Progenitor and embryonic stem cell transplantation for myocardial angiogenesis and functional restoration

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Introduction

The discovery of the main risk factors, the development of potent new drugs and sophisticated procedures and interventions, have not yielded the expected ‘victory’ over coronary heart disease. In fact, as the number of heart attacks decreases, the number of patients with refractory myocardial ischaemia and congestive heart failure is rapidly on the rise. Hence, novel therapeutic approaches are urgently required.

The concept of regenerative medicine using the body’s own stem cells and growth factors to repair tissues is gradually coming closer to reality. Work regarding stem cells is ever increasing and is paving the way for medical repairs, including mending a damaged heart. This review aims to track recent developments in myocardial cell transplantation techniques.

What are stem cells? Terminology nomenclature

Every somatic or bodily cell in a human being possesses the full genetic code that makes us who we are. As we grow, however, our somatic cells become specialized or differentiated and they shut down the other parts of the DNA except for the ones relevant for their particular function. Hence, cells ‘forget’ how to become or function as another part of the body. The somatic cells that make up the heart will do only that; they will not become or function as liver cells or brain cells, even though they possess the DNA to do so. Stem cells are the most undifferentiated human cells and so possess the ability to renew and develop into different cell types and become more differentiated.1

Some stem cells are totipotent and have the ability to develop into a complete human organism; others are pluripotent and can develop into multiple cell types of an organism. There are 200 trillion cells in the human body, 200 unique cell types derive from an estimated 20–30 stem cells.2,3 Stem
cells function continuously; for instance, in bone marrow they replace more than one billion red blood cells every day. Similarly, stem cells seem to make new cells for various tissues including the heart. When physicians started using bone marrow transplants no one had seen or isolated a stem cell, they just assumed that such cells existed.\(^4\)

In late 1998 two groups of researchers, Thomson et al.\(^5\) and Solter and Gearhart\(^6\) isolated human stem cells for the first time. Embryonic stem cells are derived from early embryos and are totipotent. Embryonic stem cells can be obtained from two sources: miscarried/aborted fetus or unused fetus from in vitro fertilization. Adult stem cells reside in adult tissues and are multipotent, with a more limited differentiation capacity. Other candidate cells that have a differentiation capacity are satellite cells in skeletal muscle that can regenerate the striated muscle after injury, and stem cells in bone marrow that replenish blood cells and can potentially become cardiovascular cells.

The plasticity of adult stem cells is much greater than suspected, and they can probably generate lineages different from the organ in which they reside. As will be discussed below, adult hematopoietic stem cells show potential to regenerate myocardium—both myocytes and coronary vessels. Injection of these cells in the region bordering an infarct in mice could improve ventricular function. Embryonic stem cells were shown in vitro to differentiate into cardiomyocytes. Those latter cells could be used to grow cardiomyocytes in vitro, to be transplanted into infarcted myocardial regions. Also, adult stem cells could generate cardiomyocytes in culture, or could be injected directly into the damaged heart. Cells home in to areas of damage and generate new myocardium, including electrically coupled myocytes and coronary vessels. Appreciating the above-mentioned potential, every effort should be made to pursue adult stem cells, regardless of what the future holds for embryonic stem cell research. Thus, research in embryonic stem cells needs to be properly explored, debated, and formulated.

