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Myoblast transplantation for heart failure – From bench to bedside

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Trasplante de mioblastos en la insuficiencia cardíaca – del laboratorio a la clínica

La insuficiencia cardíaca es causa de morbimortalidad. El trasplante celular con mioblastos de músculo esquelético es prometedor en la reparación miocárdica ya que puede regenerar la zona agredida. Los mioblastos esqueléticos son células progenitoras unipotenciales que pueden ser modificadas genéticamente para liberar citocinas angiogénicas y factores de crecimiento para favorecer la angiomiogénesis. El trasplante de mioblastos inhibe la remodelación ventricular, disminuye el diámetro telediastólico, aumenta el grosor de la pared ventricular y minimiza la dilatación ventricular en animales. Los ensayos en marcha muestran mejoría de la perfusión y actividad metabólica. El problema de la generación de mioblastos antólogos para cada paciente podría solucionarse si se dispusiese de mioblastos alogénicos de donantes jóvenes sanos. El trasplante de mioblastos tiene el problema de la supervivencia celular postrasplante. Su factibilidad y seguridad se han documentado en estudios animales y de fase I. El único evento adverso postoperatorio relacionado ha sido las arritmias ventriculares. Los resultados de estudios en fase I son preliminares. Las mediciones de puntos finales confirman una mejoría en la calidad de vida, reducción del consumo de nitroglicerina, aumento de la capacidad de ejercicio, mejoría de la clase funcional NYHA y motilidad parietal por ecocardiografía y reducción de los defectos de

Heart failure causes morbidity and mortality. Cell transplantation using skeletal muscle myoblast is promising for myocardial repair as it can regenerate and repair the injury. Skeletal myoblasts are unipotent progenitor cells that can be expanded and genetically modified to deliver angiogenic cytokines and growth factors to encourage angiomyogenesis. Myoblast transplantation inhibits ventricular remodelling, decreases left ventricular diastolic dimension, increases myocardial wall thickness and minimizes global ventricular dilatation in animals. Ongoing trials with skeletal myoblast transplantation show improvement in perfusion and metabolic activity. Time constraints and the problem of generating autologous skeletal myoblasts for every patient can be overcome if allogeneic skeletal myoblasts from healthy young donors can be made available. Myoblast transplantation is confronted with the problem of donor cell survival post-transplantation. Its safety and feasibility have been documented during animal and phase I studies. The only serious postoperative adverse event related to the procedure was ventricular arrhythmias. The results of phase I studies are still preliminary. Endpoint measurements highlight improvement in quality of life, reduced nitroglycerine consumption, enhanced exercise tolerance, improvement in NYHA Class and wall motion by echocardiography, and significantly reduced perfusion defects. Future directions include concerted collaborative efforts, strict inclusion and exclusion criteria, better establishment of target

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perfusión. Futuras direcciones incluyen esfuerzos colaborativos, criterios de inclusión y exclusión estrictos y mejor caracterización de la población diana. Se necesita trabajar más en el tipo ideal de célula, número óptimo de células y ruta de administración. Se están estudiando el momento ideal del trasplante y el modo de liberación celular. El uso de técnicas celulares para la regeneración cardíaca es prometedor en el tratamiento de la insuficiencia cardíaca.

Palabras clave: **Insuficiencia cardíaca. Mioblasto esquelético. Trasplante celular. Angiomiogénesis.**

population. Further work needs to be done on the ideal cell type, optimal number of cells and route of administration. The most suitable time for cell transplantation after ischemic injury and optimal mode of cell delivery are evaluated. The use of cell-based techniques to assist with cardiac regeneration holds promise for the treatment of heart failure.

Key words: **Heart failure. Skeletal myoblasts. Cell transplantation. Angiomyogenesis.**

INTRODUCTION

Heart failure is the leading cause of morbidity and mortality in developed countries. In the United States, it affects nearly 4.7 million people and with 400,000 new patients added to the list every year. Current treatment modalities are inadequate. Even with best medical management the mortality for end stage cardiac failure is extremely high and heart transplantation is not a feasible option for most[1].

