CONGESTIVE HEART FAILURE (CHF)

1. CONGESTIVE HEART FAILURE PROTOCOL

A. Clinical response: Patients may experience improvements in both function and quality of life parameters. This could include an average improvement of about 10-15% points in ejection fraction (EF). In trials completed by Bioheart, we have demonstrated an average improvement of 100 meters in exercise capacity or six minute walk distance. Patients may also improve several heart failure classes with an overall improvement in quality of life parameters such as Minnesota Living with Heart Failure Questionnaire.

B. Objective: To provide the patient with a treatment that stimulates his / her immune system, promote cellular regeneration and improve symptoms associated with Congestive Heart Failure. The endovascular/intravenous Ad-SVF Containing Adult Stem Cell Procedure should serve to compliment the patient's current treatment regimen or to promote healing when current treatment is not responding.

2. PRELIMINARIES

A. Background: Congestive heart failure, or CHF, is a debilitating condition that occurs as the heart becomes progressively less able to pump an adequate supply of blood throughout the body resulting in fluid accumulation in the lungs, kidneys and other body tissues. Persons suffering from NYHA Class II or worse heart failure experience high rates of mortality, frequent hospitalization and poor quality of life. CHF itself may lead to other complicating factors such as pulmonary hypertension, edema, pulmonary edema, liver dysfunction and kidney failure. Although medical therapy for CHF is improving, it remains a major debilitating condition. According to the American Heart Association Heart Disease Statistics – 2010 Update, the estimated, total direct and indirect costs of cardiovascular disease and stroke in the United States for 2010 is estimated to be $503.2 billion.

B. Causes of Congestive Heart Failure**:** CHF has many causes, generally beginning in patients with a life-long history of high blood pressure or after a patient has suffered a major heart attack or some other injury to the heart. Other common causes of CHF include (1):

- Coronary artery disease
- Previous heart attack (myocardial infarction)
- High blood pressure (hypertension)
- Valve disease
- Congenital heart disease (condition you are born with)
- Cardiomyopathy (enlarged heart)
- Endocarditis
- Myocarditis (infection of the heart)
- Diabetes

C. Treatment Options:

- ***Drug Therapies:*** The ACC/AHA Guidelines recommend that most patients with heart failure should be routinely managed with a combination of ACE inhibitors, beta-blockers and diuretics. The value of these drugs has been established by the results of numerous large-scale clinical trials and the evidence supporting a central role for their use is, according to the ACC/ AHA Guidelines, compelling and persuasive. ACE inhibitors and beta blockers have been shown to improve a patient's clinical status and overall sense of well-being and reduce the risk of death and hospitalization. Side effects of ACE inhibitors include hypotension, worsening kidney function, potassium retention, cough and angioedema. Side effects of beta-blockers include fluid retention, fatigue, bradycardia and heart block and hypotension.
- ***Bi-ventricular Pacers:*** The ACC/ AHA Guidelines recommend bi-ventricular pacers for persons who, in addition to suffering from heart failure, have left and right ventricles that do not contract in sync, known as ventricular dyssynchrony and who have a LVEF less than or equal to 35%, sinus rhythm and NYHA Class III or NYHA Class IV symptoms despite recommended optimal medical therapy. Bi-ventricular pacers are surgically implanted electrical generators that function primarily by stimulating the un-damaged portion of the heart to beat more strongly using controlled bursts of electrical currents in synchrony. Compared with optimal medical therapy alone, bi-ventricular pacers have been shown in a number of clinical trials to significantly decrease the risk of all-cause hospitalization and all-cause mortality as well as to improve LVEF, NYHA Class and Quality of Life. According to the ACC/AHA Guidelines, there are certain risks associated with the bi-ventricular pacer including risks associated with implantation and device-related problems.
- ***Implantable Cardioverter Defibrillators:*** ACC/AHA Guidelines recommend ICDs primarily for patients who have experienced a life-threatening clinical event associated with a sustained irregular heartbeat and in patients who have had a prior heart attack and a reduced LVEF. ICDs are surgically implanted devices that continually monitor patients at high risk of sudden heart attack. When an irregular rhythm is detected, the device sends an electric shock to the heart to restore normal rhythm. In 2001, ICDs were implanted in approximately 62,000 and 18,000 patients in the United States and Europe, respectively. Although ICDs have not demonstrated an ability to improve cardiac function, according to the ACC/AHA Guidelines, ICDs are highly effective in preventing sudden death due to irregular heartbeats. However, according to the ACC/AHA Guidelines, frequent shocks from an ICD can lead to a reduced quality of life, whether triggered appropriately or inappropriately. In addition, according to the ACC/AHA Guidelines, ICDs have the potential to aggravate heart failure and have been associated with an increase in heart failure hospitalizations.

