

Symposium: Review Article

Myoblast transplantation for heart repair: A review of the state of the field

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Abstract Over 200 humans have been treated with myoblast transplantation for heart muscle repair since June 2000. Bioheart sponsored percutaneous delivery studies began in May 2001 in Europe. Approximately one third of the patients have exhibited substantial improvement in left ventricular ejection fraction (LVEF) of over 30% and two heart failure class improvements. Over 80% of the patients have exhibited one heart failure class improvement with moderate improvement of LVEF. Clinical trials seem to demonstrate a marked reduction in emergency hospitalizations in myoblast treated patients. Many years of careful studies have lead to randomized controlled studies that are enrolling patients now at numerous centers worldwide. A firm conclusion on the safety and efficacy of myoblast transplantation cannot be determined until these randomized studies are completed. Final results from randomized controlled studies should be available soon. (*J Geriatr Cardiol* 2006;3:165-7.)

Key Words myoblast transplantation; heart failure

Autologous immature myoblasts are obtained from a biopsy of thigh muscle. These cells are cultured to a therapeutic dosage at a central Good Manufacture Practice (cGMP) facility. The cells are suspended in a special solution which preserves their shelf life. When injected into a damaged area of the myocardium, the cells convert from fast-twitch to slow-twitch muscle and do what they do naturally - become muscle fibers thus they are able to augment cardiac function. The cells form new muscle within scar tissue which is able to contract in synchrony with the surrounding undamaged heart.

Over 200 humans have been treated with myoblast transplantation for heart muscle repair since June 2000. Bioheart sponsored percutaneous delivery studies began in May 2001 in Europe. This Phase I pilot study was completed in 2002.¹ A Bioheart sponsored Phase I/II study with one year follow-up was completed in 2004. A new Phase II/III randomized study was launched in 2005. The SEISMIC Trial sponsored by Bioheart, Inc. has enrolled 38 of 46 patients, 2/3 treated, 1/3 controls, as of July 2006. Dosing in this study is up to 800 million cells. In the US, Bioheart has been sponsoring a dose escalation study since April 2003. Dose has increased in 5 patient intervals from 25 million to 75 to 225 to 675 million. The 20th patient in this study was enrolled in July 2006. Many independent physician-sponsored studies supplement the corporate sponsored trials in the field. Genzyme and Genvec are both sponsoring

additional trials involving the surgical delivery of myoblasts.

Over 2000 animal studies have been completed since Race Kao, PhD, George Magovern, MD, and Peter Law, PhD began myoblast transplantation studies in the 1980's.^{2,3} Dr Race Kao, a Bioheart research team member, initiated and published the first heart repair studies utilizing myoblasts in dogs in 1989 and has recently co-sponsored human trials since 2001 in China.⁴ Dr Doris Taylor, Dr Charles Murry, Dr Ray Chiu, Dr Juan Chachques, Dr Felipe Prosper, Dr Peter Merrifield, Dr Nic Chronos, Dr Nabil Dib, Dr Edward Diethrich, Dr Tomasz Siminiak, Dr Stuart Williams, Dr Ren-Ke Li, Dr Richard Ham, Dr Miranda Grounds and others contributed substantially to the pre-clinical preparations that led to clinical trials. Dr Doris Taylor's landmark Nature Medicine paper in 1998 launched the final push to move myoblast transplantation to the clinical arena.⁵ Professor Philippe Menasche's independent team in Paris, France, not associated with Bioheart, was credited with the first ever human case in June 2000 after substantial pre-clinical preparations over many years.⁶ Professor Patrick Serruys and Dr Pieter Smits of the Thorax Centre in Rotterdam, The Netherlands were credited with the first ever non-surgical percutaneous case of myoblast transplantation in May 2001 utilizing Bioheart's MyoCell™ in a Phase I clinical trial (Fig. 1).¹ Most experts agree that over 90% of the future pool of patients will be treated with a percutaneous method.⁷ Bioheart has sponsored numerous pre-clinical studies including a 32-dog study with Dr Dan Burkhoff of Columbia which

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demonstrated that percutaneous delivery with Bioheart's MyoCath® is equally effective and safer than open chest surgical delivery of cells (Fig. 2).

Of the 220 human patients treated, 64 have been treated with percutaneous catheter delivery of the cells and 166 with open chest surgical delivery. All but two of the patients treated have been autologous derived cells. Approximately 1/3 of the patients have exhibited substantial improvement in left ventricular ejection fraction (LVEF) of over 30% and two heart failure class improvement. Over 80% of the patients have exhibited one heart failure class improvement with moderate improvement of LVEF. Clinical trials seem to demonstrate a marked reduction in emergency hospitalizations in myoblast treated patients. Dr Felipe Prosper's independent study in Spain included 12 myoblast treated

patients and 16 control patients. The 12 myoblast treated patients exhibited improvement of LVEF from 37% to 55% on average. The 16 control patients had virtually no improvement. Dr Prosper is now working with Bioheart, Inc.'s MyoCath® catheter delivery method to study the effect of repeat injections of myoblasts.