As cardiomyocytes retain little ability to regenerate or replace damaged cells, cell transplantation using skeletal muscle myoblast is a promising alternative therapy for myocardial repair. This novel approach seeks to compensate for the extensive loss in cardiomyocytes, which is in turn a consequence of left ventricular dysfunction. In this review we look at the overwhelming evidence to support this new and novel approach in the treatment of heart failure.

Skeletal muscle (unlike cardiac muscle) has the ability to regenerate and repair the injury due to the presence of myoblasts. They proliferate and differentiate when activated in response to muscle injury. Skeletal myoblasts are mononucleated unipotent progenitor cells that can be expanded *in vitro*. Skeletal myoblasts can be genetically modified in vitro to deliver angiogenic cytokines and growth factors to encourage angiomyogenesis. Animal studies have shown that grafted myoblasts form myotubes in the myocardium and eventually mature to become well-formed myofibers with contractile apparatus.

MYOBLAST TRANSPLANT – ANIMAL STUDIES

Kao first demonstrated the feasibility of skeletal myoblast transplantation for cardiac repair[2]. Myoblasts were injected into the center of scar using cryoinjured myocardial model. Histological study demonstrated viable myofibers in scar tissue. In the subsequent years, many researches were able to repeat these findings using different animal models of heart failure[3-8]. A landmark study by Taylor, et al. (1998) demonstrated the effectiveness of skeletal myoblast transplantation for improvement of cardiac function in rabbit heart model of cryoinjury[9]. Furthermore, skeletal myoblast transplantation improved diastolic compliance prior to systolic performance[10]. The improved diastolic function was related to increased regional strain, decreased dynamic stiffness, unaffected static stiffness and reversed diastolic creep. Both to regional and ventricular systolic function can be improved by myoblast transplantation[9,11-13].

Myoblast transplantation delimits or inhibits ventricular remodelling. Myoblast transplantation decreases left ventricular diastolic dimension increases myocardial wall thickness and minimize global ventricular dilatation[13-15].

SKELETAL MYOBLASTS IN HUMAN STUDIES

The first clinical application of cell transplantation as an adjunct to coronary artery bypass grafting (CABG) was performed by Menasché, et al.[16] using cultured autologous skeletal myoblasts in a 72-year-old male patient. The patient was in New York Heart Association (NYHA) Class III with a mean LVEF of 21 ± 2% by echocardiography. Follow-up at 5 months showed the patient was in NYHA Class II with an improvement in the LVEF to 30%.

Menasché, et al.[17] have also reported nine more patients as a part of phase I trials. The patients (mean age 60 ± 3 years) were diagnosed with severe left ventricular dysfunction (LVEF = 35%). An average of 8.74×10^8 autologous myoblasts was injected into akinetic, nonrevascularizable, and nonviable scar as assessed by dobutamine echocardiography and positron emission

tomography (PET). The cell transplantation procedure was event-free, without any perioperative complications. The nine operative survivors were followed for up to 8 months. The results showed an improvement in NYHA Class for all the patients, from NYHA Class 2.7 ± 0.2 to 1.6 ± 0.1 ($p < 0.02$), in parallel with documented improvement in LVEF from 24 ± 1 to 34 ± 1% ($p = 0.02$). Chachques, et al.[18] initiated a phase I study for autologous myoblast transplantation as an adjunct to route CABG in 4 male and 1 female patient in NYHA functional Class III. The study has been extended to include 18 patients (90% male) with an average NYHA Class 2.6. The patients were diagnosed with impaired left ventricular function (LVEF = 32 ± 5%) and left ventricular posterior wall postischemic scars (akinetic and absence of metabolic viability). The propagation of the cells was carried out in complete human medium, using the patients' own sera. There were no complications related to the cell transplantation procedure. The patients showed uneventful recovery and were discharged from the ICU 2 days after surgery. No cardiac arrhythmias were observed at follow-up (mean 9 ± 3 months). Echocardiographic studies showed an improvement in regional wall motion (from akinetic cardiomyopathy to hypokinetic ventricular wall). The infarct scar size appeared to be significantly reduced from 21 ± 5 to 8 ± 3 cm^2 ($p < 0.05$). Myocardial viability tests showed regenerating nodes, with patients moving from heart failure Class 2.6 to Class 1.3.