- ***Heart Transplantation and Other Surgical Procedure:*** According to the ACC/ AHA Guidelines, heart transplantation is currently the only established surgical approach for the treatment of severe heart failure that is not responsive to other therapies. Heart transplantation is a major surgical procedure in which the diseased heart is removed from a patient and replaced with a healthy donor heart. Heart transplantation has proven to dramatically improve cardiac function in a majority of the patients treated and most heart transplant recipients return to work, travel and normal activities within three to six months after the surgery. In addition, the risk of hospitalization and mortality for transplant recipients is dramatically lower than the risk faced by patients in NYHA Class III or NYHA Class IV heart failure. Heart transplants are not, for a variety of reasons, readily available to all patients with severe heart damage. The availability of heart transplants is limited by, among other things, cost and donor availability. In addition to the significant cost involved and the chronic shortage of donor hearts, one of the serious challenges in heart transplantation is potential rejection of the donor heart. For many heart transplant recipients, chronic rejection significantly shortens the length of time the donated heart can function effectively and such recipients are generally administered costly anti-rejection drug regimens which can have adverse and potentially severe side effects.
- There are a number of ***alternate surgical approaches*** for the treatment of severe heart failure under development, including cardiomyoplasty, a surgical procedure where the patient's own body muscle is wrapped around the heart to provide support for the failing heart, the Batista procedure, a surgical procedure that reduces the size of an enlarged heart muscle so that the heart can pump more efficiently and vigorously, and the Dor procedure. According to the ACC/AHA Guidelines, both cardiomyoplasty and the Batista procedure have failed to result in clinical improvement and are associated with a high risk of death. The Dor procedure involves surgically removing scarred, dead tissue from the heart following a heart attack and returning the left ventricle to a more normal shape. While the early published single-center experience with the Dor procedure demonstrated early and late improvement in NYHA Class and LVEF, according to the ACC/AHA Guidelines, this procedure's role in the management of heart failure remains to be defined.
- ***Ventricular Assist Devices:*** Ventricular assist devices are mechanical heart pumps that replace or assist the pumping role of the left ventricle of a damaged heart too weak to pump blood through the body. Ventricular assist devices are primarily used as a bridge for patients on the waiting list for a heart transplant and have been shown in published studies to be effective at halting further deterioration of the patient's condition and decreasing the likelihood of death before transplantation. In addition, ventricular assist devices are a destination therapy for patients who are in NYHA Class IV heart failure despite optimal medical therapy and who are not eligible for heart transplant. According to the ACC/AHA Guidelines, device related adverse events are reported to be numerous and include bleeding, infection, blood clots and device failure.

3. AD-SVF CONTAINING ADULT STEM CELLS TREATMENT OPTION

A. Ad-SVF Containing Adult Stem Cells Procedure

- ***Initial patient evaluation***: A physician reviews the medical information, lab work, and diagnostic imaging provided by the patient in order to determine the stage of the medical condition and any other secondary conditions.

- ***Pre-op Evaluation / post-op medical consultation***: A medical specialist to the specific condition to be treated provides a medical consultation at the location where the procedure will be performed. During pre-op evaluation informed consent is obtained from all patients and medical records are updated, including patient's most recent physical exam, most up-to-date lab results and imaging studies. Physician then performs surgical risk assessment.

- ***Harvesting of adipose tissue***: Adipose tissue acquisition can be summarized as three step process:

    - ***Application of anesthetic / injection of tumescent solution***

    - ***Waiting time***

    - ***Acquisition of adipose tissue:*** An area of the body with sufficient adipose tissue is selected; this is usually the periumbilical area. With the patient supine, the physician infiltrates a small amount of local anesthetic. A tissue sample is then obtained using 60 cc syringe(s) to aspirate 50 to 100 cc of adipose tissue. Immediately following lipo-aspiration, adipose tissue sample is processed (minimally manipulated) to separate stem cells for use as graft.

- ***Preparation of Platelet Rich Plasma (PRP)***: Using a standard phlebotomy technique the patient's own blood sample is obtained. After collection of whole blood, sample is centrifuged to obtain PRP aliquot. The regenerative potential of PRP is based on the release of growth factors / cytokines upon platelet rupture. PRP also enhances stem cell proliferation.

- ***Autologous implant of Ad-SVF***: The stem cells obtained from the adipose tissue sample and the PRP are applied to the patient using appropriate protocol for their condition. Autologous Ad-SVF containing adult stem cells are injected directly into the heart muscle using a catheter.

- ***Procedure for application of up to 16 injections*:** The catheter is introduced into the patient either through the femoral artery or the radial artery.

B. Risks: There are possibilities for unwanted effects related to the local anesthesia, harvesting procedure, and injection of stem cells. Even with the most established protocol, adequate technique, and careful administration; a medical team may encounter uncontrollable events. Although there is no guarantee of perfect results, excellent results can be attained. The surgeon provides services in the most responsible, professional and diligent manner, always considering that surgeries imply risks. The risks of complications of adipose tissue harvesting and stem cell infusion are very low. Possible risks include but are not limited to:

- Pain at site of injections
- Bleeding at injection site
- Malaise
- Low-grade fever
- Hot flashes
- Itching at injection site
- Vascular spasm or obstruction
- Bruising
- Nerve or muscle injury
- Allergic reaction
- Dizziness
- Nausea
- Vomiting

C. Benefit: Adipose derived stem cells seek to regenerate new myocytes to replace the damaged myocytes from patients who suffer from CHF.

D. Follow-Up Plan: Clinical response showing improvements in quality of life or quantitative parameters. International standards for follow-up:

- ***Pre-Ad-SVF implant:*** MLWHF Questionnaire, EF, 6 minute walk test
- ***3 months after Ad-SVF implant:*** MLWHF Questionnaire, EF, 6 minute walk test
- ***6 months after Ad-SVF implant:*** MLWHF Questionnaire, EF, 6 minute walk test

CHF – Adult Stem Cells Schedule of Events

1. **Initial Patient Evaluation:** A physician reviews the medical information, lab work, and diagnostic imaging provided by the patient in order to determine the stage of the medical condition and any other secondary conditions.

   A. Pre-Examination:
   - You will have a physical exam, which will include measuring your blood pressure, temperature and heart rate (vital signs).
   - Your doctor will discuss your medical history and any medications that you are taking.
   - Your doctor will assess how well you can perform your daily activities
   - If needed, you will have a urine or blood pregnancy test.
   - Blood will be taken.

   B. Additional Tests: should be done during or soon after this visit

   - Measure ejection fraction (EF)
   - Determine exercise capacity with the six minute walk distance test
   - Determine the patient's overall quality of life by completing the Minnesota Living with Heart Failure Questionnaire.

