstrate the presence and distribution of injected substances, such as gadolinium, within the myocardium. This approach may offer best opportunity to detect acute changes in wall thickness following intramyocardial injections.

Initial Clinical Experience

At this point in time the clinical experience of cellular therapy for myocardial disease using nonsurgical approaches is limited, moreso than with the surgical approach. In May 2001, a physician-sponsored study was initiated in Rotterdam (ThoraxCenter, P. Serruys). It was designed to deliver autologous skeletal myoblasts into areas of chronic myocardial infarction in patients with congestive heart failure. Five patients were initially enrolled, followed by eight additional in a collaborative effort at two other centers in Milan (Hospital San Rafael, A. Colombo) and Rostock (University Hosp., C. Niebauber). Preliminary reports, presented at both the European Society of Cardiology and TransCatheter Therapeutics meetings in 2002 (P. Smits, P. Serruys) describe a 13 subject cohort with advanced heart failure and left ventricular dysfunction, who received between 25×10^6 and 488×10^6 autologous skeletal myoblasts. All three of the devices described above were utilized in this study. Thus far, although primarily a safety study, the clinical results are suggestive of improvement in both heart failure status (New York Heart Association Classification) and ventricular function (wall thickening and ejection fraction).

However, there were two unanticipated adverse event in the initial 13 subjects: sudden death at 8 and 9 days following cell implantation. The clinical situations preceding these events are not known, but, in one, suggestive of an arrhythmic prodrome. Due to these events, clinical trials were placed on hold for the following five months to enable a full investigation of possible causes. From this investigation, the presumptive, though not proven, mechanism for sudden death was ventricular tachyarrhythmias. This position was supported by results of early studies of skeletal myoblast injections at the time of coronary artery bypass surgery, in which 4

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subjects out of 10 in one study (Dr. P. Menasche's) developed nonfatal ventricular tachycardia.

Preclinical trials using catheter-based injection methods are again underway in both Europe and the United States. All are Phase 1 safety studies and eligibility is to be restricted to patients with congestive heart failure secondary to chronic stage myocardial infarction(s). In response to the potential of developing serious ventricular arrhythmias from cell injections, implantable cardioverter defibrillators (ICD) are now a requirement for all subjects.

The Future

As data from surgical and nonsurgical trials emerge, answers to the following questions will hopefully emerge:

1. How effective is cellular cardiomyoplasty in offering a durable clinical benefit to patients with congestive heart failure? If effective, for what myocardial pathologies?
2. If cellular cardiomyoplasty does offer such benefit, are catheter-based injection systems capable of delivering sufficient numbers of cells to achieve such an effect?
3. Which are the more effective cell types in terms of ease of use, cost, durability?
4. Is ventricular tachycardia a consequence of cell implantation or is it background noise from pre-existent myocardial disease?
5. How important is local vascularity to the success of an implantation?

The next 3 years will bring new light to the prospects for catheter based delivery of myogenic cells to repair

chronic myocardial disease. Over that time, the results of Phase 1 and 2 studies will become known.

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