Myoblast transplantation as has also been carried out in association with left ventricular assistant device (LVAD) implantation as the first part of a multi-center trial sponsored by Diacrin Inc., in Massachusetts[19]. Five patients (median age 60 years) with a history of ischemic cardiomyopathy were selected for the study. These patients were on the waiting list for heart transplantation and were to receive an LVAD implantation as a bridge to transplantation. They were on maximal inotropic support with a median LVEF of 15%. A total of 300 x 10^6 cells were injected into each patient, with the exception of one patient who required urgent LVAD implantation before sufficient cells could be cultured.

Dib, et al.[20], at the Arizona Heart Institute, presented a study involving skeletal myoblast transplantation into the scarred region of the heart in 16 patients as an adjunct to CABG (n = 11), or LVAD (n = 5). The study was part multicenter industry-sponsored trial from Diacrin and involved a dose-escalation study. Autologous myoblasts were purified and proliferated *in vitro* from each patient's thigh muscle biopsy samples. A total of 10 million to 300 million cells were injected into the scar region.. There were no intraoperative or postoperative complications related to the procedure. Follow-up evaluation by MRI, echocardiography and PET showed successful survival of the transplanted cells within the heart at the site of graft, which registered improvement in LVEF from 21 to 29% at 3 weeks follow-up.

Bioheart has initiated the multicenter Food and Drug Administration approved MYOHEART clinical trial to be carried out at Mount Sinai Hospital (New York), Duke University and the American Cardiovascular Research Institute (Atlanta). Similarly, Genzyme has announced an MAGIC multicenter trial in Europe and America. Some other institute involved in myoblast transplantation include the University of California at Los Angeles, Temple University at Philadelphia, the University of Michigan at Ann Arbor and the Cleveland Clinic.

Our group in Singapore carried out the first autologous myoblast transplantation on a beating heart as a part of a phase I clinical study. A 55-year old male patient presented with acute myocardial infarction. The apex, anterior wall, and septum of the left ventricle were akinetic and the LVEF was 31%. After informed consent and as part of an institutional review board-cleared clinical trial, the patient received 3.78 x 10^8 autologous myoblasts at 20 different sites in and around the infarct region during CABG. The cells were > 98% pure for desmin expression, with > 99% viability at the time of injection. A 6-month follow-up revealed a perfusion defect involving the anterior wall and the apex with partial reversibility on 99mTc-tetrafosamine nuclear scan. These findings were in agreement with previously published reports and demonstrated the safety, viability and benefit of autologous myoblast transplantation as an adjunct to off-pump CABG. Although further patients need to be evaluated, the benefits of reduced risks associated with off-pump CABG cardiopulmonary bypass offer an attractive technique for delivering the cells for transplantation.

More recently, Zhang, et al.[21], from Nanjing Medical University, People Republic of China, have reported a phase I study including three patients with a history of coronary heart disease. Four millimeter of cell suspension divided into approximately 40 doses was injected into the ventricular wall of the ischemic area in less than 5 min. All patients survived the procedure and had an uneventful recovery. There were reports of occasional arrhythmias. However, these did not require treatment. No arrhythmia was observed during longer follow-up. Beneficial results noted at 4 months after the operation include an increase in left ventricular ejection fraction and decreased left ventricular diastolic diameter, as well as improved ventricular wall thickness observed by 2-d echocardiography. There was significant improvement in perfusion (99mTc-MIBI) and metabolic activity (18F-deoxyglucose) at the cell implantation sites.