   C. Review Results: After your doctor has reviewed the results of these tests, he or she will assess whether you are a good candidate for stem cell therapy. If you decide to obtain this therapy you will sign a consent form. A medical specialist to the specific condition to be treated provides a medical consultation at the location where the procedure will be performed. During pre-op evaluation informed consent is obtained from all patients and medical records are updated, including patient's most recent physical exam, most up-to-date lab results and imaging studies. Physician then performs surgical risk assessment.

2. **Pre-Operation / Stem Cell Procedure:**

   A. Two Weeks Before Procedure:

   - No Aspirin or medicines that contain aspirin or Ibuprofen since it interferes with normal blood clotting.
   - Discuss with your primary physician to discontinue anticoagulant drugs at least 1 week before the procedure.
   - Please discontinue all herbal medications as many have side effects that could complicate a surgical procedure by inhibiting blood clotting, affecting blood pressure, or interfering with anesthetics.
   - Please discontinue all diet pills whether prescription, over-the-counter or herbal.
   - NO SMOKING because nicotine reduces blood flow to the skin and can cause significant complications during healing.
   - You may take Tylenol or generic forms of this drug.
   - Purchase a compressive garment to wear after the lipoaspiration procedure.

B. Morning of the Procedure:

- Have a light breakfast.
- Take your regular prescribed medications
- Wear comfortable, loose-fitting clothes that do not have to be put on over your head.

3. Stem Cell Procedure:

- Preparation & Harvesting of Adipose Tissue:
  - ***Application of anesthetic / injection of tumescent solution***
  - ***Waiting time (~15 – 20 minutes)***
  - ***Acquisition of blood sample***
  - ***Acquisition of adipose tissue:*** An area of the body with sufficient adipose tissue is selected; this is usually the periumbilical area. With the patient supine, the physician infiltrates a small amount of local anesthetic. Immediately following lipo-aspiration, adipose tissue sample is processed (minimally manipulated) to separate stem cells for use as graft.

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- ***Autologous implant of Ad-SVF***: The stem cells obtained from the adipose tissue sample and the PRP are applied to the patient using appropriate protocol for their condition. Autologous Ad-SVF containing adult stem cells are injected directly into the heart muscle using a catheter.

- ***Procedure for application of up to 16 injections*:** The catheter is introduced into the patient either through the femoral artery or the radial artery.

4. Recommended Post-Operation / Stem Cell Therapy Schedule:

A. Post-Op Medical Instruction - **(Please follow these instructions closely!)**

- ***Post-op medication*** will be given to you the day of your surgery. They will consist of an antibiotic and a painkiller:
  - *Antibiotic*: Cephalexin/Cipro, please take as directed beginning the day after surgery
  - *Painkiller:* Please take as directed and only as needed for pain

  * If you are unable to take any of these medications, please contact your patient coordinator so we can arrange for other medications.
- ***Resume previous medication*** as directed by the physician
- ***Report any symptoms of feeling unwell***: fever, pain etc. Patients should be seen promptly by an ophthalmologist for full evaluation should any of the above symptoms be encountered.
- It is recommended that the ***patient have a companion stay with him or her*** for at least 24 hours after discharge.
- You should ***expect some of blood-tinged anesthetic solution to drain from the incision sites*** during the first 24 to 48 hours. This will vary from patient to patient. Maxi-pads are recommended for bandages over your incision sites. You may take a shower 24 hours after the procedure.
- ***Compressive garments should be worn*** 24 hours a day for the first week and 12 hours a day for the second week.
- ***Do not shower for the first 24 hours***. ***Do not submerge yourself in any water*** (i.e. taking a bath or swimming) for the 1st week.
- ***If you experience nausea or vomiting it is probably due to the medication***. Please try to take it with food. If it persists, please contact our office.
- ***Diet-meals are not restricted.***
- ***Drink plenty of clear fluids***. We recommend 8 glasses of water or fruit juice every day.
- ***Do not drink any alcohol*** for 48 hours and limit alcohol intake for the first week.

B. Post-Op Medical Consultation Schedule: 3 months & 6 month

- Review of medical history
- Review of medication history
- Review of any adverse events since the previous visit
- Measure ejection fraction (EF)
- Determine exercise capacity with the six minute walk distance test
- Complete the Minnesota Living with Heart Failure Questionnaire.

Your doctor will contact you by phone within the first week to follow up then future follow up visits will be arranged through your patient coordinator. If you need assistance before do not hesitate to contact us.

CHF – Minnesota Living with Heart Failure

The Minnesota Living with Heart Failure (MLWHF) Questionnaire

Did your heart failure prevent you from living as you wanted during the last month by:							
		No	**Very little**				**Very much**
		0	1	2	3	4	5
		Please Circle One Number per Column					
1	Causing swelling in your ankles, legs etc.?	0	1	2	3	4	5
2P	Making you sit or lie down to rest during the day?	0	1	2	3	4	5
3P	Making your walking about or climbing stairs difficult?	0	1	2	3	4	5
4P	Making your Working Around the house or yard difficult?	0	1	2	3	4	5
5P	Making your going places away from home difficult?	0	1	2	3	4	5
6P	Making your sleeping well at night difficult	0	1	2	3	4	5
7P	Making your sleeping to or doing things with your friend s or family difficult?	0	1	2	3	4	5
8	Making your working to earn a living difficult?	0	1	2	3	4	5
9	Making your recreational pastimes, sports or hobbies difficult	0	1	2	3	4	5
10	Making you sexual activities more difficult?	0	1	2	3	4	5
11	Making you eat less of the foods you like?	0	1	2	3	4	5
12P	Making you short of breath?	0	1	2	3	4	5
13P	Making you tired, fatigued, or low on energy?	0	1	2	3	4	5
14	Making you stay in a hospital?	0	1	2	3	4	5
15	Costing you money for medical care?	0	1	2	3	4	5
16	Giving you side effects from medications?	0	1	2	3	4	5
17E	Making you feel you are a burden to your family or friends?	0	1	2	3	4	5
18E	Making you feel a loss of self-control in your life?	0	1	2	3	4	5
19E	Making you worry?	0	1	2	3	4	5
20E	Making it difficult for you to concentrate or remember things?	0	1	2	3	4	5
21E	Making you feel depressed?	0	1	2	3	4	5

The QOL questionnaire, per publication consists of four dimensions:

1 global score (all questions);
2 physical dimension score (questions # 2-7 and 12 and 13);
3. emotional dimension (Questions 17-21)
4. economic dimension;

Rector, TS; Kubo, SH and Cohn, JN; "Content, Reliability and Validity of a New Measure, The Minnesota Living with Heart Failure Questionnaire"; Heart Failure, 1987; 198-209.

