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Heart Failure

Research is a dynamic enterprise that generates a wealth of knowledge. It provides a forum for debating ideas and working them into evidence-based theories. The clinical trial setting puts these theories to the test and may lead to evidence-based medicines that can alleviate symptoms or cure disease. But the process of taking research from bench to bedside is a lengthy one, and demands not only vision but also years of hard work and dedication on the part of scientists, physicians and patients. This document presents basic information about heart failure and frames the context for the discussion that follows about how lessons learned from stem cell research may help fight this disease. Readers may also wish to peruse additional web resources or speak with their physicians for more information about this condition.

About Heart Failure

Heart failure (HF) is a chronic cardiovascular syndrome where damage to the heart muscle prevents it from filling or pumping blood normally. Although many root causes can precipitate the syndrome, the outcome is ultimately the same: the body's organs are deprived of the blood they need to function properly. The "failing" heart keeps working, but not as efficiently as it should, and blood returning to the heart through the veins backs up causing congestion in the tissues and in the kidneys. This may lead to swelling (edema) throughout the body, most often seen in the legs and ankles.

As time goes on, the heart tries to compensate by increasing in size. Like any other muscle under strain the heart tries to thicken but progressive enlargement weakens it by further reducing how efficiently blood is pumped to the body. Eventually, the ability of the heart to circulate blood through the body is so compromised that blood pressure begins to drop and fluids back up in the lungs causing shortness of breath, especially when lying down.

Heart failure is a major burden in both developed and developing nations. The 5-year mortality rate approaches 50 per cent, which is greater than that of either breast or colon cancer. In a 2010 report from the American Heart Association, the numbers of people newly diagnosed with heart failure in the United States alone was estimated at greater than 500,000 per year. The prevalence is gauged at 5.8 million citizens over the age of 20 and the yearly costs to the US reach $39.2 billion. Not surprisingly, these numbers are expected to rise as the population ages. Better treatments for other coronary heart diseases also increase prevalence because the survivors are at higher risk of developing heart failure in the future.

Causes

There are many conditions that increase one's risk of developing heart failure. In the industrialized world, the most common cause is coronary artery disease (myocardial infarction and myocardial ischemia), resulting from a narrowing or blockage of the arteries that supply blood to the heart. Major risk factors for congestive heart failure include coronary artery disease accounting for 60 to 75 per cent of all cases of heart failure, and high blood pressure (hypertension) which is increasingly important in the elderly. Diabetes mellitus, abnormal heart valves (related to rheumatic fever or congenital heart defects), inflammation of the heart (caused by viruses), or infection of the heart valves (endocarditis) or muscle (myocarditis) also contribute to heart failure.

Symptoms and Treatment

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The most common signs of heart failure are fatigue and shortness of breath (dyspnea). Individuals living with chronic heart failure may also experience fluid retention, often observed as swollen legs or ankles, or a constant cough (from fluid in the lungs), as well as weight gain due to fluid build-up in the abdomen. These symptoms may worsen with a high-salt diet, excessive fluid intake, or medications that cause water- or salt-retention, or if the patient comes down with a cold or the flu.

There is no cure for heart failure but it can be controlled by treating the underlying conditions that cause it. The goals for treatment are three-pronged: to improve symptoms, to stop the heart failure from getting worse, and to prolong life span.

Standard treatment for people with advanced symptoms of heart failure involves medications and lifestyle changes. Frontline medications include diuretics to reduce fluid retention, and angiotensin converting enzyme (ACE) inhibitors and beta blockers to prevent or slow the progressive heart enlargement. Aldosterone antagonists act on the kidney to increase urine output as well as to reduce scarring in the heart, while drugs such as digoxin help to regulate the heartbeat. Lifestyle changes are also very important and focus on more rest, reducing dietary salt intake and modifying daily activities.

Depending upon the root cause of the heart failure, patients may require any one of a number of common heart procedures. Some heart surgeries require stopping the patient's heart and in these cases heart-lung machines substitute by pumping blood throughout the body. Other procedures are less invasive and can be accomplished with a catheter under local anesthesia. Examples of heart surgeries include repairing a faulty valve and implanting an artificial valve or mechanical pump. Blocked arteries can be bypassed with a piece of artery from the arm or chest, or a vein from the leg of the patient (coronary bypass surgery), or using a balloon catheter followed by implantation of a stent to keep the artery open.