**Does the human heart regenerate?**

Until recently, the heart of mammalians was supposed to be terminally differentiated, incapable of any cellular regeneration for replacement or repair. In the past year, several researchers\(^7\)–\(^11\) have demonstrated that bone marrow stem cells will migrate to an infarction in a rat heart and regenerate myocardium. Moreover, Beltrami et al.\(^7\) have proposed that the human heart regenerates cardiomyocytes following injury. The researchers autopsied the hearts of 13 patients who had died within 2 weeks of an extensive myocardial infarction, and the hearts of 10 control subjects who have died of unrelated causes. They quantified cardiomyocyte regeneration in the free wall as the percent of cardiomyocytes engaged in cell cycling. For a more stringent result, they also identified the number of cardiomyocytes that were in the final stage of the cell cycle, namely mitosis, and calculated the mitotic index—the ratio of cells in mitosis to cells not undergoing mitosis. In the infarct hearts, in the area bordering the infarct, 4% of cardiomyocytes were engaged in a cell cycle, 84 times as many as in control hearts, and the mitotic index was 0.08%, 70 times that of control. Regeneration was smaller in areas further away from the infarct (only 1% recycling and mitotic index of 0.03%). The researchers claim these results indicate that the adult heart has a subpopulation of myocytes that are not terminally differentiated. They even speculate that if the recorded rate of cell cycling was maintained for just 3 weeks following an MI, and assuming the cell cycling produced new cells, the process would be sufficient to replace all lost myocytes. Contrary to their calculations, it seems that the reported level of cardiomyocyte proliferation is hardly extensive enough to counter the massive necrosis that follows a heart attack, and this rather limited regenerative response cannot prevent ventricular remodeling and progression to heart failure. It might probably be merely sufficient to repair subclinical lesions after the blockage of small arteries.\(^8\) Moreover, this study did not address the issue that cardiomyocytes may be capable of undergoing karyokinesis (nuclear division), but incapable of cytokinesis (cell division). In other words the issue is whether most of the cardiomyocytes entering the cell cycle end up as bi-nucleated cells rather than undergo true cell proliferation.\(^10\) Recently, a case was described in which a male patient received a heart from a female donor, which provided an opportunity to test whether primitive cells translocate from the recipient to the graft and whether cells with the phenotypic characteristics of those of the recipient ultimately reside in the donor heart.\(^11\) In this study, the Y chromosome was used to detect migrated undifferentiated cells expressing stem-cell antigens and to discriminate between primitive cells derived from the recipient and those derived from the donor. Results showed that myocytes, coronary arterioles, and capillaries that had a Y chromosome made up 7–10% of those in the donor hearts and were proliferative. Interestingly, undifferentiated
cells were negative for markers of bone marrow origin. Putative stem cells and progenitor cells were identified in control myocardium and in increased numbers in transplanted hearts. These interesting data may indicate a regenerative capacity of the transplanted myocardium. If one could understand this natural process better and learn how to control it, it may become a powerful therapeutic tool.

Another important observation could provide keys to unlock the regenerative capacity of the human myocardium. Leferovich et al. have discovered that a mutant strain of mouse has an astonishing capacity to regenerate its myocardium. The researchers cryogenically induced cryo-infarction in the right ventricle of adult MRL mice, as well as in a normal mouse strain. Sixty days after cryo-ablation, cardiomyocyte proliferation in the MRL mice was 10-fold that in the normal mice, and was about the level previously reported in lizards and frogs who are known to have the ability to repopulate cardiomyocytes in large numbers and restore cardiac tissue. Remarkably, cardiomyocytes filled the transmural lesions, restoring normal myocardial architecture with little or no scarring. The dilatation of the right ventricle had also subsided within 3 months. Identification of the genes and molecules which are altered in the MRL mutant and that mediate this regenerative capacity is now needed to understand this unique myocardial regenerative process.

**Angiogenesis and arteriogenesis**

Understanding how blood vessels form, both physiologically and pathologically, is a challenging objective. Even though early research on angiogenesis was mainly descriptive, many molecules able to stimulate or inhibit endothelial cells are being discovered and the puzzle is gradually becoming complete. The complex cellular and molecular mechanisms by which endothelial and smooth-muscle cells interact with each other to form blood vessels are now better understood. Endothelial cells alone can initiate the formation and sprouting of endothelium-lined channels, namely angiogenesis, in response to a physiologic or pathologic stimulus. Periendothelial cells are required for vascular maturation. Recruitment of smooth muscle cells provides these vessels with essential viscoelastic and vasomotor properties and enables accommodation of the changing needs in tissue perfusion. This later stage is called arteriogenesis and has a major role in collateral growth. Strategies to promote sustainable and functional new blood vessels should not be restricted to the induction of capillary angiogenesis, but probably should include the stimulation of arteriogenesis as well.

**What could possibly be achieved using cell therapy?**

In general, cell therapy should strengthen the injured myocardium and potentially, improve symptoms related to ischaemic cardiomyopathy disease. Theoretically, this goal could be achieved by:

- Replacing dysfunctional, necrotic, or apoptotic cardiomyocytes with new functional cells, thereby decreasing infarct size and improving cardiac work.
- Increasing the number of contractile elements.
- Promoting local angiogenesis and collateralization by endothelial progenitor cells and/or induction of prolonged local delivery of vascular growth factors.
- Inducing cardiac protection and anti-apoptosis effects.