E-Emotional component | P-Physical Dimension

CHF – Ejection Fraction (EF)

Ejection Fraction (EF) is a measurement of how much blood the left ventricle pumps out with each contraction. Ejection fraction helps identify and assess heart failure by determining the heart's efficiency to pump blood.

- **Perserved ejection fraction (HFpEF)** – a.k.a. diastolic heart failure
  The heart muscle contracts normally but the ventricles do not relax as they should during ventricular filling (or when the ventricles relax).
- **Reduced ejection fraction (HFREF)** – a.k.a. systolic heart failure
  The heart muscle does not contract effectively and less oxygen-rich blood is pumped to the body.

Example of Ejection Fraction: An ejection fraction of 65 percent signifies that 65 percent of the total amount of blood in the left ventricle is pushed out with each heartbeat.

Ejection Fraction Range:

HEART'S PUMPING ABILITY IS…			
VERY BELOW NORMAL	**BELOW NORMAL**	**NORMAL**	**ABOVE NORMAL**
< 40%	**40% - 54%**	**55% - 75%**	**> 75%**

Tests for Measuring EF:

Echocardiogram (Echo)	CAT scan	Nuclear stress test
MUGA scan	Cardiac catheterization	

Ejection Fraction		Pre Treatment	3 Month	6 Month
Very Below Normal	**< 40%**			
Below Normal	**40% - 54%**			
Normal	**55% - 75%**			
Above Normal	**> 75%**			

Ejection Fraction Heart Failure Measurement. *American Heart Association*. 2013. Web. 12/10/13.

CHF – 6 Minute Walk Test (6MWT)

Details of performing Six Minute Walk Test (6MWT)

These details have been taken from the following:
American Thoracic Society (ATS) statement: Guidelines for the Six-Minute Walk Test
(Am J Respir Crit Care Med 2002; 166:111-117).

The six-minute walk test (6MW) should be performed indoors, along a long, flat, straight, enclosed corridor with a hard surface that is seldom used. The walking course must be:

- 15 m - 30 m /50 ft -100 ft in length.
- The length of the corridor should be marked every 3 m / 10 ft.
- The turnaround points should be marked with a cone (such as a traffic cone).
- A starting line, which marks the beginning and end of each 30 m - 60 m lap, should be marked on the floor using brightly colored tape.

The same course used for baseline evaluation should be used throughout the study.

The use of a treadmill for 6-minute walk testing is not recommended.

What you will need:
- A stopwatch or countdown timer;
- A mechanical lap counter;
- Two small cones to match the turnaround points;
- A chair that can be easily moved along the walking course;
- Worksheets;
- A source of oxygen;
- A sphygmomanometer;
- A telephone; and
- An automated electronic defibrillator

The patient should be told to wear comfortable clothing and appropriate shoes for the test. The patient should also be informed to use their usual walking aids during the test. The patient should continue to use their usual medicine regime and should not have had a heavy meal before the test. The patient should not have exercised vigorously within 2 hours of the test.

Instructions:

1. Repeat testing should be performed about the same time of day to minimize intra-day variability.
2. A "warm-up" period before the test should not be performed.
3. The patient should sit at rest in a chair, located near the starting position, for at least 10 minutes before the test starts. During this time, check for contraindications, measure pulse and blood pressure, and make sure that clothing and shoes are appropriate. Complete the first portion of the worksheet.
4. Pulse oximetry is optional. If it is performed, measure and record baseline heart rate and oxygen saturation (SpO_2) and follow manufacturer's instructions to maximize the signal and to minimize motion artefact. Make sure the readings are stable before recording. Note pulse regularity and whether the oximeter signal quality is acceptable.
5. Set the lap counter to zero and the timer to 6 minutes. Assemble all necessary equipment (lap counter, timer, clipboard, Borg Scale, worksheet) and move to the starting point.
6. Instruct the patient as follows:

   "The object of this test is to walk as far as possible for 6 minutes. You will walk back and forth in this hallway. Six minutes is a long time to walk, so you will be exerting yourself. You will probably get out of breath or become exhausted. You are permitted to slow down, to stop, and to rest as necessary. You may lean against the wall while resting, but resume walking as soon as you are able.

   You will be walking back and forth around the cones. You should pivot briskly around the cones and continue back the other way without hesitation. Now I'm going to show you. Please watch the way I turn without hesitation."

   Demonstrate by walking one lap yourself. Walk and pivot around a cone briskly.

   "Are you ready to do that? I am going to use this counter to keep track of the number of laps you complete. I will click it each time you turn around at this starting line.

   Remember that the object is to walk AS FAR AS POSSIBLE for 6 minutes, but don't run or jog.

   Start now or whenever you are ready."

7. Position the patient at the starting line. You should also stand near the starting line during the test. Do not walk with the patient. As soon as the patient starts to walk, start the timer.

8. Do not talk to anyone during the walk. Use an even tone of voice when using the standard phrases of encouragement. Watch the patient. Do not get distracted and lose count of the laps. Each time the participant returns to the starting line, click the lap counter once (or mark the lap on the worksheet). Let the participant see you do it. Exaggerate the click using body language, like using a stopwatch at a race.