For cases where the heart is so damaged that it cannot be repaired, a heart transplant may be the only option, whereby a severely diseased or damaged heart is replaced with a healthy heart from someone who has recently died. Modern heart transplants have been successfully performed since 1980. Today, around 85 per cent of heart recipients will live at least an additional year, 75 per cent will live five more years, and 36 per cent will live 20 years. However, donor hearts are in short supply and patients face a lengthy waiting list to receive a donor heart. In addition, to prevent the body from rejecting the transplanted heart, recipients must receive immunosuppressant therapy – powerful drugs to suppress their immune systems – for the rest of their lives, which leaves them susceptible to a range of other diseases.

In addition to these existing therapies, researchers continue to investigate and test new ways to treat heart failure, including improved surgical methods and equipment, and identifying genetic links or drugs that can help to regenerate heart muscle. However, despite the myriad of treatments available for heart failure that slow the progression of heart failure and alleviate the symptoms, none are unable to regenerate heart tissue. Novel treatments that can achieve enduring cures are in short supply and stem cells offer the promise of future therapies that may achieve this lofty goal.

How can stem cells help?

Stem cell therapy for treating heart failure is an exciting prospect and the field has already seen scores of experimental trials evaluating this approach. In theory, the ability of stem cells to grow into specific cell types and produce growth factors means that they could be a ready source of precursors to make heart cells (cardiomyocytes), blood vessel cells (endothelial cells), supporting cells and regulatory signals. In the case of heart failure, it is hoped that coaxing stem cells into action will contribute to a healthier heart microenvironment and promote the growth of heart tissue and blood vessels for the purpose of restoring at least some of the lost function of the heart.

Many different types of stem cells are being explored as potential therapies for heart failure. The first to be tested in the clinical trial setting, in 2003, were skeletal muscle stem cells, also called myoblasts. In the past 10 years tremendous gains have been made in preclinical research and now bone marrow stem cells, endothelial stem cells, mesenchymal stem cells, cardiac progenitor cells and fat-derived stem cells are all being explored as potential therapeutic sources and have even progressed to the clinical trial stage. Some stem cells, such as induced pluripotent stem cells and embryonic stem cells, are still at the animal model testing stage, which is a crucial step towards vetting the potential and safety of using such cells in human studies.

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Research directions

Although preclinical studies and clinical trials to date have yet to illuminate a cure for heart failure, they have helped to identify the many parameters that must be better understood before the full potential of stem cells can be applied to heart failure. Below are but a few of the major challenges that researchers are grappling with to achieve this goal.

Expanding stem cells

Many transplanted stem cells never reach their target so it is vital to be able to transplant high numbers of stem cells in order to maximize the number of cells that are able to reach damaged heart tissue. Researchers are busy devising better methods for isolation, identification and expansion of large numbers of stem cells in the laboratory, and have added some newer techniques to the arsenal as well. Nanofibers are being saturated with growth factors that can boost stem cell numbers, and some types of stem cells, such as HSCs, are being seeded onto a bed of stromal cells that nurture the growth and expansion of HSCs. Delivering growth factor genes through genetic engineering, either into a particular site in the body or into stem cells harvested from patients, is also being tested.

Delivery

A number of different routes are currently being used to deliver stem cells into patients with heart failure. The least invasive is injection of cells by way of a vein (intravenous injection). Injection into the heart from the outside (transepicardial injection), requires surgery for direct visualization. This route is the most invasive but also the most dependable. Injection through the inner wall (transendocardial injection) uses a catheter and is less invasive, but requires sophisticated imaging or guidance systems to ensure delivery to the right areas. Injection directly into the arteries of the heart (i.e. intracoronary injection) by way of a balloon-like catheter is the most common route used following myocardial infarction. The main issue with this approach is making sure that the injected cells do not plug up small vessels and reduce blood flow to the heart. However, this approach has been used in more than 2000 patients in dozens of separate clinical trials and has shown an excellent safety profile. Similarly, blockages or embolisms are the main concerns with the trans-venous coronary sinus injection technique.

All the delivery routes suffer similar problems: retention of enough transplanted cells in the heart; cells becoming lodged in the lungs; or cells circulating to other organs in the body. To overcome some of these issues, researchers are developing new strategies such as tissue engineered biodegradable scaffolds or sheets loaded with stem cells. A recent trial has corroborated this approach, showing that transplantation of a bioengineered sheet loaded with cardiac progenitor cells was able to promote cardiogenesis and improve heart function in patients with myocardial infarction.