Concerns with myoblast transplantation include lack of consistent bioretention and engraftment and arrhythmias. The primary cause of lack of bioretention is loss of cells from the vacuum effect of channels communicating with veins which causes cells to exit the heart. The use of contrast visualization agents introduced in Bioheart's clinical trials this year to test the site of injection before full cell delivery has reduced this source of cell loss and is expected to improve results. The concern over arrhythmias has been

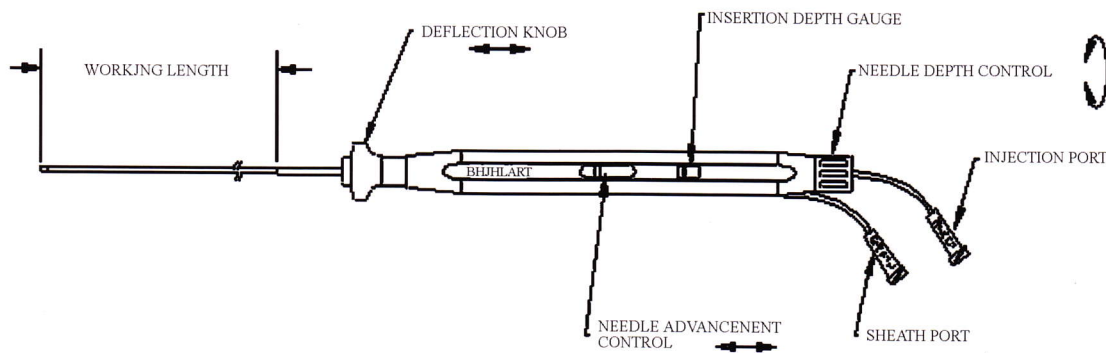


Fig.1. SR200 MyoCath™ - Percutaneous Catheter Delivery System

The MyoCath® Percutaneous Catheter Delivery System is indicated for assisting in the percutaneous delivery and controlled myocardial injections of biologic solutions to a desired endoventricular treatment site. It provides for multiple injections to a pre-determined needle insertion depth with a single core needle that can be advanced and retracted from the tip of the catheter.



Fig.2. Pictures of MyoCath® Needle Injection Catheter

reduced over the past year with well controlled electrophysiology/ECG studies. In Bioheart's study PVC's, an indicator of arrhythmia risk, in 15 patients were reduced from 1.89% at baseline to 0.04% at 12 months. A slight increase in PVC's was observed in the first 3 weeks following myoblast transplantation. Less than 10% of the patients in the early myoblast transplantation studies had exhibited serious arrhythmias. This percentage has been reduced substantially with the use of anti-arrhythmic drug (amiodarone) for only 30 days pre- and post-myoblast transplantation. The rate of arrhythmias in myoblast treated patients is less than that in untreated heart failure patients.

Bioheart has sponsored over \$54 million in research related to myoblast transplantation from June 1999 to May 2005. This research included studies comparing myoblasts with raw pluripotent bone marrow derived stem cells. A study series with Dr Ray Chiu at McGill University in large animals focused on this comparison. These studies as well as others have demonstrated the superiority of myoblasts over stem cells in repairing large areas of scarred myocardial tissue. Raw pluripotent stem cells injected into scar tissue become fibroblasts which have limited usefulness.⁸ Myoblasts can form contractile muscle within previous scar tissue which can more consistently improve systolic function compared to raw stem cells.

Bioheart's second generation myoblast composition includes stromal derived factor-1 (SDF-1) protein, a contrast visualization agent and a nutrient filled hydrogel. Our processes have been modified to select out and favor a more specific sub-population of myoblasts which are more readily able to convert to a cardiac workload handling phenotype without losing their properties of ischemia resistance. The SDF-1 protein promotes stem cell recruitment to increase muscle formation volume and also promotes angiogenesis and increased cell survival with AKT release. The nutrient-filled hydrogel improves 24-hour bioretention and survival of cells in the myocardium from 15% to over 40%.

Conclusion

Many years of careful studies have led to randomized controlled studies that are enrolling patients now at numerous centers worldwide. A firm conclusion on the safety and efficacy of myoblast transplantation cannot be determined until these randomized studies with statistical significance are completed. Early uncontrolled studies have demonstrated that approximately 30% of treated patients improve two heart failure classes. A substantial reduction in unplanned hospitalizations has been observed. Final results from controlled randomized studies should be available in the early part of next year.

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