

# Cell Therapy in the Cath Lab for Heart Failure: A look at MyoCell® Therapy and the SEISMIC Trial

*Cath Lab Digest* talks with Warren Sherman, MD, Director, Cardiac Cell-based Endovascular Therapies, Columbia University Medical Center, New York, New York and Principal Investigator of the Phase II/III MARVEL Study

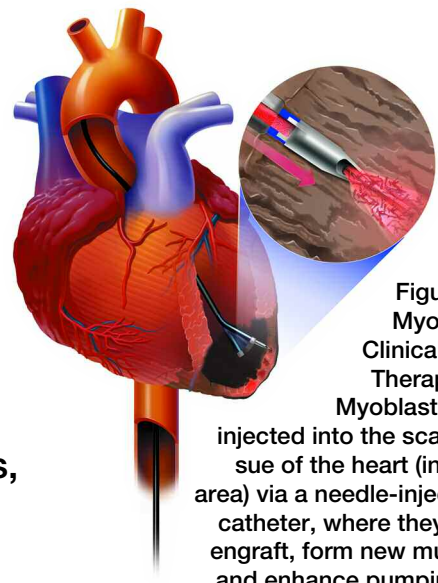


Figure 1. MyoCell® Clinical Cell Therapy – Myoblasts are injected into the scar tissue of the heart (infarct area) via a needle-injection catheter, where they can engraft, form new muscle and enhance pumping of the heart.



**What is MyoCell therapy and what are the advantages of using myoblast cells in particular for treatment of myocardial tissue?**

MyoCell therapy utilizes autologous (patient-derived) skeletal myoblast cells injected percutaneously into damaged myocardium via catheter with the intended purpose of improving ventricular function. Myoblasts are muscle progenitors and fulfill two of the criteria of adult stem cells: they can differentiate into mature skeletal muscle cells and they can divide to replenish themselves. Progenitor cells, which are present in all of us at birth, serve to replace damaged skeletal muscle throughout the body. Autologous cells, utilized for MyoCell therapy, are harvested from the patient in whom they are to be later re-implanted, a very

personalized form of medical therapy.

Unfortunately, the heart is not blessed with an abundance of cells having the same capabilities of differentiation and division. While “resident” stem cells have been identified in the heart, they seem unable to effectively repair the myocardium in the way that skeletal myoblasts can repair skeletal muscle. When this began in the 1990’s, the thought was to see whether implanting skeletal myoblasts into the heart could somehow take over or replace some of the function lost by patients having previous heart attacks or those suffering other forms of cardiac injury, even though skeletal myoblasts are programmed to do a different kind of work than heart muscle. Animal studies leading up to human studies, both in the U.S. and in Europe, indicated that when a skeletal myoblast is implanted into a cardiac environment, it can take on a hybrid form of function. Interestingly, it no longer resembles a pure skeletal muscle cell, nor does it achieve a full cardiac muscle cell phenotype. Instead, it functions somewhere in between. In doing so, these myoblast cells convert from a fast-twitch to a slow-twitch phenotype and are then able to contribute to the cardiac workload.

After a large number of confirming preclinical studies, the first series of human studies with autologous skeletal myoblasts were conducted in early 2000-2001. Among them was the first study in

which a catheter was used to implant the cells. Many of the early studies with either stem cells or other biologic agents involved cardiac surgery (frequently still the case today), with the surgeon injecting cells, genes or other investigational biologic products when a patient was undergoing bypass surgery.

The first catheter-based delivery of a myoblast was in 2001, in Prof. Patrick Serruys’ cath lab at the Erasmus University Thoraxcenter, in The Netherlands. I was fortunate to be working along with other investigators on the Bioheart team, including Prof. Serruys. We treated the first series of patients using a catheter to implant these cells. The results from this early work were published in the *Journal of the American College of Cardiology* in 2003 (Smits et al., *JACC*, Vol. 42, No. 12, 2003: 2063-2069).