Homing

Endogenous stem cells reside in many different locations throughout the body. Stimulating them into action is one challenge and getting them to travel to the desired site is another. Similarly, exogenous stem cells, harvested from patients or donors and transplanted into the patient's body, also need cues to find their way to the desired location.

Researchers are faced with the conundrum of how to encourage stem cells to home specifically to sites of damage. In their search, they have identified a number of different intercellular messengers (cytokines) released by damaged heart tissue that can attract stem cells. However, some of the factors, such as SDF-1, are only found for a very short period of time after cardiac damage. One solution might be to deliver genetically engineered cells that express SDF-1 to cardiac tissue. In that way, the SDF-1 expressing cells will act like a beacon for stem cells to follow. Experimentation in animals has proven this approach to be successful in that stem cells from the bone marrow home to damaged heart tissue expressing the SDF-1 beacon.

Detecting stem cell niches

Finding new environments, or niches, within the body that harbour stem cells is an ongoing challenge and one that is

not only important for identifying new stem cell sources but also for understanding basic stem cell biology. The bone marrow is an example of a niche where the self-renewal of hematopoietic stem cells is maintained. Other niches containing stem cells include the heart, intestine, skin and neural tissue. Lineage mapping is a new method used for finding stem cell niches and involves genetically tagging stem cell markers so that they can be tracked to their niche in the body. This technique has been used by a Japanese researchers who showed that neural crest stem cells (derived from the embryo) located in the heart could migrate and develop into cardiomyocytes following myocardial infarction.

Canadian contributions

The Canadian Cardiovascular Society estimates that there are 500,000 Canadians currently living with congestive heart failure. Ten per cent will likely experience advanced heart failure and 50 per cent will survive one year.

In light of such a grim outcome, the Ontario Ministry of Economic Development and Innovation recognized the need to fund the development of novel therapies for cardiovascular disease and pledged 4.3 million dollars in 2010 from the Ontario Research Fund to the CREST project – Cardiovascular Repair using Enhanced Stem Cell Therapy. Partner institutions involve in the project include Ottawa Hospital Research Institute, University of Ottawa Heart Institute, St. Michael's Hospital, University Health Network, and University of Ottawa, as well as private sector companies. Together these organizations are collaborating to attack the enormous burden of cardiovascular disease in our society by developing stem cell therapies that can repair and regenerate damaged cardiac tissue.

As head of the CREST program, Canadian scientist Duncan Stewart in Ottawa is examining the use of gene-enhanced endothelial progenitor cells to repair both damage to blood vessels caused by pulmonary hypertension (increased blood pressure in the pulmonary arteries, which carry blood from the heart to the lungs) and damage to the heart muscle caused by heart attack. For this approach, researchers take cells from a patient's own blood, differentiate them into endothelial-like cells that line the inside of blood vessels, load them with a therapeutic gene called endothelial nitric oxide synthase (eNOS), and return them to the patient. Stewart's group was the first in Canada to initiate clinical trials using a combination of gene and cell therapy for cardiovascular disease. Poised to begin in September 2012 is the phase II, randomized, double-blind, placebo controlled study called ENACT-AMI. The trial will involve five different centres where autologous early endothelial progenitor cells (with or without the eNOS gene) will be delivered via intracoronary injection into patients who have suffered from acute myocardial infarction. The study hopes to recruit 100 participants over two years and will primarily measure heart function in addition to safety and how long patients are protected before they may decline clinically.

Ongoing clinical studies

Skeletal myoblasts

The first stem cells to be used for cardiac therapy were skeletal myoblasts isolated from muscle biopsies. This trial took place in 2008 and since then a number of other trials using skeletal myoblasts have been initiated. Although some trials have been discontinued, two are still ongoing: PERCUTANEO, for patients who suffered from myocardial infarction; and MARVEL, for patients with congestive heart failure. Only time will tell whether these trials show sustained improvements in heart function and integration of skeletal stem cells into the damaged hearts of the participants.