In order to achieve these endeavours, the choice of the particular cell type will be dictated largely by the nature of the injury being treated and the desired therapeutic effect. For example, if the goal of the graft were to increase the number of functional myocytes and thereby improve ventricular ejection function, cardiac myocytes (of fetal or stem cell origin) would likely be the donor cell of choice. Skeletal myoblasts are easier to obtain and might work as well. For the purpose of limiting infarct expansion any engraftable cell, including skeletal myoblasts, smooth muscle cells, cells engineered to secrete cardioprotective or anti-apoptosis proteins, may potentially be suitable. If induction of angiogenesis or arteriogenesis is sought then progenitor cells and bone marrow derived cells might be the best choice. However, other cell types engineered to produce and excrete vascular growth factors might be a reasonable solution as well. For xenotypic cells may be used if cell surface markers can be altered to reduce immunorejection. Because of the disadvantages of immunorejection, autologous cell transplantation seems currently an immunocompetent technique.

**Utilization of stem cells for myocardial regeneration**

Several investigators have shown that animal embryonic stem cells can be induced to develop into...
tissue-specific cells by bioengineering techniques. Kehat et al.\textsuperscript{17} have provided the first compelling evidence that human embryonic stem cells can be differentiated into cardiomyocytes. They have demonstrated, on the basis of gene expression, ultrastructure, immunofluorescence, and basic functional tests, that the human embryonic stem cell line H9.\textsuperscript{2} can differentiate into cardiomyocytes. Spontaneously contracting areas appeared in 8.1\% of the embryonic bodies' aggregates and these areas contained myocytes portraying properties consistent with early stage cardiomyocytes.

A cardiomyocyte cell line from mouse bone marrow stromal cells was induced to differentiate in vitro by 5-azacytidine treatment.\textsuperscript{18} This constitutes a powerful model for the study of cardiomyocyte differentiation. Bone marrow cells cultured with 5-aza differentiated into cardiac-like muscle cells in culture and in vivo in ventricular scar tissue and improved myocardial function.\textsuperscript{19} The precise mechanism by which 5-aza induces bone marrow cells to differentiate into muscle cells is still unknown.

Stem cell lines that neither are of embryonic origin nor committed to a muscle lineage will engraft in the adult heart in vivo and differentiate into well-organized mature cardiac myocytes.\textsuperscript{20} The adult heart micro-environment expresses the appropriate signals that allow the exit of these extra cardiac liver cells from their stem-cell state and differentiation into myocytes. This raises the possibility that adult-derived human stem cells can be isolated from a patient, propagated in culture, and used to support the patient's diseased heart.

Injection of granulocyte colony stimulating factor (G-CSF)-mobilized adult-human CD34\textsuperscript{+} cells with phenotypic and functional properties of embryonic hemangioblasts can stimulate neoangiogenesis in the infarct vascular bed, thus preventing myocyte apoptosis and reducing collagen deposition and scar formation after experimental myocardial infarction.\textsuperscript{21} Primitive bone marrow cells mobilized by stem cell factor and granulocyte-colony stimulating factor, home to infarct regions, replicate, differentiate and ultimately promote myocardial repair.\textsuperscript{9,22} The ability to home and differentiate into cells of the cardiogenic lineage, including arterioles and capillaries, was shown by local transplantation of Lin\textsuperscript{−} c-kit\textsuperscript{+}Sca-1\textsuperscript{+} cells into the border of an acute infarct, however, thoracic surgery and injection of foreign cells was required and the success rate of this invasive approach was limited. A superior method resulted in 100\% success rate.\textsuperscript{9} In the presence of an acute myocardial infarct, cytokine-mediated translocation of BMC resulted in significant tissue regeneration 27 days later. Mortality was decreased by 68\%, infarct size by 40\%, cavity dilation by 26\%, and diastolic stress by 70\%. Ejection fraction progressively increased and hemodynamics improved because of the formation of 15×10\textsuperscript{6} new myocytes with arterioles and capillaries connected with the circulation of the unaffected ventricle.\textsuperscript{22} Bone marrow cells injected or mobilized to the damaged myocardium behave as cardiac stem cells with remarkable plasticity, giving rise to myocytes, endothelial cells, and smooth muscle cells.