Time constraints and the logistic problem of generating autologous skeletal myoblasts for every patient can be overcome if allogeneic skeletal myoblasts from healthy young donors can be made available. The safety and feasibility of allogeneic myoblast transplantation were tested for the first time in human subjects on January 17, 2003, at the Bakoulev Center in Moscow, Russia. Two patients (mean age 59) received between 1 and 1.2 billion skeletal myoblasts as an adjunct to CABG on nonbeating hearts. The patients received 5-7 mg/kg/d cyclosporine starting 5 days prior to until 2 months after cell transplantation. Despite cyclosporine discontinuation, immuno-rejection was not observed. At 3 months follow-up, subjects were in stable condition with angina at Class I-II (CCS) instead of Class IV. Echocardiography demonstrated 14.6 and 10.5% increases in LVEF. Nuclear imaging using single photon emission computed tomography demonstrated positive dynamics, with an increase in LVEF, and a reduction in perfusion defects both at rest and during exercise. The results of this study support the concept of using allogeneic myoblasts as an alternative therapy for heart failure using only a short course (2 months) of immunosuppressive therapy.

IMPORTANT CONSIDERATIONS

Cell survival and mechanism of improvement of function

Myoblast transplantation is confronted with the problem of donor cell survival posttransplantation. It has been shown in animals that up to 90% of grafted cells die within the first 24 to 48 h after transplantation[12,22]. In addition, total myoblast survival is not known. This poor cell survival has been attributed to inflammatory changes at the site of implantation. Inflammation is the result of trauma due to needle puncture, immune-mediated rejection of myoblasts, or release of immune modulators as a result of myoblast cell death[23]. In particular, natural killer cells have been shown to play a central role in the early death of grafted myoblasts[24]. The exposure of myoblasts to the culture medium containing animal proteins *in vitro* may lead to changes in the surface antigen characteristics of the myoblasts and expression of neoantigens[25]. To overcome this problem, Chachques, et al. are used human serum-supplemented myoblast culture medium for myoblast purification and culture. However, a recent investigation has revealed the poor ability of human serum supplemented culture medium to support myoblast growth *in vitro*[26]. The presence of nonviable cells in the myoblast preparation for transplantation renders them vulnerable to immune rejection[23]. Other mechanisms proposed for low cell survival include mechanical cell damage during grafting and cell leakage from the sites of needle puncture.

Histological data of the grafted areas in the human patients have been reported by Hagege, et al.[27] and Pagani[19]. The patient of Menasché's landmark study died 17.5 months after receiving myoblast transplantation. The heart was explanted *post mortem* and subjected to histological studies[27]. The results showed the presence of myofibrils that stained for skeletal muscle-specific myosin heavy chain in the injected areas. They were seen to be aligned in a direction parallel to host myocardial fibers. Slow-twitch isoforms and fast-twitch isoforms as well as coexpression of both forms were seen in percentages of 32, 35, and 33%, respectively. Percentages of 44, 55, and 0.6% are seen in human skeletal muscle. This switch of phenotype toward the slow-twitch isoform is thought to be caused by repeated stretch as a result of contraction of the adjacent myocardium or by incomplete elimination of the fibers expressing only the fast isoform. Compared to no injected areas, areas where myoblasts were injected showed a significant increase in number of blood vessels (72 f 17 cells vs. 229 f 24 cells, $p < 0.0001$). Multinucleated giant cells have also been seen in grafted segments in the myocardium, associated with noncellular material introduced during transplantation[19]. Aside from these cells, no sign of ongoing inflammation was reported. There was an absence of connexin-43 staining on immunohistochemistry, thus suggesting impaired electrophysiological coupling between the grafted cells and the surrounding host cardiomyocytes.

The safety and feasibility of cell transplantation have been repeatedly documented during multiple preclinical animal experiments and clinical phase I studies. The only serious postoperative adverse event related to the procedure was the occurrence of ventricular arrhythmias[17,19].