Hematopoietic progenitor/stem cells (HPSCs)

There are currently 30 plus NIH-registered experimental trials evaluating stem cell therapy for heart disease. The majority test for the safety and efficacy of using hematopoietic progenitor/stem cells (HPSCs) from bone marrow for treating various cardiovascular diseases. Over 1000 patients have now been transplanted with various populations of bone marrow stem cells and the procedure has shown to be safe and modestly beneficial. Although the transplanted bone marrow stem cells are not actually generating new heart cells, they appear to be providing some benefit by way of a mechanism that has yet to be determined. Future studies may focus on using particular subsets of HPSCs in an effort to pinpoint the most efficacious cells.

Cardiac stem cells

Until very recently, it was thought that the heart was incapable of repairing itself after injury. In 2003 researchers isolated cardiac stem cells from human heart tissue and over the next 6 years, researchers characterized the cells and showed that cardiac stem cells do slowly renew a fraction of heart cells over the course of one's life. These results kindled much hope for the possibility of using cardiac stem cells to treat cardiovascular diseases. Over 10 years of basic research has finally provided enough proof to warrant clinical trials in humans. Currently, four ongoing trials are testing autologous (from the patient) cardiac progenitor cells: ALCADIA for ischemic heart disease, CADUCEUS for recent myocardial infarction, TICAP for heart failure and SCIPIO for heart failure due to myocardial infarction. Interim results from the phase I, open label SCIPIO trial are promising. Patients in the treatment arm of the trial received their own cardiac stem cells, which were isolated from heart biopsies and expanded in vitro. Up to 1 million cardiac stem cells were injected via balloon catheter into the coronary artery supplying the damaged heart tissue. Although the study was designed to test the safety and feasibility of the procedure, and successfully did so, post-study follow-up has shown some increase in heart function and a decrease in infarct size up to one year after the treatment in 14 of the 16 patients. The next step will be to perform larger phase 2 trials that specifically test for the ability of cardiac stem cells to regenerate heart tissue that has died following myocardial infarction.

Endothelial progenitor cells (EPCs)

Endothelial progenitor cells are thought to originate from stem cells in the bone marrow and are characterized by their ability to make the endothelial cells that line blood vessels throughout the body. The process of making new blood vessels, called neovascularization, is a critical step towards promoting the regeneration of damaged heart tissue. Scientists are still debating how to precisely characterize EPCs, but CD34 and CD133 have been suggested to be important markers. A handful of clinical trials posted on clinicaltrials.gov are exploring the potential of these cells to contribute to the formation of new blood vessels in regions of cardiac damage found in patients with cardiomyopathy, myocardial infarction, coronary artery disease or heart failure.

Mesenchymal stem cells

Although mesenchymal stem cells can be found in many different tissues throughout the body, the most common source for the purpose of clinical trials today is bone marrow or fat tissue. MSCs offer some advantages over HSCs in that they are extremely versatile and easily differentiated into a variety of cell types, including fat cells, fibroblasts, bone and muscle cells. Also in their favour is that MSCs secrete survival factors that protect cardiomyocytes. Most importantly, MSCs have a moderating effect on the immune system and because of this they can be transplanted from one individual to another without the same need for immune suppressing drugs normally required. This asset will allow them to be manufactured in large batches in a more commercially viable way, unlike some other stem and progenitor cells. Many clinical trials are currently underway to assess the potential of MSCs to treat cardiovascular disease; for example, APOLLO for the treatment of myocardial infarction, PRECISE for nonvascularizable (no new blood vessel formation) ischemic myocardium and PROCHYMAL for acute myocardial infarction. PROCHYMAL was a phase I, randomized, double blind, placebo controlled, dose escalation study which demonstrated that allogeneic (not from the patient) human mesenchymal stem cells could be safely transplanted into patients after acute myocardial infarction. At six months after the procedure, patients in the treatment arm had improved cardiac function. Taken together these results have provided justification for further trials using MSCs.

It is generally accepted by the scientific community that it takes decades to bring new therapies to patients. The fact that clinical trials using stem cells for heart failure are being actively pursued speaks to the great achievements that have already been made in basic and clinical research. As these trials progress, their results should help to inform, refine and define future research questions which may provide a platform from which to launch new trials and bring the field ever closer to using stem cells as frontline treatments for heart failure.

Web Resources

For more information about heart failure in general and the possible application of stem cells in particular, readers may

wish to peruse the recommended sites below.

- Heart and Stroke Foundation of Canada: http://www.heartandstroke.com/
- American Heart Association: http://www.heart.org/

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