The premise of MyoCell therapy is that a heart lacking muscle requires muscle progenitor cells to effectively recover function. Other stem cells, that may not mature into a muscle cell, may not offer the same potential for recovery as those cells that are programmed to become muscle. Myoblasts are inherently ischemia-resistant, and as an autologous therapy, lack the immunologic response associated with allogeneic cells. The 6-month final results of the SEISMIC study, presented by Prof. Serruys at the American College of Cardiology (ACC) in April 2008, add to prior data

## About the SEISMIC [Safety and Effects of Implanted (Autologous) Skeletal Myoblasts (MyoCell®) using an Injection Catheter] Trial

The SEISMIC trial, a 40-patient, randomized, multicenter, controlled, Phase II-a study conducted in Europe, evaluated the catheter application of autologous skeletal myoblasts in patients with congestive heart failure (CHF). Proprietary cell (MyoCell®) and endoventricular needle-injection catheter (MyoCath®) products of Bio-heart, Inc. were used in this study. Patients were required to be stable on standard medical therapy for CHF, as well as previously fitted with implanted cardiac defibrillators (ICDs). On admission to the trial, patients were randomized at a 2:1 ratio into the treatment versus control groups with 26 patients receiving MyoCell therapy and 14 patients randomized to the control group and receiving optimal medical therapy alone.

“The results from the SEISMIC Trial are encouraging,” said Prof. Patrick W. Serruys, MD, PhD, Principal Investigator and Chief, Department of Interventional Cardiology, Thoraxcenter, Erasmus Medical Center – Rotterdam, the Netherlands. Final six-month, follow-up patient data were presented by Prof. Serruys during the late-breaking clinical trial sessions at the April 2008 American College of Cardiology Scientific Session.

“While the study was specifically designed to show safety, the findings also suggest positive trends in clinical benefits when evaluating the treated group versus the control group at six months.”

Patients in both groups were evaluated at three- and six-month intervals using a variety of tests, including digital imaging and standard quality-of-life measurement such as the six-minute walking test, New York Heart Association (NYHA) heart failure classification and Minnesota Living with Heart Failure (MLHF) questionnaire. Final six-month results observed in the SEISMIC trial include:

- Average left ventricular ejection fraction for patients in the cell therapy and control arms remained essentially unchanged. For the treatment arm, ejection fraction slightly increased from 30.9% at baseline to 31.2% at six months, while patients in the

control arm under standard medical therapy essentially remained unchanged (32.6% and 32.5%, respectively). At six months, however, the end systolic diameter of the left ventricle was smaller in the cell-therapy treated patients (54.6 mm vs. 51.7 mm), suggesting a trend toward positive remodeling.

- 84% of treated patients experienced improved or unchanged six-minute walking test scores compared to 31% of the control group, while 69 percent of the control group’s results worsened, versus only 16% of the treated group.
- 94% of treated patients experienced improved or unchanged NYHA classification compared to 58% of the control group, while 42% of the control group’s results worsened versus only 6% of the treated group.

Prof. Serruys also noted that reports of arrhythmia among the patients evaluated in SEISMIC, both in terms of total number of episodes as well as timing of episodes, were no different between the treatment and control arms in the study. This suggests that MyoCell is not associated with a higher prevalence of arrhythmias; rather, that arrhythmias are an expected occurrence for this subset of heart failure patients.

“These data support the need for a randomized, double-blind, placebo-controlled study involving the MyoCell technology,” said Prof. Serruys. “We look forward to applying our learning from this trial to the larger, more comprehensive MARVEL trial currently underway in the U.S. and Europe.” MARVEL is a phase II/III, double-blind, randomized, placebo-controlled multicenter study to assess the safety and cardiovascular effects of MyoCell implantation by a catheter delivery system in congestive heart failure patients post-myocardial infarction(s).

presented at the ACC (March 2007) and the American Heart Association (November 2007).

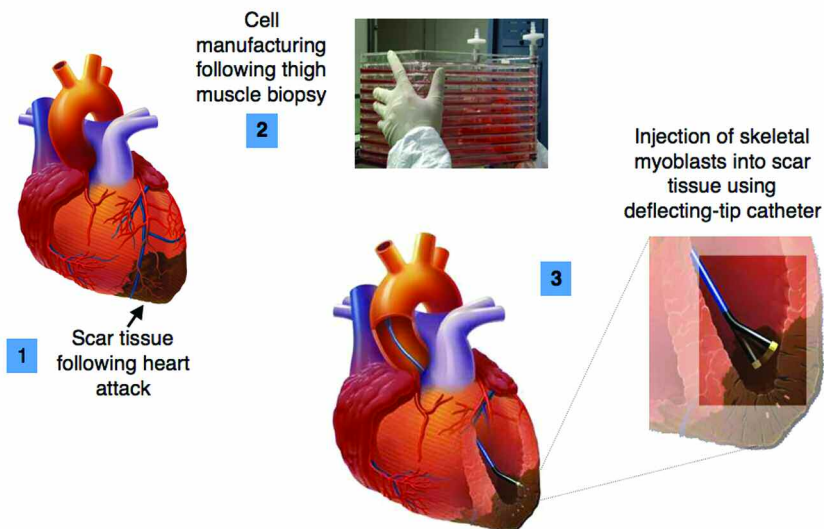
We are in a unique position to make important inroads that hopefully will lead to clinical benefit for patients. Virtually all signals from preliminary studies, such as SEISMIC, suggest this to be the case.