Sorting cells automatically by flow-cytometry is based on several parameters including light scatter (forward and side scatter, indicative of cell surface properties and intra-cellular organelles, respectively) and immunophenotyping by fluorescence. Taken together, this technique gives a morphological fingerprint of whatever is flowing through the cytometer. Transplanted murine highly enriched hematopoietic stem cells, the so-called side population (SP) cells (CD34\textsuperscript{−}/low, c-Kit\textsuperscript{−}, Sca-1\textsuperscript{−} based upon flow cytometry), migrated into ischaemic cardiac muscle and blood vessels, differentiated to cardiomyocytes and endothelial cells, and contributed to the formation of functional tissue.\textsuperscript{23} In this report, it was estimated that only 3\% of the blood vessels (mostly capillaries) contained cells derived from donor SP cells, and 0.02\% of all cardiomyocytes were derived from such cells. The biological relevance of this observation is thus uncertain.\textsuperscript{24}

Utilization of progenitor cells for myocardial angiogenesis

Endothelial progenitor cells (EPCs) could be isolated from peripheral blood and/or bone marrow, and showed incorporation into sites of physiological and pathological neovascularization in vivo, following either systemic injection or direct intra-myocardial transplantation using and injection technique.\textsuperscript{25,26} In contrast to differentiated endothelial cells, transplantation of EPCs successfully enhanced vascular development by in-situ differentiation and proliferation within ischaemic organs.\textsuperscript{27} Based on such a novel concept of closed up function on EPCs in postnatal neovascularization, the beneficial property of EPCs is attractive for cell therapy as well as cell-mediated gene therapy applications targeting regeneration of ischaemic tissue.

Endothelial cell progenitors, angioblasts, have been detected in the peripheral blood of adult humans, mice and rabbits. These cells have been shown to incorporate into the endothelium of newly
forming blood vessels in pathological and non-pathological conditions.\textsuperscript{23,24} Exogenous CD34\textsuperscript{+} cells may be used for therapeutic angiogenesis in type-I diabetic mice that suffer from impaired angioblast function.\textsuperscript{28} Flow was restored to 60% of pre-surgery levels in 10 days and 90–100% by 14 days.

Since bone marrow is a natural source of multiple angiogenic growth factors and because of the essential involvement of several bone-marrow derived cells including vascular progenitors, several groups have investigated whether transplantation of the entire bone marrow or specific progenitor-enriched cell populations, or their direct implantation into ischaemic tissues would enhance tissue vascularization and function.

Using freshly aspirate bone marrow cells, catheter-based intramyocardial injection of autologous bone marrow cells was shown to promote collateral development in ischaemic porcine myocardium.\textsuperscript{29} Moreover, angiogenic cytokine concentrations in vitro increased progressively over time and induced endothelial cell proliferation.

Experimental hindlimb ischaemia in mice increases EPC differentiation, and the frequency of EPC-enriched population in the circulation is increased by more than 400%.\textsuperscript{30} Neovascularization of the normally avascular mouse cornea was enhanced and there was a significant increase in reporter gene expression in the corneas of mice with hindlimb ischaemia. EPCs may thus participate in repair following ischaemic injury in a process controlled by the bone marrow via circulating cytokines and soluble receptors and/or adhesive molecules.

**Non stem cell sources for myocardial regeneration**

The unique reproducible cardiomyocyte differentiation system from human embryonic stem cells might have a potentially attractive application in cell replacement therapy. Adult cardiomyocytes withdraw permanently from cell cycle during differentiation; hence, any significant loss of cardiomyocytes is irreversible and leads to progressive heart failure. Nonetheless, several studies have proposed that implantation of fetal myogenic cells within the infarcted tissue might be beneficial for restoring myocardial function.\textsuperscript{31,32}

Although several myocyte preparations have been suggested, the inherent electrophysiological, structural and contractile properties of cardiomyocytes make them an attractive candidate. Because human fetal cardiomyocytes cannot be obtained in sufficient numbers for clinical purposes, the use of cardiomyocytes derived from embryonic stem cell lines may become a preferred option.\textsuperscript{17} Nevertheless, generation of enriched relatively pure cultures and establishment of a reliable strategy to counter immune rejection and prolong cells survival in the engrafted milieu must be achieved first.