Cardiac arrhythmia as a postoperative complication has been reported after myoblast transplantation. Menasché reported that 4 of the 10 patients suffered from sustained monomorphic ventricular tachycardia (VT) that was resistant to treatment by amiodarone and beta-blockers and necessitated the implantation of an automatic internal cardioverter/defibrillator. Pagani reports that 4 of 5 patients suffered from atrial fibrillation (n = 2) or ventricular tachycardia (n = 2). The patient in the Poland trial also suffered from an episode-sustained ventricular tachycardia that was resolved by treatment with amiodarone. Six of eight patients who developed arrhythmias had a prior history of arrhythmias. Most episodes of arrhythmias were clinically well tolerated and did not result in any deaths. The etiology of arrhythmia

after myoblast transplantation is probably multifactorial and includes an inhomogeneous distribution of gap junctions, a difference in the isotypes of ion channels on skeletal muscle cells and cardiomyocytes, and the release of inflammatory mediators after needle puncture. The presence of a nonmyogenic population present in the myoblast cell population that is transplanted may further aggravate the situation. Further more the complication of arrhythmias was not consistent and other studies did not seem to have the same problems.

On the other hand the end-point measurements in these studies highlight improvement in the quality of life, reduced nitroglycerine consumption, enhanced exercise tolerance, improvement in NYHA Class, improvement in wall motion by echocardiography, and significantly reduced perfusion defects.

FUTURE DIRECTIONS

The results of phase I human studies, although encouraging, are still preliminary. A more concerted collaborative effort between the various research groups involved is likely to further the knowledge in this field. The development of strict inclusion and exclusion criteria, better establishment of the target population of patients who may benefit from cell transplantation and more widespread trials will allow the real benefit of this concept to be established. The methods for endpoint measurements of the studies should be made more uniform so that the results emanating from various centres may be more uniformly interpreted. To date, studies on myoblast transplantation have been carried out as an adjunct to routine surgical procedures such as CABG and mechanical-assist device implantation. This makes it hard to realize the true effectiveness of the cell transplantation approach. The beneficial effects could be related directly to the injected cells or indirectly to a combined effect of surgical manipulation and cell transplantation. Further investigative work needs to be done on the basic issues such as the ideal cell type, the optimal number of cells, and the route of administration. The beneficial effects seen to date may be related directly to the injected cells or mediated indirectly by angiogenic or growth factors secreted by the transplanted cells. The most suitable time for cell transplantation after ischemic injury has also not been resolved. If cells are transplanted too early after the injury, their survival could be impaired by the ongoing inflammatory response at the injured site; if they are injected too late, transplantation may not successfully prevent fibrosis from developing in the injured region. The optimal mode of cell delivery continues to be evaluated. Without exception, in all the previous clinical studies reported, direct intramyocardial injection has been used for myoblast delivery. This is the simplest approach but is too invasive if considered in the perspective of the clinical scenario in which cell therapy will be used as the sole therapy. Furthermore, loss of cells due to leakage from the site of injection after direct injection needs to be prevented. In addition to the surgical route of direct intramyocardial cell transplantation, intravenous, intracoronary, intra-arterial, and catheter-based delivery systems are currently being intensively evaluated as alternative approaches for cell delivery[28,29]. The results in the animal studies have shown the feasibility of an endovascular route of delivery to an infarcted area[30]. Cells can be delivered accurately with the assistance of NOGA electromechanical mapping. Catheter-based needle endomyocardial injection is associated with equivalent or superior injectate retention compared with open chest epicardial injection. The percutaneous procedure raises the possibility of repeated grafting of cells without the need to perform an open chest procedure. The use of myoblasts from other than autologous sources may result in on-the-shelf availability of cells, which will help solve some of the logistic problems. The mechanisms responsible for the beneficial effects seen with cell transplantation remain controversial. Elucidation of the exact mechanism of cell survival and exactly how the transplanted cells contribute to improvement in overall cardiac function remain the focus of intense investigation. In addition, the spectrum of cardiovascular pathologies that could benefit from myoblast transplantation needs to be assessed. Clinical trials must be designed to address these basic issues. Further to this, there is a need for blinded and placebo-controlled studies to assess the true efficacy of this approach. There is much theoretical and practical advantage to combining angiogenic gene therapy with myoblast transplantation using myoblasts as carriers of the exogenous genes encoding one or more angiogenic factors. In conclusion, the use of novel cell-based techniques to assist with cardiac regeneration holds much promise for the treatment of heart failure and could complement other available therapies.

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