**What kind of system is used to deliver the cells?**

While the biologics side, or the stem cell side, of this research is rapidly progressing, catheter delivery systems might take longer to mature. As mentioned, some of the studies that have implanted myoblasts into the heart muscle or the damaged regions of hearts in patients involved direct injection at the time of surgery, using a needle that enters the wall of the heart from the outside, rather than entering the wall of the heart from the inside, as with an endoventricular catheter. There have been a few catheters designed for the percutaneous approach. Our preliminary work was done with a catheter designed and manufactured by Bioheart. The MARVEL study (sponsored by Bioheart) is using a different catheter, developed by a Johnson & Johnson company.

Catheter systems used for this purpose are all still investigational in the United States and function similarly. The catheter is placed in the left ventricle and the interventional cardiologist navigates it to the region where a previous heart attack has occurred (target area). A needle is extended at the distal tip of the catheter, through which cells are injected. The initial placement of the catheter is by fluoroscopic guidance, although some catheters do have advanced guidance mechanisms. In the MARVEL study, as with other cell and gene studies, we will utilize the NOGA® XP Cardiac Navigation System (Biosense Webster). This will enable the operator to detect the location of the catheter tip in three-dimensional space and make measurements of local ventricular function, such as its ability to contract or to generate voltage. It allows us to more precisely localize target regions for injection. Even though this technology requires additional guidance and imaging equipment, it should not be a barrier for most cath labs in moving forward with either clinical studies or approved therapies that use these techniques.

## MyoCell®: Heart Failure Treatment Process



**SEISMIC**  
**Response to Treatment**  
**NYHA HF / 6MWT / MLFQ / LVEF**

	control		myoblast		control		myoblast		control		myoblast	
<b>Improved or No Change</b>	58%	94%	31%	84%	57%	67%	50%	56%				
<b>Worsened</b>	42%	6%	69%	16%	43%	33%	50%	44%				
	<b>NYHA HF</b>		<b>6MWT</b>		<b>MLFQ</b>		<b>LVEF</b>					

**How are the cells stored? Does anything need to be done with them at the cath lab before they are injected into the patient?**

Fortunately, Bioheart and others working with these types of cells have created a user-friendly system for cell procurement.

The first step in the process involves a skeletal muscle biopsy of the patient, removing a 5-10 gram piece of tissue from the patient’s leg muscle. The tissue is sent to Bioheart, progenitor cells (myoblasts) are isolated and then put into a series of culture cycles that

increase their number to whatever the target is for a given study. (In the SEISMIC study, this number ranged from 150–800 million cells, with a mean of around 600 million cells.) It takes approximately two weeks to produce the desired yield of cells. The total timeframe between the biopsy and the re-injection of those cells into the heart is about 2-3 weeks.

Once the cells are harvested, they are placed in a self-contained shipping unit. This unit includes a cooling element to maintain the cells at a certain temperature and a digital thermometer

to monitor changes during transportation to the clinical site. Cells remain stable for 96 hours, offering a fair-sized window around which a clinical team can plan the injection procedure. The cells arrive at the clinical site in a small sterile intravenous infusion bag. At the procedure table, the cells are drawn up into 1 ml syringes for injection. It is all very straightforward and qualifies as 'minimal processing', the idea being to keep it simple and not to be faced with a complex recipe of cell preparation for each patient.