Transplantation of skeletal myoblasts (mainly satellite cells) into cryo-infarcted myocardium of the same animal is another technique that holds promise for myocardial regeneration.\textsuperscript{16} Islands of different sizes comprising elongated, striated cells that retained characteristics of both skeletal and cardiac cells were found in scar regions in a rabbit model of cryo-infarction. In rabbits in which myoblasts were incorporated, myocardial performance was improved. The same study is now being performed in coronary occlusion model in pigs. The advantage of this technique is lack of immune response and cellular availability since the implanted cells are derived from the patient’s thigh muscle. There are no ethical issues associated with this method. Nonetheless, it should be acknowledged that the relevance of the cryo-infarction model to the human myocardial infarction scenario remains to be established as does the ability to duplicate these results in larger animal studies using coronary occlusion with or without reperfusion.

**Initial experiences in patients**

Over the last 2 years, the cumulative evidence gathered from more than a decade of pre-clinical studies have finally enabled clinicians to begin various limited safety and feasibility clinical studies. Some have used skeletal muscle derived myoblasts as cell candidates. Menasche et al. (Hôpital Bichat, Paris) pioneered the first autologous myoblast implantation in a human patient in June 2000.\textsuperscript{33} They acquired a muscle biopsy from the 72-year-old patient’s leg, and following two weeks of isolation and expansion implanted the cells surgically while the patient underwent bypass surgery. Ten patients with previous infarction, akinetic myocardial segments and an ejection fraction of less than 35% have been treated so far, all in conjunction with bypass surgery.\textsuperscript{34} The clinical application of myoblasts was done in non-grafted areas of infarcted myocardium in which no evidence of viability was present prior to surgery, including using positron emission tomography (PET) metabolic nuclear imaging. Although the investigators reported an improvement in mean ejection fraction (an increase from 24 to 34%) and improved congestive symptoms, it is impossible to differentiate the impact of
cell transplantation from that of ‘conventional’ surgical revascularization in those patients, thus no definite conclusion could be drawn from this experience. Interestingly, in four patients, sustained ventricular tachycardia occurred at 2–3 weeks following surgery that raises concern about the arrhythmogenic potential of this treatment strategy. Smiths and Serruys, (Thorax Center, Rotterdam) have used a similar approach using an intramyocardial injection catheter for cellular delivery during cardiac catheterization.

Several groups have initiated clinical studies with autologous bone marrow derived cells. Hamano et al. (Yamaguchi University, Ube, Japan) initiated a clinical trial in 1999 in five patients. Induction of therapeutic angiogenesis was attempted by local implantation of autologous bone marrow cells concomitant with bypass surgery. The cells were implanted into the non-graftable area and postoperative cardiac scintigraphy showed specific improvement in coronary perfusion in three of the five patients. Several groups in the USA, Hong-Kong, Japan and Israel have started performing percutaneous implantation of autologous bone marrow cells by transcatheter electromagnetic guided transendocardial delivery. The rationale has been derived from experimental works showing improved perfusion and function in treated ischaemic myocardial regions.

Strauer et al. (Heinrich Heine University, Düsseldorf) have reported successful selective intracoronary implantation of autologous adult stem cells. They extracted bone marrow 14 h after myocardial infarction onset while the patient underwent coronary angioplasty and stent placement to the left anterior descending artery.

The bone marrow cells were transplanted 6 days following the transmural myocardial infarction. Ten weeks later, the patient showed a reduction of the transmural infarct area from 24.6 to 15.7% of the left ventricular circumference; a 20–30% increase in ejection fraction, cardiac index and stroke volume; a 30% decrease in end-diastolic volume on exercise and a fall in left ventricular filling pressure. Even though myocardial biopsy was not obtained, the researchers attributed the illustrated cardiac recovery to the cell transplantation that led to cardiomyogenesis. However, as with the surgical experience, it is unknown whether the hemodynamic improvement that was reported was the result of opening the artery to allow perfusion of the peri-infarct ischaemic bed, rather than the effect of stem cells. Since the time of publication, a few more patients have been treated using the same technique, although the results, still pending, may be confounded not only by the angioplasty procedure, but also by the spontaneous recovery of viable, stunned myocardium.