9. Do not use other words of encouragement (or body language to speed up). Only the standardized phrases for encouragement (as specified previously here) must be used during the test, as follows:
    - *After the first minute, tell the patient the following (in even tones): "You are doing well. You have 5 minutes to go."*
    - *When the timer shows 4 minutes remaining, tell the patient the following: "Keep up the good work. You have 4 minutes to go."*
    - *When the timer shows 3 minutes remaining, tell the patient the following: "You are doing well. You are halfway done."*
    - *When the timer shows 2 minutes remaining, tell the patient the following: "Keep up the good work. You have only 2 minutes left."*
    - *When the timer shows only 1 minute remaining, tell the patient: "You are doing well. You have only 1 minute to go."*

10. If the patient stops walking during the test and needs a rest, say this: "You can lean against the wall if you would like; then continue walking whenever you feel able." Do not stop the timer. If the patient stops before the 6 minutes are up and refuses to continue (or you decide that they should not continue), wheel the chair over for the patient to sit on, discontinue the walk, and note on the worksheet the distance, the time stopped, and the reason for stopping prematurely.

11. When the timer is 15 seconds from completion, say this: "In a moment I'm going to tell you to stop. When I do, just stop right where you are and I will come to you."

12. When the timer rings (or buzzes), say this: "Stop!" Walk over to the patient. Consider taking the chair if they look exhausted. Mark the spot where they stopped by placing a bean bag or a piece of tape on the floor.

13. **Post-test**: Record the postwalk Borg dyspnea and fatigue levels and ask this: "What, if anything, kept you from walking farther?"

14. If using a pulse oximeter, measure SpO_2 and pulse rate from the oximeter and then remove the sensor.

15. Record the number of laps from the counter (or tick marks on the worksheet).

16. Record the additional distance covered (the number of meters in the final partial lap) using the markers on the wall as distance guides. Calculate the total distance walked, rounding to the nearest meter, and record it on the worksheet.

17. Congratulate the patient on good effort and offer a drink of water.

CHF – Supporting Studies

A double-blind, randomized, controlled, multicenter study to assess the safety and cardiovascular effects of skeletal myoblast implantation by catheter delivery in patients with chronic heart failure after myocardial infarction

Thomas J. Povsic, MD, PhD, FACC, [a] Christopher M. O'Connor, MD, FACC, [c] Timothy Henry, MD, FACC, [b] Andrew Taussig, MD, FACC, [c] Dean J. Kereiakes, MD, FACC, [d] F. David Fortuin, MD, FACC, [e] Alan Niederman, MD, FACC, [f] Richard Schatz, MD, FACC, [g] Richard Spencer, IV, JD, [h] Douglas Owens, RN, [h] Missy Banks, BA, [a] Diane Joseph, BS, [a] Rhonda Roberts, MSPH, [a] John H. Alexander, MD, MHS, FACC, [a] and Warren Sherman, MD, FACC [i] Durham, NC; Minneapolis, MN; Orlando, Fort Lauderdale, and Sunrise, FL; Cincinnati, OH; Phoenix, AZ; La Jolla, CA; and New York, NY

Background
We sought to determine the safety and preliminary efficacy of transcatheter intramyocardial administration of myoblasts in patients with heart failure (HF).

Methods
MARVEL is a randomized placebo-controlled trial of image-guided, catheter-based intramyocardial injection of placebo or myoblasts (400 or 800 million) in patients with class II to IV HF and ejection fraction b35%. Primary end points were frequency of serious adverse events (safety) and changes in 6-minute walk test and Minnesota Living With HF score (efficacy). Of 330 patients intended for enrollment, 23 were randomized (MARVEL-1) before stopping the study for financial reasons.

Results
At 6 months, similar numbers of events occurred in each group: 8 (placebo), 7 (low dose), and 8 (high dose), without deaths. Ventricular tachycardia responsive to amiodarone was more frequent in myoblast-treated patients: 1 (placebo), 3 (low dose), and 4 (high dose). A trend toward improvement in functional capacity was noted in myoblast-treated groups (Δ6- minute walk test of −3.6 vs +95.6 vs +85.5 m [placebo vs low dose vs high dose; P = .50]) without significant changes in Minnesota Living with HF scores.

Conclusions
In HF patients with chronic postinfarction cardiomyopathy, transcatheter administration of myoblasts in doses of 400 to 800 million cells is feasible and may lead to important clinical benefits. Ventricular tachycardia may be provoked by myoblast injection but appears to be a transient and treatable problem. A large-scale outcome trial of myoblast administration in HF patients with postinfarction cardiomyopathy is feasible and warranted. (Am Heart J 2011;162:654-662.e1.)

CHF – Supporting Studies

Exp Biol Med (Maywood). 2013 March ; 238(3): 294–300. doi:10.1177/1535370213477982.

Cardiac-derived stem cell-based therapy for heart failure: progress and clinical applications

Yaoliang L Tang, Yingjie J Wang, Lijuan J Chen, Yaohua H Pan, Lan Zhang, and Neal L Weintraub

Division of Cardiovascular Disease, Department of Internal Medicine, College of Medicine, University of Cincinnati, Cincinnati, Ohio 45267, USA

Abstract
Stem cell-based therapy is emerging as a promising strategy to treat end-stage heart failure, a leading cause of morbidity and mortality. Stem cells can be isolated from a variety of sources and exhibit unique characteristics that impact their potential therapeutic utility. The adult heart contains small populations of committed, multipotent cardiac stem cells (CSC), which are adapted to the cardiac microenvironment and participate in postnatal physiological and pathological cardiac renewal or repair. These cells can be isolated, expanded in culture, and administered therapeutically to improve cardiac function in the setting of heart failure. CSC can be differentiated into three distinct cardiovascular lineages and exhibit enhanced paracrine factor production and engraftment as compared with other types of mesenchymal stem cells, which in turn may translate into improved therapeutic efficacy. The cell surface marker expression and phenotype of these CSC, however, depends on the method of isolation, selection and propagation, which likely explains the variable experimental results obtained to date. Moreover, invasive procedures are required to obtain CSC from humans. Early trials using autologous CSC in patients with ischemic cardiomyopathy have demonstrated feasibility and safety, along with variable degrees of therapeutic efficacy in terms of enhancing myocardial viability and cardiac function. Further studies are needed to optimize methods of CSC isolation, manipulation and delivery. If fully realized, the potential of CSC therapy could fundamentally change the approach to thetreatment of end-stage heart failure.