### **What did you find most important about the results of the SEISMIC trial?**

There are several very key points that came out of this study which support findings in other studies and put to rest prior concerns with myoblast strategies. First of all, there had been some concerns of arrhythmogenicity, that might increase the incidence of arrhythmias. SEISMIC showed us that this seems not to be the case, and is further supported in the recent surgical study, the Myoblast Autologous Graft in Ischemic Cardiomyopathy (MAGIC) trial, in results reported by Dr. Philippe Menasché a little over a year ago. I think we can be much, much less concerned about adverse rhythm, although we will remain vigilant in our data.

In terms of efficacy, even though this was not a double-blinded study, SEISMIC demonstrated positive signals that were alluded to earlier, such as suggested improvement in symptoms (New York Heart Association functional class level and 6-minute walk distances), ventricular performance and volumetric changes. While an important result of SEISMIC is safety, it adds to the aggregate clinical trial experience of improvement in ventricular function.

**One of the very early reports about SEISMIC (which we should note came out prior to Prof. Serruys' presentation at ACC) stated that patient symptoms improved but heart function essentially remained unchanged.**

Yes, on the surface, there is a disconnect. However, there are several ways to look at these observations. First, we need to reconsider how best to measure ventricular function. The clinical and scientific communities have depended on a number, the ejection fraction (EF), as the

principal measure of cardiac function. In fact, EF is a fairly imprecise and somewhat variable number even in a single patient, because it represents the summation of the contribution of every wall of the heart and its loading conditions. The EF misses changes occurring at a regional level, such as improvement in wall motion with exercise. This is especially important in evaluating areas that have been injected with cells. Importantly, even small changes in EF may result in significant clinical outcome for individuals, as well as for groups of patients. While we may envision an increase in EF from 35% to 50% (normal), that degree of improvement is unlikely to be achieved. So I would caution the use of EF as a primary efficacy endpoint in clinical studies, especially in the stem cell field.

Still, in a study like SEISMIC, where patients were not blinded, there may be a placebo effect. That's the advantage of a placebo-controlled study and the logical next step to eliminate patient and investigator bias. We have introduced this in the MARVEL study.

### **Can you discuss the upcoming MARVEL study?**

The first thing people should be looking for are potential subjects — this is a recruitment pitch!

The MARVEL study has the potential to transform how we will treat congestive heart failure patients in the future. This is an exciting opportunity for study site teams, to fully engage in enrolling patients and be a part of history. Patients we refer for treatment today, or never get a chance to treat in the cath lab, may become our patients tomorrow.

The target population, and the largest component of the heart failure patient population in the U.S., is comprised of patients who have had heart attacks, who have had coronary disease, and who may have undergone percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery (CABG) to rectify coronary disease and salvage whatever is possible by way of ventricular function. We are looking for a group of patients who have New York Heart Association class II, III or early IV heart failure; patients whose prognosis clearly sets them apart from those who have class I or early II heart failure, and those who have no heart failure.

MARVEL is a randomized, placebo-controlled study of patients with heart failure after a heart attack, with two treatment groups and one placebo group. The two treatment groups will each have a different MyoCell dosing level based on dose-finding data gathered prior to MARVEL. The low-dose group will receive 400 million cells and the high-dose group will receive 800 million cells. The control group will receive injections of a control media (placebo), such that the patients will not know what they received. We are looking to enroll a minimum of 330 patients, evenly distributed between the three groups. Each group will be carefully followed to assess both efficacy and safety. In the follow-up period their levels of activity will be monitored. The primary efficacy endpoint relates to how they feel and how far they can walk. These are the key elements of what the patients and their physicians are looking for: to feel better and to be more active. Hopefully, in doing so, we will enable them to live longer. (*Note: the study is not powered to look at differences in mortality.*)

At the same time, we are investigating very careful parameters of ventricular function, building on what I had mentioned about EF and the other components that go into it. MARVEL will involve a very meticulous analysis of how various regions of the heart are working in response to either cell injection or placebo injection over time (at 3, 6 and 12 months).

The other very, very important aspect for patients and physicians taking care of them is how we can keep patients out of the hospital. With current therapies, the incidence of admission of patients to the hospital is quite high, especially in those patients with class IV heart failure. This is a burden to all, especially to patients and their families and the healthcare system. In MARVEL, we will monitor the frequency of admissions for heart failure or worsening of heart failure in each treatment group. As a result, we expect the MARVEL trial to provide us with a better clinical handle on the effects of skeletal myoblast therapy than that of any other study undertaken to date.

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