What is still required and open questions

A workshop of the National Heart, Lung, and Blood Institute has recommended short- and long-term goals to assist in realizing the potential of cell transplantation. The group has concentrated mainly on standardization issues and highlighted the importance of carefully conducting clinical trials using sensitive and specific end-points.

Because the cell-based myocardial treatments are so new and biologically complex, moving ‘straight away’ into humans might be problematic. Much more research on primates and then extensive clinical testing must be completed first. Moving towards major clinical trials is anticipated within 2 years, thus stem cell boosting treatments could be available in 5–10 years. Making entire organs ‘from scratch’, however, lies much further in the future. Optimally, fixing organs with stem cell therapy could become so effective that such organ fabrication might never be needed. In the long term, further understanding of normal development, gained by studying the newly available stem cells models, would enable the achievement of an ultimate medical tool: activating specific stem cells and inducing self regeneration. The potential risk of enhanced stem-cell cell proliferation and even carcinogenesis should be excluded, as uncontrolled electrical properties within regions that are already prone for myocardial ‘instability’ such as infarcted and peri-infarction zones.

Whether one elects to inject ‘enriched’ EPCs into the systemic circulation, the optimal dose and amount of intra-myocardial uptake should be determined. For direct injection of cellular compounds, potential side effects may include local inflammatory responses and tissue damage secondary to the injection procedure itself. Thus, the optimal mode of delivery should be defined for each cellular compound used for transplantation. For various cell types, many questions still remain concerning cell-based treatment in the context of its goals. For example, does spontaneously occurring angiogenesis sufficiently support the grafted cells? Can angiogenesis be augmented using progenitor cells and if so, what are the potential advantages of stem cells over current therapeutic approaches, such as administration of plasmid or viral vectors encoding one or more angiogenic growth factors? What is the optimal cell source?
What would be the role of human embryonic stem cells? Is the transdifferentiation of embryonic or adult stem cells possible? For myocardial regeneration, should human angioblast infusion in conjunction with pharmacologic agents such as angiotensin-converting-enzyme (ACE) inhibitor drugs or angiotensin-1 receptor blockade reduce angiotensin-2-dependent cardiac fibroblast proliferation and collagen secretion? What is the therapeutic window for cell transplantation? Is it dose (i.e. cell count) dependent? Are stem cells ubiquitous and present in all tissues? If not, how do they differ? What signals induce a bone marrow derived cell to migrate to the heart and assume a novel function in that tissue? Finally, if the cells do not need to reside in the damaged tissue, could plasticity and transdifferentiation between cell types become normal aspects of tissue repair throughout life?

Several intriguing questions should be asked regarding stem cells per se: if stem cells in the marrow are able to become muscle or brain, are there mechanisms ensuring tissue’s ‘self’ and prohibiting muscle or brain presence in the marrow? How much of the ‘stemness’ (self renewal and multipotency) observed in experimental systems is inherent to the cells that we manipulate, and how much is due to manipulation? Are we discovering unknown and unexpected cells, or rather unknown and unexpected effects of manipulation of cells in culture?

Conclusions

Preliminary results raise hopes that various cellular transplantation strategies may enable the restoration of myocardial function and perfusion in ischaemic cardiomyopathy syndromes. Candidate cells for transplantation range from skeletal myoblasts, embryonic stem cells, and non-contractile elements such as bone marrow or systemic blood expanded populations of endothelial progenitor cells (EPCs) used to achieve improved myocardial perfusion and function. Bone marrow derived cells or progenitors might expand the armamentarium of therapeutic angiogenesis and myocardial regeneration, in particular during senescence or disease when the reparative growth potential of vessel-associated vascular cells becomes limited. Vascular progenitors could be also useful to treat ischaemic heart disease, as this requires growth of both endothelial and smooth muscle cells. Despite great hope and enthusiasm, more research is needed in order to transform the basic research data into clinical reality. Additional careful research is warranted in order to explore the therapeutic merits of cell transplantation techniques while accepting the likelihood that possible adverse side effects may occur. Understanding the signals that mediate cellular growth and differentiation, and identifying markers specific to these progenitor cells may provide novel tools for myocardial regeneration in ischaemic cardiomyopathic disease. This awareness, coupled with a rigorous scientific analysis of carefully conducted experimental and clinical studies, will lead to a risk vs benefit analysis of these potentially extremely important therapeutic interventions and may provide new hope for patients with ‘end stage’ cardiac disease.

References