CHF – Supporting Studies

Can Vet J. 2011 Aug;52(8):869-74.

Cardiac function in dogs with chronic Chagas cardiomyopathy undergoing autologous stem cell transplantation into the coronary arteries

Sousa MG, Paulino-Junior D, Pascon JP, Pereira-Neto GB, Carareto R, Champion T, Camacho AA. Source

The Federal University of Tocantins State (UFT), College of Veterinary Medicine and Animal Science, Tocantins, Brazil. john.ellis@usask.ca

Abstract

This study assessed the effects of a single intracoronary injection of autologous stem cells on the cardiac function of dogs with Chagas cardiomyopathy. Bone-marrow-derived stem cells were delivered into the right and left coronary arteries of 5 mature dogs with mildly compromised cardiac function due to chronic Chagas cardiomyopathy. Blood pressure and electrocardiographic and echocardiographic parameters were recorded at monthly intervals for 6 mo in the 3 dogs that survived. Although no changes were observed in the electrocardiogram and blood pressure, there was a significant increase in peak velocity of aortic flow 3 mo after stem cell transplantation. Pre-ejection period, isovolumic relaxation time, and the Tei index of myocardial performance were reduced significantly 4 mo after the procedure. All significant changes persisted to the end of the study. The results suggest that the transplantation of autologous bone-marrow-derived stem cells into the coronary arteries of dogs with Chagas cardiomyopathy may have a beneficial effect but the small number of dogs studied was a limitation.

PMID: 22294793 [PubMed - indexed for MEDLINE] PMCID: PMC313503

CHF – Supporting Studies

PLoS One. 2013;8(2):e54963. doi: 10.1371/journal.pone.0054963. Epub 2013 Feb 7.

In vivo MR imaging of intraarterially delivered magnetically labeled mesenchymal stem cells in a canine stroke model

Lu SS, Liu S, Zu QQ, Xu XQ, Yu J, Wang JW, Zhang Y, Shi HB. Source
Department of Radiology, The First Affiliated Hospital of Nanjing Medical University, Nanjing, Jiangsu Province, China.

Abstract

BACKGROUND:

This study aimed to evaluate the feasibility of intraarterial (IA) delivery and in vivo MR imaging of superparamagnetic iron oxide (SPIO)-labeled mesenchymal stem cells (MSCs) in a canine stroke model.

METHODOLOGY:

MSCs harvested from beagles' bone marrow were labeled with home-synthesized SPIO. Adult beagle dogs (n=12) were subjected to left proximal middle cerebral artery (MCA) occlusion by autologous thrombus, followed by two-hour left internal carotid artery (ICA) occlusion with 5 French vertebral catheter. One week later, dogs were classified as three groups before transplantation: group A: complete MCA recanalization, group B: incomplete MCA recanalization, group C: no MCA recanalization. 3×10(6) labeled-MSCs were delivered through left ICA. Series in vivo MRI images were obtained before cell grafting, one and 24 hours after transplantation and weekly thereafter until four weeks. MRI findings were compared with histological studies at the time point of 24 hours and four weeks.
PRINCIPAL FINDINGS:

Home-synthesized SPIO was useful to label MSCs without cell viability compromise. MSCs scattered widely in the left cerebral hemisphere in group A, while fewer grafted cells were observed in group B and no cell was detected in group C at one hour after transplantation. A larger infarction on the day of cell transplantation was associated with more grafted cells in the brain. Grafted MSCs could be tracked effectively by MRI within four weeks and were found in peri-infarction area by Prussian blue staining.

CONCLUSION:

It is feasible of IA MSCs transplantation in a canine stroke model. Both the ipsilateral MCA condition and infarction volume before transplantation may affect the amount of grafted cells in target brain. In vivo MR imaging is useful for tracking IA delivered MSCs after SPIO labeling.

PMID: 23408953 [PubMed - indexed for MEDLINE] PMCID PMC3567107

CHF – Supporting Studies

Int J Stroke. 2009 Apr;4(2):101-10. doi: 10.1111/j.1747-4949.2009.00253.x.

Stem cells for enhancing recovery after stroke: a review

England T, Martin P, Bath PM. Source Stroke Trials Unit, Institute of Neuroscience, University of Nottingham, Nottingham, UK.

Abstract

The potential application for stem cell therapy is vast, and development for use in ischaemic stroke is still in its infancy. Access to stem cells for research is contentious; however, stem cells are obtainable from both animal and human. Despite a limited understanding of their mechanisms of action, clinical trials assessing stem cells in human stroke have been performed. Trials are also underway evaluating haematopoietic precursors mobilised with granulocyte-colony stimulating factor, an approach offering an autologous means of administrating stem cells for therapeutic purposes. This review summarises current knowledge in regard to stem cells and their potential for helping improve recovery after stroke.

PMID: 19383051 [PubMed - indexed for MEDLINE]

CHF – Supporting Studies

Curr Opin Mol Ther. 2008 Dec;10(6):611-21.

MyoCell, a cell-based, autologous skeletal myoblast therapy for the treatment of cardiovascular diseases

Haider HKh, Lei Y, Ashraf M. Source University of Cincinnati, Department of Pathology and Laboratory Medicine, Cincinnati, OH 45267-0529, USA. haiderkh@ucmail.uc.edu

Abstract

Cell therapy is fast emerging as a potential therapeutic option in cardiovascular therapeutics. Because of their inherent myogenic differentiation potential, skeletal myoblasts (SkMs) have been extensively assessed in preclinical and clinical studies for their feasibility, safety and effectiveness for myocardial repair. Bioheart Inc is developing MyoCell, autologous SkMs delivered by MyoCath and MyoStar catheter delivery systems, for the treatment of cardiovascular diseases such as myocardial infarction and congestive heart failure. MyoCell is undergoing phase II/III clinical development and has so far demonstrated safety and efficacy, including improvements in cardiac function in phase I/II clinical trials.

PMID: 19051139 [PubMed - indexed for MEDLINE] PMCID: PMC2668534

CHF – Supporting Studies

ARYA Atheroscler. 2013 Sep;9(5):306-310.

Suggested indications of clinical practice guideline for stem cell-therapy in cardiovascular diseases: A stepwise appropriate use criteria for regeneration therapy

Behjati M. Source Isfahan Cardiovascular Research Center, Isfahan Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran.

Abstract

Despite astonishing progress concerning cardiovascular diseases, patients are still suffering from complications of acute insults. Due to reverse remodeling and improper myocyte rebuilding, heart failure has become a common problem these days which needs more powerful myocardial reconstructing strategies. Indeed, no option cases afflicted with non-healing peripheral vascular diseases; refractory stable and unstable angina is the other field with paucity of proper treatments. For these cases, stem cell-based therapies became optimistic treatment, but lack of guideline-based indications regarding stem-cell is still a major problem which limits application of these cells for such end-stage cases. Here, an outline of appropriateness criteria for stem cell-based therapy is suggested.

CHF – Supporting Studies

Regen Med. 2012 Nov;7(6 Suppl):17-24.

Key developments in stem cell therapy in cardiology

Exp Biol Med (Maywood). 2013 Mar;238(3):294-300. doi: 10.1177/1535370213477982.
Cardiac-derived stem cell-based therapy for heart failure: progress and clinical applications.
Tang YL, Wang YJ, Chen LJ, Pan YH, Zhang L, Weintraub NL. Source Division of Cardiovascular Disease, Department of Internal Medicine, College of Medicine, University of Cincinnati, Ohio 45267, USA. tangyg@ucmail.uc.edu

Abstract

Stem cell-based therapy is emerging as a promising strategy to treat end-stage heart failure, a leading cause of morbidity and mortality. Stem cells can be isolated from a variety of sources and exhibit unique characteristics that impact their potential therapeutic utility. The adult heart contains small populations of committed, multipotent cardiac stem cells (CSC), which are adapted to the cardiac microenvironment and participate in postnatal physiological and pathological cardiac renewal or repair. These cells can be isolated, expanded in culture, and administered therapeutically to improve cardiac function in the setting of heart failure. CSC can be differentiated into three distinct cardiovascular lineages and exhibit enhanced paracrine factor production and engraftment as compared with other types of mesenchymal stem cells, which in turn may translate into improved therapeutic efficacy. The cell surface marker expression and phenotype of these CSC, however, depends on the method of isolation, selection and propagation, which likely explains the variable experimental results obtained to date. Moreover, invasive procedures are required to obtain CSC from humans. Early trials using autologous CSC in patients with ischemic cardiomyopathy have demonstrated feasibility and safety, along with variable degrees of therapeutic efficacy in terms of enhancing myocardial viability and cardiac function. Further studies are needed to optimize methods of CSC isolation, manipulation and delivery. If fully realized, the potential of CSC therapy could fundamentally change the approach to the treatment of end-stage heart failure.

PMID: 23598975 [PubMed - indexed for MEDLINE] PMCID: PMC3800692

CHF – Supporting Studies

Methodist Debakey Cardiovasc J. 2013 Jan-Mar;9(1):6-10.

Stem cell therapy in patients with heart failure

Vrtovec B, Poglajen G, Haddad F. Source Ljubljana University Medical Center, Ljubljana, Slovenia.

Abstract

Heart failure results from injury to the myocardium from a variety of causes, including ischemic and nonischemic etiologies. Severe heart failure carries a 50% 5-year mortality rate and is responsible for more than one-third of cardiovascular deaths in the United States.1 Heart failure progression is accompanied by activation of neurohormonal and cytokine systems as well as a series of adaptive changes within the myocardium, collectively referred to as left ventricular remodelling. The unfavorable alterations may be categorized broadly into changes that occur in the cardiac myocytes and changes that occur in the volume and composition of the extracellular matrix.2 Since remodelling in heart failure is progressive and eventually becomes detrimental, the majority of treatment strategies are aimed at stopping or reversing this process. Although medical management, cardiac resychronization therapy, and long-term or destination mechanical circulatory support have been successful in this regard, a considerable number of patients still progress to end-stage heart failure with limited therapeutic options. For these patients, stem cell therapies are being investigated as a safe treatment strategy for decreasing cardiac remodelling on top of conventional medical and device treatment.

PMID: 23518819 [PubMed - indexed for MEDLINE] PMCID: PMC3600877

CHF – Supporting Studies

Biomed Res Int. 2013;2013:547902. doi: 10.1155/2013/547902. Epub 2012 Dec 27.

Current stem cell delivery methods for myocardial repair

Sheng CC, Zhou L, Hao J. Source School of Medicine, Vanderbilt University, 2220 Pierce Avenue, Nashville, TN 37232, USA.

Abstract

Heart failure commonly results from an irreparable damage due to cardiovascular diseases (CVDs), the leading cause of morbidity and mortality in the United States. In recent years, the rapid advancements in stem cell research have garnered much praise for paving the way to novel therapies in reversing myocardial injuries. Cell types currently investigated for cellular delivery include embryonic stem cells (ESCs), induced pluripotent stem cells (iPSCs), and adult stem cell lineages such as skeletal myoblasts, bone-marrow-derived stem cells (BMSCs), mesenchymal stem cells (MSCs), and cardiac stem cells (CSCs). To engraft these cells into patients' damaged myocardium, a variety of approaches (intramyocardial, transendocardial, transcoronary, venous, intravenous, intracoronary artery and retrograde venous administrations and bioengineered tissue transplantation) have been developed and explored. In this paper, we will discuss the pros and cons of these delivery modalities, the current state of their therapeutic potentials, and a multifaceted evaluation of their reported clinical feasibility, safety, and efficacy. While the issues of optimal delivery approach, the best progenitor stem cell type, the most effective dose, and timing of administration remain to be addressed, we are highly optimistic that stem cell therapy will provide a clinically viable option for myocardial regeneration.

CHF – Supporting Studies

Mol Ther. 2012 Jan;20(1):168-77. doi: 10.1038/mt.2011.181. Epub 2011 Sep 20.

Long-term engraftment of multipotent mesenchymal stromal cells that differentiate to form myogenic cells in dogs with Duchenne muscular dystrophy

Nitahara-Kasahara Y, Hayashita-Kinoh H, Ohshima-Hosoyama S, Okada H, Wada-Maeda M, Nakamura A, Okada T, Takeda S.

Source
Department of Molecular Therapy, National Institute of Neuroscience, National Center of Neurology and Psychiatry, Tokyo, Japan.

Abstract
Duchenne muscular dystrophy (DMD) is an incurable genetic disease with early mortality. Multipotent mesenchymal stromal cells (MSCs) are of interest because of their ability to differentiate to form myogenic cells in situ. In the present study, methods were developed to expand cultures of MSCs and to promote the myogenic differentiation of these cells, which were then used in a new approach for the treatment of DMD. MSC cultures enriched in CD271(+) cells grew better than CD271-depleted cultures. The transduction of CD271(+) MSCs with MyoD caused myogenic differentiation in vitro and the formation of myotubes expressing late myogenic markers. CD271(+) MSCs in the myogenic cell lineage transplanted into dog leukocyte antigen (DLA)-identical dogs formed clusters of muscle-like tissue. Intra-arterial injection of the CD271(+) MSCs resulted in engraftment at the site of the cardiotoxin (CTX)-injured muscle. Dogs affected by X-linked muscular dystrophy in Japan (CXMD(J)) treated with an intramuscular injection of CD271(+) MSCs similarly developed muscle-like tissue within 8-12 weeks in the absence of immunosuppression. In the newly formed tissues, developmental myosin heavy chain (dMyHC) and dystrophin were upregulated. These findings demonstrate that a cell transplantation strategy using CD271(+) MSCs may offer a promising treatment approach for patients with DMD.

CHF – Supporting Studies

PMID: 21934652 [PubMed - indexed for MEDLINE] PMCID: PMC3255589
Circulation. 2005 Aug 23;112(8):1128-35. Epub 2005 Aug 15.

Transplantation of mesenchymal stem cells improves cardiac function in a rat model of dilated cardiomyopathy

Nagaya N, Kangawa K, Itoh T, Iwase T, Murakami S, Miyahara Y, Fujii T, Uematsu M, Ohgushi H, Yamagishi M, Tokudome T, Mori H, Miyatake K, Kitamura S.

Source
Department of Regenerative Medicine and Tissue Engineering, National Cardiovascular Center Research Institute, Osaka 565-8565, Japan. nnagaya@ri.ncvc.go.jp

Abstract
BACKGROUND:
Pluripotent mesenchymal stem cells (MSCs) differentiate into a variety of cells, including cardiomyocytes and vascular endothelial cells. However, little information is available about the therapeutic potency of MSC transplantation in cases of dilated cardiomyopathy (DCM), an important cause of heart failure.

METHODS AND RESULTS:
We investigated whether transplanted MSCs induce myogenesis and angiogenesis and improve cardiac function in a rat model of DCM. MSCs were isolated from bone marrow aspirates of isogenic adult rats and expanded ex vivo. Cultured MSCs secreted large amounts of the angiogenic, antiapoptotic, and mitogenic factors vascular endothelial growth factor, hepatocyte growth factor, adrenomedullin, and insulin-like growth factor-1. Five weeks after immunization, MSCs or vehicle was injected into the myocardium. Some engrafted MSCs were positive for the cardiac markers desmin, cardiac troponin T, and connexin-43, whereas others formed vascular structures and were positive for von Willebrand factor or smooth muscle actin. Compared with vehicle injection, MSC transplantation significantly increased capillary density and decreased the collagen volume fraction in the myocardium, resulting in decreased left ventricular end-diastolic pressure (11+/-1 versus 16+/-1 mm Hg, $P<0.05$) and increased left ventricular maximum dP/dt (6767+/-323 versus 5138+/-280 mm Hg/s, $P<0.05$).

CONCLUSIONS:
MSC transplantation improved cardiac function in a rat model of DCM, possibly through induction of myogenesis and angiogenesis, as well as by inhibition of myocardial fibrosis. The beneficial effects of MSCs might be mediated not only by their differentiation into cardiomyocytes and vascular cells but also by their ability to supply large amounts of angiogenic, antiapoptotic, and mitogenic factors.

PMID:16103243 [PubMed - indexed for MEDLINE]

CHF – References

[1] Congestive Heart Failure. *American Heart Association.* 2013. 12/11/13

Vrtovec B, Poglajen G, Haddad F. Source Ljubljana University Medical Center, Ljubljana, Slovenia. (2013). Stem cell therapy in patients with heart failure.